



Lymphatic filariasis

research and control in
Eastern and Southern Africa

Edited by
Paul E. Simonsen
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Edwin Michael
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DBL – Centre for Health Research
and Development · Denmark

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Preface

Lymphatic filariasis (LF) is a disabling and disfiguring disease which results from a mosquito transmitted parasitic infection. It is widespread and a major public health problem in many developing countries with a warm and humid climate and it is one of the most prevalent of the neglected tropical diseases. Current estimates suggest that more than 1 billion people live in endemic areas and are at risk of infection, and more than one third of these are in Sub-saharan Africa.

The common clinical manifestations of LF (e.g. elephantiasis, hydrocele, acute filarial fever) often cause considerable incapacity to the affected individuals, with consequent loss of income and social and psychological stress. Research during recent years has increased knowledge on its extensive geographical distribution and its disabling effects on the victims, and LF has been recognized as a leading cause of long-term disability in the world. LF is moreover an economic burden to the endemic communities and to the health system in endemic countries. However, research has also provided new and better tools for diagnosis, and improved measures and strategies for control. In recent years forces have been united internationally in the fight against LF through the formation of the Global Programme for Elimination of Lymphatic Filariasis (GPELF).

Right from the beginning of these global efforts, one of the countries in Eastern and Southern Africa - Tanzania - has been in the forefront of efforts to implement LF control. The Tanzanian National Programme for Elimination of Lymphatic Filariasis was launched in 2000 and has expanded rapidly. As a consequence of this commitment, Tanzania was invited to host the fifth biennial meeting of the Global Alliance to Eliminate Lymphatic Filariasis (GAELF; a public-private partnership with the purpose of supporting GPELF in advocacy and resource mobilisation for programme implementation) in April 2008.

Other countries in the Eastern and Southern African region have now also initiated, or taken steps to initiate, control programmes. However, despite these efforts, LF is still a widespread and debilitating disease in large parts of the region. For control efforts to expand further and to succeed there is a need to stimulate and support local interests and initiatives. To comply with this, a workshop on 'Lymphatic Filariasis Research and Control in Eastern and Southern Africa' was arranged in Bagamoyo, Tanzania, during November 13-15, 2007. It was organized as a

forum for senior LF researchers and programme managers to review currently available knowledge and ongoing activities, and to provide a platform for future networking and cooperation, within LF research and control activities in this region of Africa. The workshop was organized jointly by the National Institute for Medical Research (Tanzania) and DBL - Centre for Health Research and Development (Denmark), in collaboration with scientists from Michigan State University (U.S.A.) and Imperial College (U.K.).

The workshop provided an excellent opportunity for taking stock of available knowledge on LF and its control in the Eastern and Southern African region, ahead of the fifth GAELF meeting in 2008. On the basis of the presentations and stimulating discussions the workshop organizers took the initiative to prepare and edit the present book. The aim was to provide a written overview of current knowledge on LF research and control activities in Eastern and Southern Africa. It is our hope that the book will be useful to colleagues in this part of Africa as well as elsewhere, and that the information provided will be of benefit to the LF patients, who are and always will be the most important part of the Programme to eliminate Lymphatic Filariasis.

We, the editors, would like to gratefully acknowledge the financial support to both arranging the workshop and preparing this book, which has generously been provided by the Tanzanian Ministry of Health and Social Welfare, DBL – Centre for Health Research and Development (DBL), the Global Alliance for Elimination of Lymphatic Filariasis (GAELF), the Mectizan Donation Program (MDP), GlaxoSmithKline (GSK), the Schistosomiasis Control Initiative (SCI), and the Liverpool LF Support Centre. We would also like to thank Kirsten G. Andersen (DBL) for secretarial assistance during preparation and setting up of the book.

Paul E. Simonsen
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Chapter 1



WHO/AFRO perspective

Lymphatic filariasis elimination in Eastern and Southern Africa: The WHO/AFRO perspective

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Abstract

Among the 14 known endemic countries in the Eastern and Southern Africa sub-region, mapping has been completed in seven and is in progress in four. Five countries have active mass drug administration programmes, and up to six rounds of mass treatment have been given in some of the implementation areas. Three countries have initiated disability prevention and management as part of their programme. The programmes face considerable resource constraints that also restrict the expansion of activities.

Introduction

In 1997, the World Health Assembly passed a resolution (WHA 50.29) calling for elimination of lymphatic filariasis (LF) as a public health problem by the year 2020 (Ottesen, 2000, 2006; Molyneux and Zagaria, 2002). The target was to be achieved by (i) interruption of transmission through mass administration of drugs to the entire at-risk populations; and (ii) management and prevention of LF related disability. Mosquito control, e.g. in conjunction with malaria control programmes, was assigned a supportive role as a tool for interrupting transmission. The stages of programme implementation involve an initial assessment and mapping of the distribution of infection (identification of the at-risk population) followed by mass drug administration (MDA) and disability management and prevention. Monitoring and evaluation is conducted as an integral part of the programme implementation.

Within the African Region of the World Health Organization (WHO), LF is endemic in 39 of the 46 member countries. The population at risk in these countries is estimated at 390 million, which is 38% of the estimated global at-risk population (Zagaria and Savioli, 2002). By the end of 2006, 25 of the 39 endemic countries had LF elimination programmes. Eleven of these were implementing MDA, and disability prevention and management activities had commenced in seven of the countries that implemented MDA.

The Eastern and Southern African sub-region according to WHO categorization consists of 18 countries (Uganda, Kenya, Ethiopia, Eritrea, Tanzania, Seychelles, Mauritius, Comoros, Madagascar, Mozambique, Malawi, Zambia, Zimbabwe, Namibia, Botswana, Lesotho, Swaziland, South Africa). Burundi, Rwanda and Angola are included for the purpose of this write-up.

Mapping and mass drug administration

The status of mapping and MDA implementation in the Eastern and Southern African sub-region is shown in Table 1. Seven countries (Comoros, Kenya, Madagascar, Malawi, Mozambique, Tanzania, and Uganda) have completed mapping and have identified 90.7 million of their populations to be at risk. The mapping results and the population at risk are summarized in Table 2. The pattern of LF distribution in these countries shows a high level of endemicity in the coastal areas from the equatorial zones (Kenya) down to the sub-tropical zones (part of Mozambique). The observed pattern can be seen in Figure 1.

Five countries representing 69.8 million (76.9%) of the identified at risk population in the sub-region were carrying out MDA (Tanzania and Uganda with the ivermectin/ albendazole combination; Kenya, Comoros and Madagascar with the diethylcarbamazine/ albendazole combination). By the end of 2006, a total of 18.3 million (26.3%) of the identified at-risk population were covered in these five countries, corresponding to 20.2% of the total at-risk population identified in the sub-region. Tanzania was among the first countries to start MDA in 2000. Two programmes (Comoros and Zanzibar) are covering the entire at-risk population. Cumulatively, 28.7 million treatments have been given under the Global Programme for Elimination of LF in Eastern and Southern Africa between its inception in 2000 till the end of 2006. The maximum number of people to have received treatment in 2006 under the programmes in the five

countries conducting MDA is shown in Table 3.

The lowering of parasite densities in human populations through MDA to levels not believed to support transmission has been shown to be achievable in the Zanzibar programme. Thus, six rounds of MDA in this programme reduced the microfilarial prevalence to zero in the sentinel sites (Figure 2). The programme now continues with the process of verifying if transmission has been interrupted.

Table 1. Status of mapping and MDA implementation in Eastern and Southern Africa. Botswana, Lesotho, Namibia, South Africa and Swaziland are not endemic for LF.

		Mass Drug Administration		
		<i>Not yet started</i>	<i>In process of scaling up</i>	<i>National scale activity</i>
Mapping	<i>Not yet started</i>	Angola Ethiopia Eritrea		
	<i>In progress</i>	Burundi Rwanda Zambia Zimbabwe Mauritius* Seychelles*		
	<i>Completed</i>	Malawi Mozambique	Kenya Madagascar Tanzania Uganda	Comoros

*Mauritius and Seychelles were historically endemic but the current situation indicates absence of continued endemicity. These two countries are therefore in the process of verifying interrupted LF transmission.

Disability prevention and management

Programme activities in lymphoedema management aim at (i) assisting in lymph flow through elevation, exercise, bandages; (ii) prevention of acute inflammatory episodes; and (iii) preventing secondary bacterial infections.

In the latter two aspects, personal hygiene is promoted through encouragement of frequent washing of affected body parts with soap and water; and through skin care by treatment of “entry lesions”. Management of hydroceles is through surgical repair. Three countries in the Eastern and Southern African sub-region (Uganda, Tanzania and Madagascar) have initiated LF disability and prevention aspect as part of their programme.

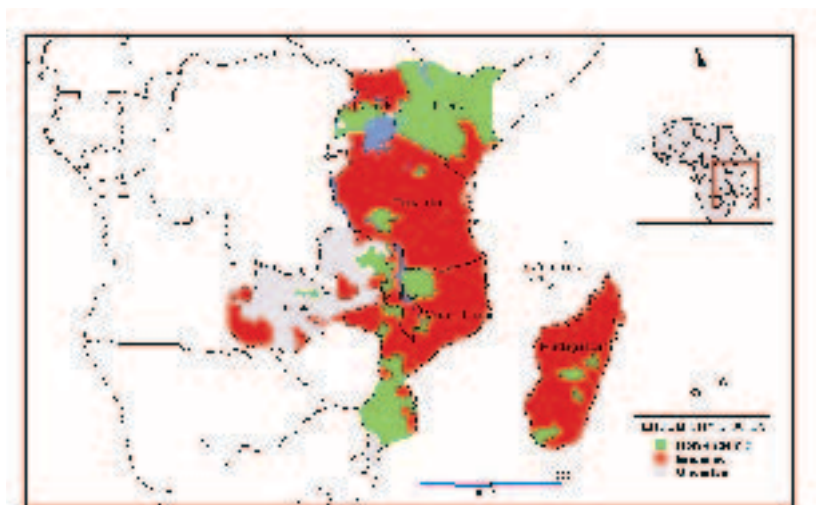


Figure 1. Map showing the distribution of LF in Eastern and Southern Africa in fully mapped countries (Comoros, Kenya, Madagascar, Malawi, Mozambique, Tanzania, and Uganda) and one partially mapped country (Zambia) (from: WHO, Lymphatic Filariasis Elimination Programme, 2007).

Challenges and perspectives in programme implementation

The interventions in the programmes for elimination of LF are leading to a move forward towards the desired outcome of alleviating suffering of the disabled population as well as interrupting transmission of the infection. However, the programmes face considerable resource constraints that restrict expansion of implementation, and therefore the goal of elimination by 2020 may not be achieved. For example, countries that started MDA have been unable to reach a national scale even six years after the initiation of activities. At sub-regional level, mapping remains incomplete in some

Table 2. Mapping results and populations at risk in Eastern and Southern Africa (from: WHO, Lymphatic Filariasis Elimination Programme, 2006).

Country	Mean prevalence in % (range) ¹	Total no. of IUs ²	No. IUs endemic	Endemicity coverage in %	Total population ³	No. at-risk population (%)
Comoros	Other method	3	3	100.0	572,171	572,171 (100.0)
Kenya	2.2 (2–3)	70	7	10.0	34,054,259	2,987,266 (8.8)
Madagascar	9.0 (1–56)	111	98	88.3	19,503,739	15,821,728 (81.1)
Tanzania	29.2 (1–72)	127	125	98.4	38,531,568	37,977,922 (98.6)
Uganda	11.3 (1–47)	62	32	51.6	28,389,477	12,429,409 (43.8)
Malawi	29.5 (1–79)	27	25	92.6	9,925,794	9,798,995 (98.7)
Mozambique	23.1 (1–82)	142	90	63.4	19,792,000	11,152,614 (56.3)
Total	-	542	380	70.1	150,769,00	90,740,105 (60.2)

¹Results from areas where circulating filarial antigen positive cases were detected

²Implementation Units

³Total population are provided by countries through annual reports and/or activities reports

Table 3. MDA achievements in Eastern and Southern Africa from 2000 to 2006 (from: WHO, Lymphatic Filariasis Elimination Programme, 2006).

Country (programme)	Total population at risk ¹	Year of first MDA	Max. no. of rounds	Max. no. of people treated in MDA	Cumulative number treatments delivered
Tanzania (M) ²	36,816,293	2000	6	5,098,797	11,501,706
Tanzania (Z) ³	1,161,629	2001	6	968,992	5,126,050
Comoros	572,171	2001	5	572,171	1,099,650
Kenya	2,987,266	2002	3	1,677,824	2,847,597
Uganda	12,429,409	2002	3	4,914,818	5,375,651
Madagascar	15,821,728	2005	2	2,130,005	2,715,555
Total	69,788,496	-	-	15,362,607	28,666,209

¹Numbers calculated from district population figures provided by the respective countries.

²Mainland

³Zanzibar

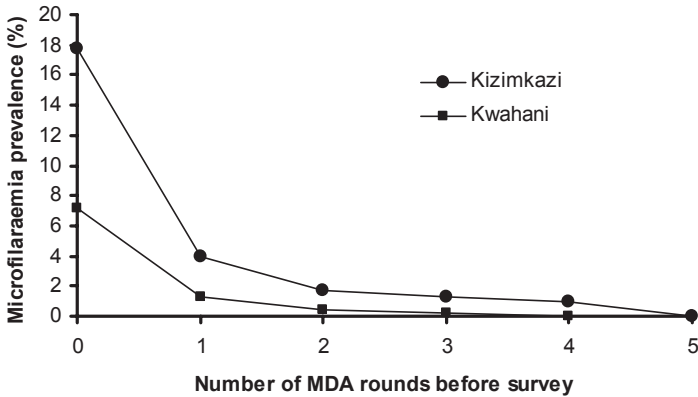


Figure 2. Effect of MDA on microfilarial prevalence in two sentinel sites in Zanzibar (from: Ministry of Health of Tanzania, Lymphatic Filariasis Elimination Programme of Zanzibar, 2007).

countries and has not started in others. Two countries have completed mapping but have been unable to progress to initiate MDA.

Implementation of the LF programmes as an integrated part of programmes for control of other neglected tropical diseases (NTDs) that use MDA as the main strategy provides a great potential for the future. In addition to the obvious logistic benefits, there are new funding opportunities that support an integrated approach as a cost-effective means to disease control.

In a long term perspective, the LF elimination programmes will lead to significant reduction in the public health impact of filarial infection and disease; additionally the drugs used in the programmes have a broader public health impact by acting on onchocerciasis, soil-transmitted helminthiasis and scabies.

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Chapter 2



LF diagnostic techniques

Diagnostic techniques and their role in lymphatic filariasis control programmes in Eastern and Southern Africa

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Abstract

Correct diagnosis of any etiologic agent is crucial to the proper management, monitoring of outcome of treatment and - in the case of an eliminable or eradicable infectious disease - certification. Additionally, any diagnostic technique has to be reliable and reproducible. Thus, the test must meet certain minimal criteria that would be both intrinsic and extrinsic. In this chapter, we briefly review the generally available battery of diagnostic techniques for lymphatic filariasis and assess their application and role in programmes for elimination of lymphatic filariasis in the Eastern and Southern Africa region.

Introduction

Lymphatic filariasis (LF) is caused by nematode worms belonging to the superfamily Filarioidea and family Onchocercidae. *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori* are the species responsible for the global burden of human LF. By 1996, over 120 million persons were estimated to be affected by LF in 83 countries chiefly located in the tropics (Michael et al., 1996). The infection is transmitted by mosquitoes and causes profound physical and social disability. It is estimated that over 40 million people are living with LF disabilities, mainly due to swelling of the limbs and of the male genitals, while to a lesser extent, of breasts and female genitals.

In a joint effort by the global research and public health communities and with the support of development partners and pharmaceutical industries, important research progress has been made. Elucidation of disease severity, economic impact at household, community and national levels, new diagnostic tools, and new treatment, management and control strategies have given impetus to LF elimination efforts. The International Task Force for Disease Eradication identified LF as one of six eradicable, or potentially eradicable, infectious diseases (CDC, 1993). Consequently, the 50th World Health Assembly of 1997 launched an ambitious initiative to eliminate LF globally as a public health problem (WHO, 1997), namely a Global Programme for Elimination of Lymphatic Filariasis (GPELF). This initiative has offered hope to millions of suffering persons globally. The twin pillars of the initiative are:

- Interruption of infection transmission through annual mass drug administration (MDA)
- Alleviation of suffering and morbidity through prevention and management of disease manifestations

Since the launch of GPELF, many LF endemic countries have embarked on National Programmes for Elimination of LF with the assistance from WHO and support by development partners and non-governmental development organizations. One major strategy for interrupting transmission of infection is by decreasing the parasite population in human hosts through annual MDA with single-dose diethylcarbamazine (DEC) or ivermectin in combination with albendazole (Ottesen, 2000). The desired decrease in circulating microfilaraemia is expected to reach a threshold below which infection of the vector mosquitoes is rendered impossible. Cooking salt fortified with DEC has previously been used successfully as a principal public health tool to eliminate LF in China and less extensively in other countries including Brazil, Japan, Tanzania, India and Taiwan (Houston, 2000). Based on successes in these countries DEC-fortified salt has also been proposed as an additional option for the elimination of LF. Despite reports of a high effectiveness of DEC-fortified salt in LF control, experience with its use in many endemic areas is still limited. Earlier community-based studies in Tanzania in 1969 demonstrated reduction in mean microfilarial densities by 90% following six months administration of DEC-fortified salt (Davis and Bailey, 1969). Later community-based studies also in Tanzania have

demonstrated that DEC-fortified salt is an effective strategy for control of LF (Meyrowitsch et al., 1996).

Lymphatic filariasis diagnostic techniques

The subject of LF diagnostic techniques has raised research interest for a long period and existing literature bear overwhelming testimony to this effect. Following the launching of GPELF, various LF diagnostic gaps have emerged. We wish to give a brief description of generally available diagnostic techniques for LF followed by a discussion of options that may be applied in the LF control programmes in the Eastern and Southern African region.

Detection of microfilariae

Direct demonstration of microfilariae in blood, also known as definitive diagnosis, has been used for the longest time and still claims a significant role in the GPELF. As the microfilariae of *W. bancrofti* in Africa have nocturnal periodicity, the blood specimens for diagnosis should be collected at nighttime (normally between 22.00 and 02.00 hours). The frequently used microfilarial detection methods are:

- i. The thick blood smear method. – The Giemsa stained thick smear is the most frequently used method for diagnosis of LF in most of the endemic regions. The blood sample (20–60 μ l) is applied on a clean microscope glass slide and dried overnight before dehaemoglobinization and subsequent fixation and staining. The slide is later examined for microfilariae under a microscope. Limitations of this method include a low sensitivity due to the small volume of blood sample used and loss of microfilariae during the dehaemoglobinization step (McMahon et al., 1979).
- ii. The Knott's concentration method. – This is a very sensitive concentration method for detecting microfilariae (Knott, 1939). One ml of venous blood collected in a tube containing anticoagulant is mixed with ten ml of 2% formalin. The mixture is left for at least 15 min before centrifugation. The supernatant is discarded and the remaining sediment examined for microfilariae as a wet smear on a microscope glass slide. A drop of 1% methylene blue may be added to the sediment to aid examination. The amount of sediment may be large, especially in people with elevated levels of gamma globulin, thus making the

Knott's concentration method difficult to perform because of the longer time required examining the specimen. In the field setting specimens may be stored until return to a laboratory with a centrifuge because the formalin solution in addition to lysing the red blood cells also preserves the microfilariae. A modified Knott's concentration method in which the blood sample is mixed with 2% Triton X-100[®] instead of formalin has been proposed (Melrose et al., 2000). The major benefit of this modified method is that it saves time for examination due to the smaller volume of resultant sediment.

- iii. The counting chamber method. – This is the diagnostic tool of choice in many countries in the Eastern and Southern African region, but it is infrequently used in other regions (McMahon et al., 1979). 100 µl of finger prick-blood is transferred to a tube containing 0.3% acetic acid and mixed gently. The acetic acid serves as a preservative as well as a lysing solution for the red blood cells and thus specimens collected in the field can be stored at ambient temperature until transport to a laboratory. In the laboratory, the specimen is transferred to a Sedgewick Rafter counting chamber and examined for microfilariae under a microscope. This technique has been used extensively during studies conducted in Kenya (Estambale et al., 1994; Wamae et al., 1998; Njenga et al., 2000; Mukoko et al., 2004), Tanzania (McMahon et al., 1981, Meyrowitsch et al., 1995, Simonsen et al., 2002), Uganda (Onapa et al., 2001) and Malawi (Nielsen et al., 2002). Although the counting chamber can be home-made (Denham et al., 1971) plastic or glass chambers are commercially available, the latter being durable but expensive. A drawback of the plastic chamber is that it easily gets scratches which under the microscope may appear as microfilariae. The advantages of the counting chamber method include relative convenience because specimens preserved in the acetic acid can be stored for later examination in the laboratory. Unlike the thick blood smear method, where some microfilariae may be lost during processing, there is little chance of losing parasites in the counting chamber method because the specimen is transferred directly into the chamber for examination. Earlier studies reported that the counting chamber method is much more sensitive than the thick blood smear method (Denham et al., 1971; McMahon et al., 1979).
- iv. The membrane filtration technique. - In this method, a measured volume of venous blood collected in a tube containing anticoagulant (1-

5 ml) is first mixed with a solution to lyse the red blood cells and then filtered through a 5 µm pore size Nuclepore® (or Millipore®) filter. The filter is carefully held between plastic supports within a leak-proof reusable filter holder. After filtration, the filter is removed using forceps and placed on a glass slide for examination and counting of microfilariae under a microscope. The filter can be stained before examination (Wamae et al., 1998) or examined directly without staining (Njenga et al., 2000). There is good correlation between the membrane filtration method (using one ml of venous blood) and the counting chamber method (using 0.1 ml of finger-prick blood) (McMahon et al., 1979). However, the requirement of venous blood, which most communities are reluctant to give, is a major disadvantage for the membrane filtration technique. Additionally, collection of venous blood requires a trained phlebotomist, whereas finger pricking can be done with minimal training. Another limitation of the method is that the blood sample must be processed promptly after collection (Dickerson et al., 1990). Otherwise, the filters may get clogged, thus preventing the blood specimen from passing through with a potential of even contaminating the user. Researchers in the Centers for Disease Control and Prevention, Atlanta, have proposed an improved membrane filtration method in which the blood sample is first mixed with 2% formalin/10% Teepol® solution (Dickerson et al., 1990). This improved method preserves the blood specimen without deterioration of the microfilarial structure and allows the specimen to pass through the filter easily.

Detection of circulating filarial antigen

Diagnostic techniques based on direct detection of microfilariae can be insensitive because microfilariae may be absent from the circulation despite infection with other parasite stages or may be present in ultralow numbers. It may also be inconvenient particularly in geographical regions where the microfilariae exhibit nocturnal periodicity (Wamae, 1994). Methods based on detection of molecules shed by adult worms or microfilariae may instead be used as a proxy for active infection. In the case of *W. bancrofti*, there are two commercially available diagnostic tests that detect circulating filarial antigen (CFA). The development of these tests has offered the convenience of daytime examination and greater sensitivity than detection of microfilariae (More and Copeman 1990; Weil et al., 1997).

- i. The immunochromatographic test (ICT). – This is a rapid card test manufactured by Binax (Scarborough, U.S.A.) which is specific for *W. bancrofti* CFA. 100 µl finger-prick blood is added to the sample pad of the card. The pad contains a gold-labeled polyclonal anti-filarial antibody that binds to filarial antigen from the blood. When the card is closed, the pad touches a nitrocellulose strip. The antibody-antigen complexes move along the strip and are trapped by an immobilized anti-filarial monoclonal antibody (AD12.1) in the strip's coating. The result is read after 10 minutes, and appears as a pink test line (in case of a positive test) next to a control pink line that appears in all valid cards. Thus, blood samples from antigen negative individuals show one pink line, whereas those from antigen positive individuals show two pink lines. Evaluation of the ICT test in a study conducted in Kenya reported that the sensitivity of the test was greater than that of microfilarial detection (Njenga and Wamae, 2001). The unit price is a major limitation for extensive field application of the ICT card test but several factors such as use of finger prick whole blood specimens, high sensitivity, ease of performance, daytime application and short time to obtain results make the test convenient in field settings.
- ii. The Og4C3 ELISA. – An enzyme-linked immunosorbent assay (ELISA) test kit for *W. bancrofti* specific CFA is manufactured by TropBio Pty. Ltd. (Queensland, Australia). Plasma samples of 100 µl from the test individuals are boiled in a diluent containing EDTA. This releases the heat stable CFA in positive specimens. The supernatant obtained after centrifugation is added in duplicate to polystyrene microtitre plates pre-coated with a monoclonal anti-filarial antibody (Og4C3). Antigen standards with known concentrations of CFA are added to some of the wells on the microtitre plate, in order to be able to prepare a standard curve for determination of the antigen concentration in the unknown test samples. After incubation and washing, a rabbit anti-CFA antibody is added. After another incubation and washing, an anti-rabbit horse-radish-peroxidase-conjugate is added. Finally, the plate is developed by addition of a substrate, and the optical density is determined with an ELISA reader. The assay is very sensitive when compared to microfilarial detection (Simonsen et al., 1996; Njenga et al., 2007). The prevalence of infection obtained with the Og4C3 ELISA is about twice of that shown by membrane filtration method (Wamae et al., 1998) or the counting chamber method (Njenga et al., 2007). However the usefulness of the Og4C3 ELISA is limited by the

requirement of a well equipped laboratory with staff trained in ELISA technology.

Detection of anti-filarial antibodies

Since development of anti-filarial antibody responses is a characteristic feature of infection with filarial parasites, this might be exploited to develop diagnostic tools (Lammie et al., 2004). Although antibody detection tests utilizing crude filarial extract as the antigen are limited by cross-reactivity (Maizels et al., 1985), early studies have also suggested that detection of anti-filarial immunoglobulin (Ig)G4 antibody has greater specificity for filarial infection in such tests (Lal and Ottesen 1988).

In an effort to get more specific antigens for antibody-detection based diagnostic tests, selected recombinant proteins developed from filarial cDNA libraries have been identified for further research (Lammie et al., 2004; Noordin et al., 2007). For *W. bancrofti* infection, a recombinant protein designated Bm14 has given promising results when used in an ELISA for detection of anti-filarial IgG4 (Chandrashekar et al., 1994, Dissanayake et al., 1992). This ELISA has been employed in longitudinal studies in Egypt (Ramzy et al., 1995; Weil et al., 1999) and is now undergoing further evaluation in a multicenter trial (Lammie et al., 2004).

An ELISA that detects filarial-specific IgG4 antibodies in urine has also been devised (Itoh et al., 2001). The assay was reported to have high sensitivity (96%) and specificity (99%) and ought to be validated in other regions as well. Urine samples are generally easier to collect than blood samples, and a urine IgG4 ELISA may become a useful diagnostic tool in LF. However, ELISA based diagnostic tests require a well-equipped laboratory and equally well trained staff to conduct the assays.

Mosquito dissection

Dissection and examination of female vector mosquitoes for filarial larvae has been used for a long time as a diagnostic tool for assessing presence of filarial infection and for monitoring the progress of control programmes in endemic areas. There are several methods for collecting mosquitoes including human-landing catches, light trap catches and knockdown spray catches. All three methods were used in a comprehensive epidemiological study in Uganda (Onapa et al., 2001). In the laboratory, the mosquitoes are sorted by species before dissection in a drop of saline under a dissecting microscope and examination for filarial larvae (McMahon et al., 1981). A major advantage of mosquito dissection is that it allows calculation of entomological measures of transmission intensity in the endemic areas.

Molecular based tests

Polymerase chain reaction (PCR) technology has been developed for detection of parasite deoxyribonucleic acid (DNA) extracted from mosquitoes or from human blood samples. The PCR is performed to amplify specific segments of the DNA. For *W. bancrofti*, the set of primers commonly used allows the amplification of a species specific 188 base pair repeat DNA sequence called SspI (Williams et al., 1996). It has been used to detect parasite DNA in human blood (Williams et al., 1996; Zhong et al., 1996) as well as in the mosquito vectors (Ramzy et al., 1997; Bockarie et al., 2000). The blood meals from engorged vector mosquitoes may be taken to represent blood samples from the human population (WHO, 2002). The testing of such vector blood meals for parasite specific DNA sequences is referred to as molecular xenomonitoring, and the technique has been proposed as an important diagnostic tool especially for monitoring transmission during LF elimination programmes (Bockarie et al., 2000, Ramzy, 2002; Goodman et al., 2003). However, most of the available sampling methods for mosquito vectors have limitations associated with their use because the different vector species are attracted differently because of their different behaviour (Davis et al., 1995). Thus in areas with different species of vector mosquitoes it is difficult to recommend a single method as an appropriate tool for trapping host-seeking mosquitoes. The human landing catch method is the gold standard for determining human contact with mosquitoes, but there are ethical concerns about the use of the method (Service, 1993).

Another PCR assay amplifying a 254 base-pair sequence termed AccI has been proposed for diagnosis of *W. bancrofti* infection by using sputum. In a study conducted to evaluate this assay using diurnally collected sputum samples from individuals with bancroftian filariasis, 32 of 34 specimens (94%) were PCR positive (Abbasi et al., 1999). However, the test has not been used widely or compared with other diagnostic tools. In general, PCR assays have higher sensitivity than most other tests but major drawbacks are the costs of equipment and reagents and requirements for relatively highly trained personnel.

Ultrasonography

Research in Brazil for the first time visualized living adult worms in their natural habitat (the lymphatic vessels and lymph nodes) by the use of ultrasound (Amaral et al., 1994). In this non-invasive technique, the adult

worms show characteristic movements which have been referred to as the filarial dance sign (FDS). Ultrasonographical monitoring of the FDS has been used as a tool to assess the adulticidal efficacy of anti-filarial drugs in vivo (Dreyer et al., 1995a, Dreyer et al., 1995b; Hussein et al., 2004).

Diagnostic tools and lymphatic filariasis control programmes

Within the framework of LF control programmes, diagnostic tests should ideally meet the following criteria:

- Easy to perform (highly trained technical staff not a pre-requisite)
- Rapid (short period required to obtain the result)
- Low cost (affordable and without stringent customs/importation regulations)
- Field applicable (field-based tests preferable to laboratory-based)
- Robust (no cold chain or electricity requirements)
- Reliable (good specificity and sensitivity)
- Standardized (results from various programmes should be comparable)

Additionally, acceptable diagnostic tests should satisfy the demands of the unique phases of LF control programme. When the GPELF was launched in 2000 microfilarial detection and ICT test were the two diagnostic tools recommended for mapping and subsequent monitoring of impact of the MDA campaigns (WHO, 2000). However, any given LF control programme would be expected to progress through four phases and each phase places phase specific demands on the diagnostic tests. These four distinct phases have been clearly outlined by Weil and Ramzy (2007) as mapping and planning, monitoring of progress, reaching the endpoint and post-MDA surveillance. Clearly, diagnostic tools which are useful for phases 1 and 2 may not necessarily be useful in the later phases of the programme. In this section we discuss the benefits and limitations of the diagnostic tools described above when used during the different phases.

Phase 1: Mapping and planning

In this phase, the goal is to identify endemic areas correctly for inclusion in the LF control programme. Demonstration of microfilariae, CFA or specific filarial antibodies in humans, or demonstration of parasite DNA in pooled mosquitoes (molecular xenomonitoring) or in human blood samples, are the options. A diagnostic test that misclassifies areas either through under-diagnosis or over-diagnosis is unacceptable, as omitting some endemic populations that would otherwise benefit from the programme or including non-endemic populations puts the programme success at risk. Microfilarial detection or testing for CFA should be sufficient for Phase I, because these methods give fast results with relatively minimal resources. In this respect, the counting chamber method was previously mentioned to have greater sensitivity than the thick blood smear method. In Uganda and Malawi, as in several other countries in the Eastern and Southern African region, the ICT test alone has been used for rapid assessment of the geographical distribution of LF (Onapa et al., 2005; Ngwira et al., 2007). On the other hand, antibody detection and molecular tests may not be ideal during phase I because of the relatively greater inputs required to undertake these tests.

Phase 2: Monitoring of progress

Formative assessment of the programme is essential to progress demonstration, problem identification to perform fine tuning and accountability of utilization of resources. Diagnostic performance requirements for this phase are different from those for phase 1 since intervention is already underway. Within 12 months after initiation of MDA, microfilarial prevalences as well as community microfilarial loads show a marked decrease. While this observation may be a positive verifiable indicator, the longevity of the microfilarial clearance must be considered to avoid overestimation of results. On the other hand, CFA prevalences decrease more slowly following MDA and may underestimate the MDA impact. Since CFA prevalences have been shown to decrease substantially after several rounds of MDA, it has been recommended that both microfilarial and CFA testing be used to complement each other (Weil and Ramzy, 2007).

In Phase 2, monitoring of impact on transmission is also useful and both antibody testing and molecular xenomonitoring are valuable tools (Williams et al., 2002; Lammie et al., 2004). While these two tests are responsive to changes resulting from MDA and are good indicators of LF transmission, they fail to meet most of the criteria listed above. Both tests

require more research and development before becoming useful in practice. The anti-Bm14 IgG4 ELISA has been proposed for long-term monitoring of LF elimination programmes (Lammie et al., 2004; Ottesen, 2006).

Phase 3: Reaching the endpoint

Any parasite elimination programme by definition must progress to and reach a surveillance phase. To advise and direct the programme to this phase, endpoints should not be turned on to “over-drive” with the aim of reaching parasite levels that are way below transmission thresholds, thereby incurring unnecessary programme costs. The current WHO guidelines recommend administration of additional rounds of MDA in Implementation Units showing a positive CFA test in one out of 3000 children born after the initiation of MDA (WHO, 2005). While this target may have served the GPELF so far, it is arbitrary. The recommendation may have been designed to ensure that programmes are not stopped before interruption of transmission is achieved, but does not take into account the logistic and financial obstacles in some areas, thus giving it an unrealistic air. The authors concur with Weil and Ramzy (2006) on the need to identify evidence-based targets. Mathematical modeling suggests that microfilarial prevalences of $< 0.5\%$ for areas with *Culex*-transmitted LF would be a rational endpoint (Michael et al., 2006). If this suggestion could be accepted and applied to all LF control programme areas irrespective of the vector species it would be a softer and less costly target that would be evidence-based. Clearly, the diagnostics of choice for determination of endpoints is yet to be established. Demonstration of parasite DNA in pooled human sputum and/or urine samples may also find their niche in the near future. Since antibody detection assays are limited by inability to distinguish current and past infections use of these tests for making programmatic decisions on whether to stop or continue MDA campaigns should be confined to a specific category of the population e.g. children born after start of the control programme (Lammie et al., 2004).

Phase 4: Post-MDA surveillance

Ideal diagnostics for this terminal phase are largely a subject of research. In 2007, at a regional LF workshop in Ouagadougou, it was reported that four countries plus Zanzibar had reached 100 % MDA coverage, and were thus gearing themselves to this terminal phase. The demand for this phase’s diagnostic techniques can only rise with the number of MDA rounds

completed in tandem with the increasing number of national LF control programmes.

Conclusion

At the time of launching of GPELF, the new and unique ICT test was generally considered the key diagnostic tool for the programme. The research community was and is well aware of the need to look for and improve on other diagnostic tests with specific capacities for the different programme phases, in order for GPELF to be able to progress to elimination certification. The launching and implementation of national programmes in many regions has helped to identify the gaps in the available diagnostics. As the programmes move up the phases with cumulative rounds of MDA, varied demands and expectations are being placed on the diagnostics. Further research and subsequent validation of new diagnostic techniques is ongoing as a response to programme needs. In view of the different demands by different programme phases, the varied social and environmental conditions in programme areas, the different MDA strategies implemented, and other unforeseen issues that will slowly emerge with the volume of MDA expansion, it is impractical to recommend any of the currently available diagnostic tests as a “one size fits all”.

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Chapter 3



LF drug studies

Lymphatic filariasis drug studies in Eastern and Southern Africa

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Summary

The lymphatic filariasis drug studies carried out in East Africa since the late 1940's are reviewed. By far the majority of studies have focused on diethylcarbamazine (DEC), and these have covered a multitude of aspects from early investigations on pharmacology and dose optimization via efficacy studies to large scale pilot control trials assessing how best to use the drug for controlling the infection in endemic communities. More recent trials have assessed the effect of ivermectin and its combination with albendazole, and a promising effect of doxycycline on the filarial parasites has been documented. Research on drugs for treatment of lymphatic filariasis has thus been intense in this region, and the knowledge and experience gained has provided a solid background for initiating control programmes based on mass drug administration.

Introduction

Many studies of significance for understanding and managing lymphatic filariasis (LF) have been undertaken in Eastern and Southern Africa. Here, the LF drug studies documented from this region are reviewed. These have all been carried out in Tanzania and Kenya. The presentation particularly focuses on studies published after the discovery of the antifilarial activity of diethylcarbamazine (DEC) in animal filariases (Hewitt et al., 1947) and the subsequent demonstration of its activity in human LF (Santiago-Stevenson et al., 1947). Both of these findings were documented in 1947, meaning that DEC has now been known as a human filaricide for more than 60 years.

Table 1. Drugs investigated for antifilarial activity in East Africa since the late 1940's (++ = most are eliminated; + = few/some are eliminated; +/- = effect variable but generally low; - = no effect).

Drug	Effect on		References
	Mf	Adult worms/CFA	
Diethylcarbamazine	++	+	Numerous, see text
MSbB	++	+ / ++	Friedheim, 1962a and 1962b
Metrifonate	-	Not investigated	Abaru and McMahan, 1978
Levamisole	+ / -	Not investigated	McMahan, 1979 and 1981; Temu and McMahan, 1981
Amodiaquine	+ / -	Not investigated	McMahan, 1979
Ivermectin (\pm albendazole)	++	-	Makunde et al., 2003; Simonsen et al., 2004
Doxycycline	++	+ / ++	Taylor et al., 2005; Makunde et al., 2006

Overview of drugs

An overview of the various drugs tested against LF in Tanzania and Kenya since 1947 is shown in Table 1. The majority of studies have focused on DEC, and these have covered a multitude of aspects ranging from investigations on pharmacology and efficacy to large scale pilot control trials. These studies will be presented in detail in the next section.

In the early 1960's, Friedheim (1962a, b) examined the effect of MSbB (an arsenical compound) on *Wuchereria bancrofti* infections in Tanzania. The drug appeared to be both micro- and macrofilaricidal, but has not received further attention, probably because of its potential toxicity. In the late 1970's, John McMahon and colleagues in Tanga, Tanzania, screened a number of other drugs with known antiparasitic properties for their antifilarial activity. Metrifonate did not show any effect on microfilaraemia (Abaru and McMahon, 1978). Considerable individual variation in microfilarial response was seen after treatment with amodiaquine and levamisole (alone or in combination), but generally there was little effect (McMahon, 1979, 1981; Temu and McMahon, 1981). Other drugs like amnoscanate, ornidazole and oxaminiquine were also tested (McMahon, 1979), but the effects were poor and details were not published.

More recent studies have assessed the effect of ivermectin and its combination with albendazole in LF, and most recently a promising effect of the antibiotic doxycycline on both microfilariae and adult filarial parasites has been documented. These investigations will also be covered in more detail in later sections.

Diethylcarbamazine

Pharmacology and effect on microfilaraemia

In 1948, soon after the antifilarial activity of DEC was discovered, Frank Hawking initiated pharmacological studies and treatment trials with this drug in humans in Tanga (Hawking, 1950; Hawking and Laurie, 1949). As regards uptake and excretion it was noted that following a single dose of DEC given by mouth, the drug was rapidly absorbed and reached a peak concentration in the blood after about 3 hours. The concentration thereafter fell gradually to reach zero in about 48 hours. It was found that much of the drug was excreted unmetabolized in the urine, and that most of this excretion took place within the first 24 hours. The drug apparently

penetrated well into the different body fluids and organs, and was not concentrated anywhere in the body.

DEC treatment of *W. bancrofti* infected individuals demonstrated a very rapid action of DEC on the microfilariae in the peripheral blood. As soon as 24 hours after a single dose, the microfilarial count had almost reached zero. It was characteristic, however, that in most patients a few microfilariae persisted in the blood after this rapid decrease. Studies using different dosages indicated that DEC had a very wide therapeutic dose range. It was noted that as little as 0.1 mg DEC per kg body weight could greatly reduce microfilaraemias, whereas increase of the dose to even much higher levels was no guarantee of complete clearance. The maximum tolerated dose appeared to be about 20 mg per kg body weight daily.

Already during these early studies, Hawking concluded that “the chief promise of DEC seems to lie in the mass treatment of whole villages or districts to destroy the microfilariae of *W. bancrofti* and thus prevent any new infections being contracted”. By this statement he was probably the first to put forward the concept that we now know as “transmission control”.

Pilot control trials

After demonstration of the safe and effective use of DEC for reducing the *W. bancrofti* microfilaral count in individual patients, interest soon rose in the prospects for use of this drug on a larger scale for control. In the late 1950's, Peter Jordan established the first mass treatment trial for LF in Africa, in which three communities on Ukara Island in Lake Tanganyika were treated with low monthly or bimonthly dosages of DEC (Jordan, 1958a, 1959). East Africa has since benefited from a large number of DEC based pilot control trials, in which different dosages and delivery strategies have been applied in endemic populations. Table 2 gives an overview of these trials, in which a total of more than 45,000 individuals have been included and treated with DEC.

The different trials are generally difficult to compare in detail since they differ in many aspects. The populations covered had different sizes and baseline levels of infection, the groups targeted for treatment differed in composition (some excluded children below a certain age, others did not; some used selective treatment to microfilaria positive individuals, others gave treatment to all), treatment coverage differed (and was at times not reported), and follow-up periods and diagnostic methods used differed. However, the studies demonstrate the immense overall power of DEC to

Table 2. Major pilot control trials with DEC in East Africa (+ = yes; - = no; (+) = effect mentioned, but not quantified; -/+ = only in later follow-ups).

No.	Study site	Strategies	Parameters monitored			References
			Mf	Clinical disease	CFA Trans-mission	
1	Ukara Island, Tanzania	200 mg monthly (a), 200 mg every 2 months (b), 100 mg monthly (c). For 1-2 years.	+	-	-	Jordan, 1958a; 1959
2	Pate Island, Kenya	Adults 2.2 g, children > 5 yrs 1.1 g, children 2-5 yrs 0.55 g total dose, spread over 6 days.	+	-	-	Heisch et al., 1959
3	Tanga Region, Tanzania	6 mg/kg bw, 9 times over 6 months (a) or 12 times over 12 months (b).	+	-	+	Kolstrup et al., 1981
4	Coast Province, Kenya	6 mg/kg bw, 13 times over 6 months (a), 3 weeks (b) or 2½ weeks (c).	+	(+)	+	Wijers and Kaleli, 1984
5	Galana River, Kenya	6 mg/kg bw, once monthly (all in a), once 3 monthly (children in b) or once 6 monthly (all in c) for 4 years.	+	-	-	Wijers et al., 1988

Table 2. Continued.

No.	Study site	Strategies	Parameters monitored			References
			Mf	Clinical disease	CFA Trans-mission	
6	Zanzibar, Tanzania	72 mg/kg bw in 13 spaced dosages over 4 months, combined with vector control.	+	-	-	Maxwell et al., 1990, 1999
7	Tanga Region, Tanzania	6 mg/kg bw daily for 12 days (a) or twice with ½ years interval (b), to mf positives only.	+	+	-	Simonsen et al., 1995
8	Tanga Region, Tanzania	6 mg/kg bw, daily for 12 days (a) or 3 times with ½ years interval (b); 100 mg (50 mg to children) monthly (c); DEC medicated salt (d); for one year.	+	+	-/+	Meyrowitsch et al., 1996 a, b, c; 1998; 2004
9	Tanzania + Kenya coast	6 mg/kg bw twice with ½ years interval, in community with high (a) and low (b) endemicity.	+	-	+	Simonsen et al., 2004

reduce microfilaraemias effectively for a considerable period, and they provide a profound background and knowledge for planning and implementing control programmes on a larger scale.

One study not listed in the table, as it was not carried out in a natural community, deserves special mentioning, namely that of Davies and Bailey (1969) on the use of DEC medicated cooking salt. The study was carried out in Pongwe Prison near Tanga. All salt used in the prison was mixed with DEC in a 0.1% w/w concentration. It was demonstrated that this salt-drug mixture reduced the microfilarial intensities in the prison population by 90% after 6 months, and that tolerance was good. The study concluded that medication of salt with DEC may prove useful for control of transmission in populations with no or limited access to other salt sources.

The pilot control trials carried out in Tanga Region by Meyrowitsch et al. (1996a, b, c; 1998; 2004) are among the most detailed and have the longest follow-up period of those listed in Table 2. Four different DEC mass treatment strategies were implemented in four different communities, and the effects were compared by using the same survey methodology. Strategy 1 was the standard regimen of 6 mg/kg daily for 12 consecutive days, Strategy 2 was a single dose of 6 mg/kg given three times with half a years interval, Strategy 3 was a low monthly dose (100 mg to adults, 50 mg to children) given for one year, and Strategy 4 was DEC medicated salt (0.3% w/w) used for one year. In Strategy 4, the normal salt was removed from the community and the inhabitants were provided with free medicated salt. The effect at 1, 2, 4 and 10 years after start of treatment is shown in Figure 1, where prevalence and mean intensity of microfilaraemia among pre-treatment microfilaria positive individuals are expressed in percent of the pre-treatment values. In general, all four strategies resulted in dramatic declines of microfilarial intensities. In particular the DEC medicated salt strategy produced very low intensities and high cure rates at one and two years after start of treatment. Some increase in mean intensity and especially in proportion of positive individuals was seen at 4 years after start of treatment, but even after 10 years the mean intensities were still very low compared to pre-treatment for all the strategies (unfortunately, the DEC salt strategy community could not be included in the 10-years follow-up survey). Subsequent analyses based on data from the first two years indicated that the DEC medicated salt strategy was the most cost-effective (Michael et al., 1996).

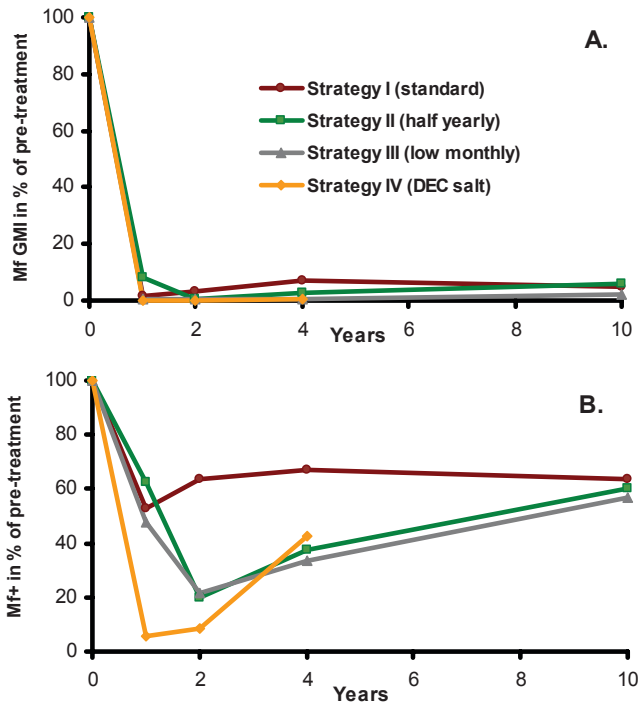


Figure 1. Effect of DEC on geometric mean intensity (A) and prevalence (B) of *Wuchereria bancrofti* microfilaraemia in individuals who were microfilaraemic during the pre-treatment survey. Strategy I = standard treatment of 6 mg DEC/kg once daily for 12 consecutive days. Strategy II = single dose treatment (6 mf DEC/kg) given three times with half a years interval. Strategy III = monthly low dose treatment (50 mg DEC to children, 100 mg DEC to adults) for one year. Strategy IV = DEC medicated cooking salt (0.3 % w/w) for one year (data from: Meyrowitsch et al., 1998 and 2004).

Adverse reactions

It was noted in the early dose-optimization studies in Tanga (Hawking and Laurie, 1949; Hawking, 1950) that high to moderate doses of DEC may cause nausea and vomiting with or without epigastric pain, especially if the drug is taken on an empty stomach. Other systemic adverse reactions reported were headache, diarrhoea, fever and pruritus. From many of the

pilot control trials it appeared that these adverse reactions were less frequent and less severe after low and spaced doses of DEC and after DEC-medicated salt than after the standard treatment regimen of 6mg/kg daily for 12 days (Jordan, 1958; Davis and Bailey, 1969; Kolstrup et al., 1981; Wijers and Kaleli, 1984; Meyrowitsch et al., 1996a, b). Whereas systemic adverse reactions following the 12 day course of DEC often made large scale treatment with this regimen troublesome, reactions following low and spaced dose regimens were generally well tolerated, especially if the population was well informed in advance about potential side effects.

Localized adverse reactions with pain and nodule formation in the scrotum, and occasionally elsewhere in the body, also sometimes follow treatment with DEC (Hawking, 1950). These reactions appear to be due to the killing and encapsulation of adult filarial worms in the lymphatic tissues, and thus can be seen as an indication of an adulticidal effect of DEC.

It is important to note that DEC may provoke severe reactions in individuals with onchocerciasis, which is also the cause of the current recommendation of not using DEC in programmes for control of LF in countries where both infections occur. DEC may also provoke severe adverse reactions in individuals with *Loa loa*, but these infections are not known to be present in the Eastern and Southern African region.

Effect on clinical manifestations

It has long been debated whether DEC treatment can relieve the chronic manifestations of LF. It is not likely that DEC treatment by itself will have much effect on the gross deformities of body parts sometimes seen in longstanding cases. However, these are generally exceptional cases. Most hydroceles and lymphoedemas in LF endemic areas are less developed and appear to be rather dynamic in nature, and there are indications that DEC treatment could have a beneficial effect on these.

During the DEC pilot control trials in Tanga Region in the mid 1990's, it was frequently observed that small hydroceles detected at baseline had disappeared after treatment (Simonsen et al., 1995; Meyrowitsch et al., 1996a, b). Thus, among a total of 85 males with hydrocele at baseline, 31 (36.5%) did not present with a hydrocele during follow-up one year after start of treatment (Table 3). That this was not due to only a temporal disappearance of small dynamic hydroceles is suggested by the fact that the same trend was observed in subsequent surveys carried out 2, 4 and 10 years after start of treatment (Meyrowitsch et al., 1996c, 1998, 2004).

Table 3. Effect of treatment with DEC on hydroceles (data from: Meyrowitsch et al., 1996a, 1996b; Simonsen et al., 1995).

Village	Treatment regimen	No. males with hydrocele at pre-treatment	No. showing complete disappearance after one year (%)*
Mkwakwa	Half-yearly single dose (12 x 6 mg/kg)	7	2 (28.6)
Tawalani	Standard 12 day regimen (12 x 6 mg/kg)	19	7 (36.8)
Kwale	Half-yearly single dose (2 x 6 mg/kg)	22	10 (45.5)
Mkokora	Low monthly dose (12 x 50/100 mg)	13	6 (46.2)
Kwemwale	DEC-salt	24	6 (25.0)
All	-	85	31 (36.5)

*) Complete disappearance was only seen in males who had small hydroceles (6-8 cm) at pre-treatment

Although the number of cases was much lower, a similar trend was observed for early cases of lymphoedema.

In a controlled study in the same area, Bernhard et al. (2001) did not observe a significant effect of DEC treatment on hydrocele volumes. However, most hydroceles in this study were large and had been present for many years. Wijers and Kaleli (1984) noted that one of the most spectacular results of population wide DEC treatment was the sudden disappearance of acute attacks of funiculitis and orchitis, which had previously been common.

Effect on CFA

A major breakthrough in LF research in recent years has been the development of methods for detection of *W. bancrofti* circulating filarial antigens (CFA) in the blood of infected individuals. The target antigens for these tests (metabolic products released from the worms) circulate in the blood and can be detected with high sensitivity and specificity at any time of the day. As the antigens primarily appear to originate from adult filarial worms, these tests have also been used to assess the effect of drug treatment on adult worm burden (although the actual relationship between CFA intensity and adult worm burden is not entirely clear).

The effect of repeated half-yearly treatments with DEC (6 mg/kg) on CFA was investigated in detail in 79 infected individuals in Tanga Region (Simonsen et al., 2004, 2005). The treatments resulted in a progressive decrease in both microfilaraemia and circulating antigenemia, but in contrast to the rapid decrease of the former, the decrease in CFA occurred at a much slower rate (Figure 2). However, after 8 treatments, the mean CFA intensity was reduced by 98 % in pre-treatment CFA positive individuals and 43% had turned CFA negative. The individual variation in treatment response was considerable. Overall, DEC thus appears to have a slow but profound macrofilaricidal effect, which in the long run may be beneficial to individuals undergoing treatment with this drug by reducing the probability of future development of clinical disease.

Effect on transmission

Transmission of LF in Eastern Africa is facilitated by three different species of vectors: *Anopheles gambiae*, *An. funestus* and *Culex quinquefasciatus*. The relative contribution of these varies from place to place, depending on environmental conditions, thus leading to very complex transmission patterns. Despite the current emphasis on

transmission control in LF, knowledge on the effect of mass drug administration on parasite transmission is surprisingly limited, both overall and for the different vector-parasite combinations.

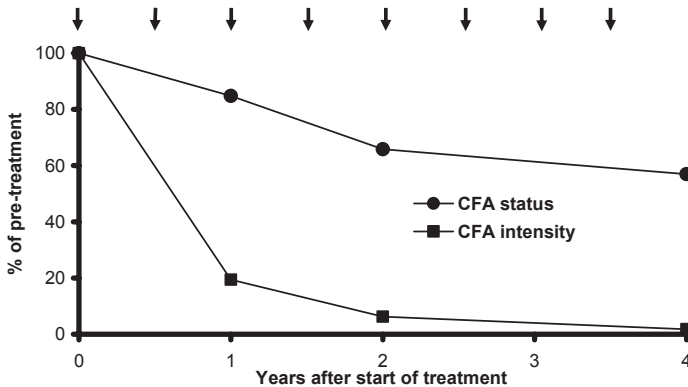


Figure 2. Effect of eight half-yearly treatments with DEC (6mg/kg) on *Wuchereria bancrofti* specific circulating filarial antigens (CFA) in individuals who were CFA positive at pre-treatment. Arrows indicate treatments (data from: Simonsen et al., 2004).

Mass administration of DEC in spaced doses over six months in two communities in Tanga Region, Tanzania (Kolstrup et al., 1981) and in two communities in Coast Province, Kenya (Wijers and Kaleli, 1985) resulted in considerable reductions in overall vector infection and infectivity rates. In the Kenyan communities reductions of over 90% in number of infective larvae in the vector mosquitoes were observed, and in the Tanzanian communities the potential infective bites per person per year decreased from 189 and 41 to 13 and 0, respectively. Follow-up in the Tanzanian communities one year later showed, however, that these indicators were again on the increase.

A study that compared the effect of half-yearly mass treatment with DEC in a low and a high endemicity community in Kenya and Tanzania, respectively (Simonsen et al., 2004) observed a gradual decrease in annual transmission rates during a two-year period after start of treatment. Further analyses of the data revealed that the reduction in transmission was not a

reflection of the vector infectivity rates, since the proportion of mosquitoes containing infective larvae actually increased. More likely, the reduction in transmission could be due to a marked decrease in mosquito densities resulting from reduced rainfall during the follow-up years.

Combination of DEC with vector control

A comprehensive study carried out in Makunduchi, Zanzibar, documented that vector control can significantly add to the decrease in microfilaraemia and transmission following mass DEC treatment, and to maintaining this decrease afterwards (Maxwell et al., 1990, 1999). In the town of Makunduchi, which had about 12,000 inhabitants, and a pre-intervention microfilarial prevalence of 49.5%, wet pit latrines were the major breeding sites for the *Cx. quinquefasciatus* vectors. Following mass treatment with DEC (72 mg/kg in 13 spaced doses over 4 months), expanded polystyrene beads were applied to form a floating layer on all infested pits to prevent vector breeding. Annual biting rates decreased from about 25,000 to about 440 per person. Treatment of new wet pit latrines continued for 5 years and the already low microfilarial prevalence declined further during this period. Five years after the activities ended (i.e. 10 years after DEC treatment) the microfilarial prevalence was on the increase, although it was still low compared to pre-treatment. In a control town that only received mass DEC treatment, the one-year post treatment follow-up effect was similar to that seen in Makunduchi, but increase in the microfilarial prevalence was already seen after two years and the prevalence approached pre-treatment level at 5 years after treatment. Vector control also reduced the mosquito biting nuisance, and thereby provided immediate visible benefit to the affected communities, which helped to provide a positive attitude to the study.

Effect on other infections

DEC treatment of LF has frequently been noted to cause expulsion of adult *Ascaris* worms. A study was set up in Tanzania to assess the efficacy of a single dose of DEC (6 mg/kg) on *Ascaris* infections (Meyrowitsch and Simonsen, 2001). As many of the *Ascaris* infected children also excreted hookworm eggs, the efficacy on hookworm infection was also evaluated. Treatment with DEC resulted in a considerable reduction in *Ascaris* mean egg count (Table 4), but most of the reduction occurred in a few high intensity infections and the overall effect was not statistically significant. 40% of the children expelled adult *Ascaris* worms after the DEC treatment,

Table 4. Effect of treatment with DEC (6 mg/kg) on *Ascaris* and hookworm infection in schoolchildren in Tanzania (data from: Meyrowitsch and Simonsen, 2001)

Infection	Treatment	No. children	Geometric mean of eggs per gram faeces		No. children expelling adult worms (%)
			Day 0	Day 30 (% of Day 0)	
<i>Ascaris</i>	Placebo	25	15488	16218 (104.7)	0
	DEC	26	13490	5370 (39.8)	10 (38.5)
Hookworm	Placebo	18	550	724 (138.0)	-
	DEC	20	676	562 (83.1)	-

whereas none of those receiving placebo did so. The effect of DEC treatment on the hookworm infections was negligible. With a single dose of DEC, the greatest benefit of the occasional expulsion of *Ascaris* worms thus appears to be its importance in improving community acceptance and co-operation in filariasis control programmes.

A surprising effect of DEC treatment was recently observed during a study in Tanga on the interaction between LF and HIV infection (Nielsen et al., 2007). Treatment with a single dose of DEC (6 mg/kg) in a double-blind placebo-controlled cross-over trial showed a statistically significant effect of DEC on the HIV infection in individuals with both HIV and LF, with a 54% decrease in HIV load and improved CD4% and CD4/CD8 ratio at 12 weeks after treatment. No such effect was seen in individuals with HIV but no filarial infection. The further perspectives of this observation need to be investigated, both with respect to the effect of DEC-based LF control programmes on the current HIV epidemic, but also as a potential basis for development of alternative anti-retroviral drugs.

DEC provocative day test

The DEC provocative day test was originally devised in Japan. It is based on the observation that a low dose of DEC given to the individual stimulates microfilariae of nocturnally periodic *W. bancrofti* to appear in the peripheral blood during daytime. This allows diagnosis of microfilaraemia during daytime, and therefore has been a relief to both patients and those working with diagnosis of this infection.

The DEC provocative day test was first adopted in East Africa by Manson-Bahr and Wijers (1972, 1973). They demonstrated that administration of 100 mg of DEC induce a peak of microfilaraemia in the peripheral blood 45-60 minutes later, and as such the test was widely adopted for field examinations in Kenya (Wijers, 1977) and Tanzania (McMahon et al., 1979; Wegesa et al., 1979; Abaru et al., 1980). It was also used as a preliminary screening method for assessing potential filaricides (Abaru and McMahon, 1978; McMahon, 1979, 1981; Temu and McMahon, 1981) and for evaluating the parasitological response to mass DEC administration (Kolstrup et al., 1981).

McMahon et al. (1979) and McMahon (1982) analysed the microfilarial response in detail following a DEC provocative test. Among individuals on a normal daily activity, the test caused a significant increase in microfilarial intensity during daytime, whereas it caused a significant decrease during nighttime. In hospitalized patients there was no significant evidence of any

effect. Night counts (without DEC provocation) and counts after DEC provocation on the following day in the same individuals correlated significantly, but the day counts were generally lower than the night counts. The optimal time interval between DEC intake and blood sampling varied with the dose of DEC: the highest microfilarial intensity was seen 15 minutes after a dose of 6 mg/kg, whereas it was seen 45-60 minutes after a dose of 2 mg/kg.

Since DEC is well known to be a potent microfilaricide even in low doses, the long-term treatment effect of the DEC provocative day test was evaluated by Simonsen et al. (1997). It was observed that a single low dose (100 mg; corresponding to approximately 2 mg/kg) of DEC had a significant therapeutic effect, with a reduction in the microfilarial mean intensity by 86% after one year (Figure 3). This finding implies that the test should not be used for diagnosis in follow-up studies on microfilaraemias.

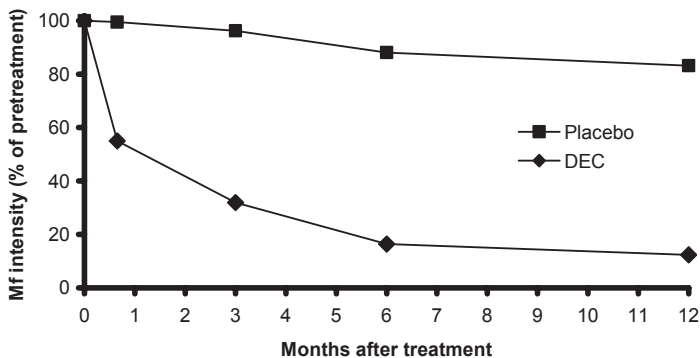


Figure 3. Effect of a single low dose of DEC (100 mg/person) on geometric mean intensity of *Wuchereria bancrofti* microfilaraemia (data from: Simonsen et al., 1997).

In vitro activity

Although DEC has now been in use as an antifilarial drug for more than 60 years, the mode of action is still not clear. In early studies (Hawking, 1950; Hawking and Laurie, 1949) it was observed, that, in contrast to the rapid elimination of microfilariae from the blood in vivo, the microfilariae survive in culture fluid in vitro with even high concentrations of DEC for several days. The same was observed when serum from a patient who had

received DEC one hour previously was added in vitro. Thus, DEC did not appear to be directly toxic for microfilariae, nor to be changed in the body into something which is. Hawking suggested that DEC modifies the microfilariae, so they can be recognized, captured and destroyed by host phagocytes.

Jordan (1958b) investigated the effect of DEC on the infective larvae of *W. bancrofti* in vitro, by adding serum collected from uninfected individuals before and after they had received a high dose of DEC. No difference was observed in survival time between larvae in normal serum and in serum from DEC treated individuals. As a consequence of the apparent lack of direct effect of DEC on the exposed filarial parasites, it has been of interest to investigate its effect on the specific immune responses in human infection. In studies on the serum mediated leucocyte attack on microfilariae of *W. bancrofti* in vitro, neither addition of DEC nor of serum from DEC treated individuals caused any visible interference with these responses (Simonsen, 1985).

Urine pH and effect of DEC

The rate of excretion of DEC into the urine has been shown to be slower, and the plasma half-life prolonged, when urine is alkaline as compared to the situation when the urine is acidic. Njenga et al. (1997) therefore investigated whether raising the pH of urine by administration of sodium bicarbonate to infected individuals would result in a more profound microfilaricidal effect of DEC. The observed increase in urine pH and serum concentration of DEC in the group receiving co-administration of sodium bicarbonate and DEC did not result in a more pronounced decrease in microfilaraemia during the first few days after treatment, but a marginally larger microfilaricidal effect was seen in this group one year after treatment.

DEC in combination with albendazole

Within Eastern and Southern Africa, Kenya, Madagascar and Comoros are different from the other LF endemic countries because there is no onchocerciasis and therefore the recommended strategy for control of LF is annual mass drug treatment with a combination of DEC and albendazole. However, no publications from this region of Africa have so far documented a comparative assessment of the effect of DEC alone and in combination with albendazole on LF.

Ivermectin with and without albendazole

In most countries within Eastern and Southern Africa, the recommended strategy for control of LF is annual mass drug treatment with a combination of ivermectin and albendazole. The documented scientific experience with ivermectin and its combination with albendazole in the treatment of LF in this region of Africa is limited. A randomized double-blind study in Tanga Region compared the effect of a single dose of ivermectin (150-200 µg/kg) to that of a single dose of the combination of ivermectin and albendazole (400 mg) on LF in schoolchildren (Simonsen et al., 2004). Both treatment regimens resulted in a considerable decrease in mean microfilarial intensities, with overall reductions for a one year period being slightly but significantly higher for the combination than for ivermectin alone (Figure 4). The effect on CFA was much less pronounced, suggesting that these drug regimens mainly are active against the microfilariae. Only few, mild and transient adverse reactions were observed after the treatment.

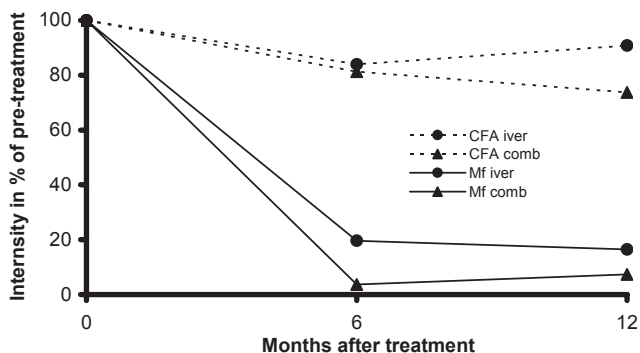


Figure 4. Effect of ivermectin alone (circles) and in combination with albendazole (triangles) on *Wuchereria bancrofti* microfilaraemia (full lines) and circulating filarial antigenemia (stippled lines) in schoolchildren (data from: Simonsen et al., 2004).

In many parts of Eastern and Southern Africa there is overlap between areas endemic for LF and onchocerciasis. To determine whether the ivermectin-albendazole combination can be used safely and effectively in such areas, Makunde et al. (2003) compared the combination treatment regimen in single and double-infected individuals in a hospital based study.

The combination treatment was found to be equally safe and effective in reducing *W. bancrofti* microfilaraemia in the two groups. To investigate for additional benefits of ivermectin treatment, Makunde et al. (2001) assessed the effect of ivermectin alone on intestinal helminthiasis and urinary schistosomiasis. The drug was reported to be very effective against ascariasis and strongyloidiasis, whereas only mild to moderate effect was seen against *Schistosoma haematobium* and hookworm infections.

Doxycycline

A new and promising approach to the treatment of filarial infections has been based on the observation that many species of filaria, including *W. bancrofti*, contain obligate endosymbiotic bacteria of the genera *Wolbachia* sp. These rickettsia-like organisms are essential for survival and development of the filarial parasites. It has therefore been of interest to examine the effect of anti-rickettsial antibiotics in filarial infections.

A recent double-blind placebo-controlled study in Tanga Region, Tanzania, assessed the effect of an intensive course of doxycycline (200 mg daily for 8 weeks) in individuals with LF (Taylor et al., 2005). Microfilaraemia decreased progressively after treatment and was almost eliminated after one year. The number of adult worms detected by ultrasonography as well as circulating filarial antigenemia also showed considerable reductions. The adverse reactions were reported to be few and mild. Although an 8-week course of daily treatment is not feasible for mass treatment, the effect of depleting the filarial parasites of their endosymbionts was so marked, that these studies could mark the beginning of a new era for development of antifilarial drugs and drug regimens targeting the *Wolbachia* sp.

The same treatment protocol was used in a hospital-based study in the same area, which in detail assessed the safety and tolerability of the doxycycline regimen (Makunde et al., 2006). The study concluded that haematological, hepatic and renal parameters during and after treatment were within the normal range, and that clinical adverse effects were mild, transient and tolerable. The most frequent adverse reaction reported was mild fever early during treatment. Microfilaraemia decreased gradually, and none of the individuals had microfilariae in their blood one year after treatment.

Conclusion and future perspectives

Research on drugs for treatment and control of LF has thus been intense in East Africa, and much of the knowledge we now have on LF drugs originate from studies carried out in this region. The knowledge and experience gained has provided a solid background for starting up control programmes based on mass drug administration. It is notable, however, that whereas most of the drug studies have focused on DEC, the recommendation from the Global Programme for Elimination of Lymphatic Filariasis (GPELF) for most of the countries in Eastern and Southern Africa (except Kenya, Madagascar and Comoros) is to base control on the ivermectin-albendazole combination, because of the widespread co-occurrence of onchocerciasis.

When considering future perspectives for LF drug studies and use in this region (Table 5), a first issue to discuss is whether DEC could still play a role in the countries where onchocerciasis is co-endemic. In this respect, the potential for DEC medicated salt in particular needs to be investigated further as a strategy e.g. in towns or as a follow-up or maintenance strategy in areas which have previously been under ivermectin-abendazole treatment for some time. Meyrowitsch et al. (2000) demonstrated that adverse reactions to DEC medicated salt in onchocerciasis patients were mild and tolerable, but further clinical studies are needed to determine whether a low dose of DEC can be delivered in salt on a longer term without provoking inflammatory pathology.

The comparative effect and safety of DEC alone and in combination with albendazole also needs to be assessed and documented from countries in Eastern and Southern Africa, preferably from countries embarking on control based on these drugs. As DEC has an effect on the adult worms, and as many children are known to harbour adult worms despite absence of microfilariae, it could be of high relevance from a morbidity control perspective to investigate the effect of DEC treatment of children for subsequent development of disease later in life. The potential of the observed effect of DEC on HIV infections (in patients with and without LF) should also be further investigated.

Another important field for future LF drug research would be a search for drugs that can eliminate the adult worms. Adulticidal drugs would probably have a more immediate and profound effect on both infection and transmission than the currently used primarily microfilaricidal drugs. In this respect, the drugs targeting the *Wolbachia* endosymbionts of the filarial parasites could be a promising new direction.

Table 5. Proposed topics for future LF drug studies in Eastern and Southern Africa.

- A role for DEC in onchocerciasis co-endemic countries
 - DEC medicated salt
 - DEC tablets in late phase of control
- Effect of DEC + albendazole combination
- Effect of DEC on morbidity (especially in children)
- Effect of DEC on HIV
- New drugs (esp. macrofilaricides)
- Improvement of treatment coverage
- Effect of MDA on transmission
- Monitoring for appearance of drug resistance
- Combination with vector control/protection measures (e.g. bed nets)

A challenge for the already ongoing control programmes has been to obtain and maintain high treatment coverage in the mass drug administration campaigns. Studies on factors that affect treatment coverage and how it can be improved are of high relevance to the success of future control efforts. Another aspect that needs more attention in future research is the effect of mass drug administration (whether with micro- or macrofilaricidal drugs) on transmission in settings with different endemicity levels and different parasite-vector species combinations. The development of methods for monitoring the possible appearance of resistance to the drugs used in mass drug administration programmes would also be highly relevant.

Finally, studies are needed that can show how best and most effectively to combine mass drug administration with bed nets and other types of personal protection or vector control.

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Chapter 4



LF morbidity

The morbidity of lymphatic filariasis in Eastern and Southern Africa

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Abstract

Lymphatic filariasis is best known for its devastating and dramatic clinical presentations, conditions that severely affect the daily life of the patients and cause suffering through debilitation, inability to work, and psycho-social problems. The main presentations of the disease are acute clinical episodes, hydrocele and lymphoedema of extremities; in all likelihood there is also sub-clinical anatomical damage to lymphatic vessels. The pathogenesis of these changes remains unclear and somewhat controversial but is understood to include reactions to the dying parasite, early lymphatic dysfunction and lymphangectasia, immunological alterations and secondary infections. The main approaches to reduction in the morbidity of the disease encompass not only improving hygiene procedures for the affected limbs, and surgical repair for hydrocele patients, but also attendance to the psycho-social issues including the ability to earn a satisfactory living. An important recent finding is that the implementation of a mass drug administration programme itself has a beneficial effect on the lymphatic filariasis patients residing in the programme areas.

Introduction

Filarial nematodes comprise a diverse and surprisingly common group of parasites of mammals and cause two of the most debilitating of all tropical diseases, lymphatic filariasis (often commonly known as “elephantiasis”) and onchocerciasis (known as “river blindness”). Lymphatic filariasis (LF)

is a clinical entity that has not always received the attention from the medical and donor communities that it truly deserves, i.e. a devastating, debilitating condition caused by a parasite that, at least in 2000, infected more than one in 20 people living on the Earth. Its primary physical feature is disfiguration, causing much incapacity, with consequent loss of income, personal shame, social stress and psychological impairment. The global burden of this disease is hard to calculate, as identification of cases requires active and careful surveillance - affected individuals, especially those with the genital manifestations, are often reluctant to be identified.

Over the last ten years there have been several successful national control programmes initiated and much progress has been made towards the goal of eliminating LF; China, for example, has in all likelihood been successful in achieving elimination of the infection. Despite these successes, Africa remains a continent where the challenge of elimination is greatest. The primary aim of any control programme, is the elimination of clinical disease from the population, and although there are many components and means to this end, the central point to all control programmes remains the patients – they are the reason why these programmes were developed.

Fundamental components of the disease

The details of the pathogenesis of the various clinical presentations of this complex disease still need to be defined; the lack of detailed autopsies, of non-invasive imaging (with the important diagnostic ultrasound studies being an exception to this), and the lack of suitable surrogate animal models (with the exception of brugian filariasis in the cat), all have limited our knowledge to date. Some confusion remains over the clinical definition of the various presentations of the disease; this is in part due to differences in presentation in different geographic areas. Nevertheless, the overall spectrum of clinical disease is well described and is summarized in Figure 1.

All of these major components of clinical LF can, and usually do, have very significant effects on the daily functions of the affected people and severely limit their ability to carry out strenuous activities, walk, ride bicycles and carry out various daily activities. It is common to find affected children limited in their ability to attend school either directly or indirectly, food-sellers shunned because of the odour of their lymphoedematous condition, and young women stigmatized and barred from marriage.

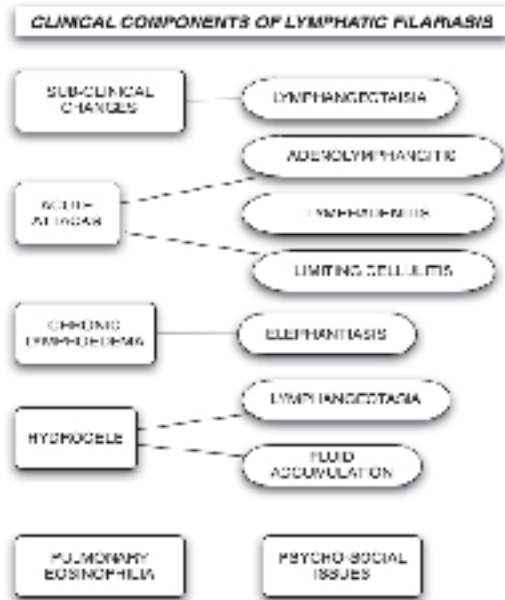


Figure 1. Clinical components of lymphatic filariasis.

Sub-clinical disease

It has been well documented that infection can occur early in life; however, the pathological changes this is actually inducing in the developing child remain to be defined. From comparison with other filarial diseases, and from what is known to be occurring in adults infected with *Wuchereria bancrofti*, it appears likely that there are both significant immunological and pathological responses in sub-clinical infections in adults and children, and that these are probably affecting health.

Acute attacks

The acute attacks that occur in people living in areas endemic for lymphatic filariasis are devastating events to both those affected and to their families; these episodes can last up to two weeks or so depending on the severity of their disease state and the treatment history of the patient. In a recent study in Tanzania (Mackenzie et al., 2008) the range of signs and symptoms

presented by the patients suffering from these attacks included swelling of an extremity, feelings of fever, lymphadenopathy of the draining area and other change such as exfoliation (Figure 2).



Figure 2. A case of lymphoedema in a Tanzanian male, showing the exfoliation of skin that often occurs in the later stages of an acute attack.

The pathogenesis of these acute attacks remains a matter of discussion although it is generally accepted that secondary bacteriae are most important participants in the development of this condition, which is why hygiene activities are so important in the treatment of these patients. However, the presence, or at least a history of presence, of the parasite is also an important component, and it has been suggested that parasite-induced immuno-suppression may be at play and responsible for increased susceptibility to bacterial invasion.

The effect that acute attacks have on the patient's daily life can be very severe and cause serious reduction in mobility and ability to earn a

livelihood. These attacks can occur every month and last up to two weeks, and can induce severe depression in the sufferer. The attacks are more severe and more intense in patients with a severe degree of overt lymphoedema or elephantiasis.

Chronic lymphoedema and elephantiasis

The persistent lymphoedema and the subsequent elephantiasis are the best known presentations of the disease, although not as common overall as hydrocele. In the early stages the volume of fluid present in the subcutaneous and deeper tissues can vary and is presumed to be accumulating because of damage to the lymphatic drainage. Over time the fluid becomes more persistent and increasingly disfigures the normal structure of the affected area, becoming replaced by scar tissue; cicatrisation of the scar tissue contributes further to the disfigurement. Epidermal changes are also believed to be a major factor in the pathogenesis, not only as contributors to the obvious alterations seen in elephantiasis, but also in the pathogenesis of the condition as a whole, particularly in the later stages of the disease. The epidermis not only acts as a barrier to the secondary bacteriae (known to be major contributors to the clinical disease) but also is a source of many factors involved in the homeostasis of the skin as well as the development of dermal pathology.

The different stages of change of affected limbs have been well described and a number of grading systems exist. Those that include ability to function are perhaps the most useful in assessing the severity of disease in LF control programmes, such as the current mass drug administration (MDA) programmes, and in determining the overall effect of the disease on the patients.

Hydrocele

Hydrocele is the most common presentation of LF disease in endemic areas, yet - because of its personal nature to the patient - it is often the condition that is least investigated and discussed. The presence of adult worms in the lymphatics draining the scrotum, most commonly those vessels approaching the inguinal canal, induces leakage of fluid (of varying composition) or lymphatic rupture, with a consequent accumulation of fluid in the scrotal sac. The presence of the parasites induces distension and enlargement of these vessels and their various cellular constituents (endothelium, muscle, blood vasculature, etc.) known as lymphangectasia.

This condition has a tremendously debilitating effect on sexual activity as well as ability to work; for example, fishermen with hydrocele cannot pull their nets onboard their boats without suffering pain. Surgery to remove the fluid or to remove the scarred tissues is the main form of treatment, and given good pre-operative and post-operative conditions usually has a successful outcome.

The question of the occurrence of an equivalent condition in females has commonly been asked. A study by Bernhard et al. (2000) found no specific genital condition in females that could be attributed to infection with *W. bancrofti*. Although LF-induced skin changes (lymphoedema and elephantiasis) can occur in this anatomical area of females, it appears that no clinical correlate with the male condition of hydrocele occurs – probably as there is no anatomical correlate. Internal lymphatic changes in this region may occur as part of a wider internal pathology of lymphatic vessels; this has been seen in experimental animals.

Pulmonary eosinophilia

This condition is most commonly described in India and involves pathological responses in the lung and other tissues to the microfilarial stage of this infection. The destruction of parasites involves eosinophil leucocytes and has many characteristics akin to allergic reactions. This filariasis-associated condition is not common in African LF and has been described as rare in Tanzania (Magnussen et al., 1995).

Psycho-social issues

LF is a disfiguring and debilitating disease not well understood in many societies, and often carries considerable stigma. It is sometimes believed that the condition is the result of witchcraft, as a penalty for marital infidelity, and other events that can victimize the affected individuals. Patients are often rejected from community activities and often suffer psychological conditions as a result. This area of the disease complex needs more investigation.

Post-treatment manifestations

A distinction must be made in describing LF disease between the manifestations seen in natural untreated infections and those seen following chemotherapy with anti-filarial agents such as ivermectin (Mectizan®) and diethylcarbamazine (DEC). As with onchocerciasis, there are clinical reactions that result directly from the chemotherapy-induced destruction of

the parasites. This is well recognized with DEC therapy, and a less dramatic form occurs, at least in some people, with ivermectin therapy against the microfilariae. However, it must be said that there are remarkably few post-treatment reactions after ivermectin and albendazole combination treatment of LF – which is very good news for control programmes.

Differential diagnosis

The diagnosis of LF is usually based on parasitological parameters (presence of parasites in the blood or lymphatics) or by detection of circulating parasite antigens. These tests are not optimal for the diagnosis of LF patients as often there are no detectable circulating microfilariae or these people are antigen negative (at least with the currently employed antigens). Thus history and presentation are important parameters for diagnosis of patients suffering the syndromes described above. A non-filarial condition that is an important differential consideration is podoconiosis which occurs in areas of a particular soil composition, and that has been reported from Ethiopia, Kenya, Tanzania, Uganda, Rwanda and Burundi within the Eastern and Southern African region (De Lalla et al., 1988; Price, 1990; Onapa et al., 2001a; Davey et al., 2007a, 2007b). Other causes and forms of cellulitis must also be considered in the case of the acute attacks.

The epidemiology of disease in Eastern and Southern Africa

The knowledge of the extent and severity of the clinical disease in a country, and in sub-regions within a country, provides very important data for management, planning and advocacy of control programmes; this is currently important as each new endemic country joins in the global LF control efforts. It must be stated that the validity of data on the true distribution of the various forms of LF varies, and in many countries such data are simply not available. In general, in Eastern and Southern Africa lymphoedema and elephantiasis is thought to be more common in coastal regions of East Africa and hydrocele is more uniformly distributed throughout all the endemic areas; this may only be partially true and better data on disease prevalence is needed. The prevalence of all these conditions appears to correlate with the level of endemicity.

Perhaps the most detailed information on the distribution of disease presently available is from Tanzania, where LF has been studied in detail for many years and where a MDA programme has been in place for over seven years (now covering almost half of this large country). Kenya, Malawi and Uganda have also focused on the disease to some extent and a number of prevalence studies have been documented; however, for most of the other countries in Eastern and Southern Africa, little data is presently available.

Tanzania

A major site for studies on the clinical aspects of LF has been the northern coastal area of Tanzania, where there have been numerous research and control activities for many years (Fleming-Hübertz et al., 1997; Bernhard et al., 2001; Friis et al., 2002; Nielsen et al., 2002a; Simonsen et al., 2002; Taylor et al., 2005). The National LF Elimination Programme has been active along the coastal belt and has gained knowledge as to the prevalence of the disease and the effects of the MDA programme on the clinical disease.

LF endemicity in the northern coastal areas of Tanzania was in the order of 15-45% overall microfilariæmia in the examined communities (Wegesa et al., 1979; Abaru et al., 1980; McMahan et al., 1981; Meyrowitsch et al., 1995; Simonsen et al., 1995, 2002; Bernhard et al., 2000; Massaga et al., 2000). Here the reported prevalences of lymphoedema among adults were 1-7%. Hydrocele, on the other hand, was some 4-16 times more common, with 27-47% reported in adult males. The increase in prevalence with age for both of these disease manifestations was demonstrated by the presence of hydrocele at 38% and 56% in the male population aged 40-59 and 60+ years, respectively, and of lymphoedema in the adult population at 3.6% and 6.3% in the same age groups, respectively (Meyrowitsch et al., 1995).

Active LF disease in the islands off the coast of Tanzania has also been well studied. Zanzibar now has an active programme against the infection and has seen success (Mohammed et al., 2006). Semi-urban communities on the island of Pemba, with overall microfilariæmia prevalences between 3 and 13%, had hydrocele prevalences of 12-36% among adult males and lymphoedema prevalences of 0-2% among adults of both sexes (Pedersen et al., 1999).

Acute episodes were reported in coastal Tanzania to occur at an annual rate of some 33/1000 people (Gasarasi et al., 2000). Simonsen et al. (2002)

reported acute attacks in up to 12.2% of their study population, a group that had some 2.2% with lymphoedema and 13% hydrocele in males.

Kenya

Kenya is setting out on the road to establishment of a strong MDA programme (Wamae et al., 2001), and it is clear that there is a significant prevalence of LF disease in the country that needs attention.

A number of studies, beginning with those of Wijers (1977a, 1977b) identified the prevalence of disease in different endemic areas of Kenya. Estambale et al. (1994) found 16.5% of the males over 14 years of age had hydrocele and 2.4% of the adults of this age group had lymphoedema. They also, as others have done, showed an increase in hydrocele prevalence with age (23.8% in those older than 49 years). Hydrocelectomy records in local hospitals in Kenya were seen as a good proxy for the community prevalence of hydrocele (Mwobobia et al., 2000); in one case in the endemic area 27.6% of the hospitals' surgeries were hydrocelectomies and this closely reflected the local situation with regards to this condition. A study by Mukoko et al. (2004) showed, in another Kenyan endemic site, a prevalence of 20% for hydrocele and 2.9% for lymphoedema in adults in an endemic area where the community microfilaraemia prevalence ranged from 8.1-27.4%, figures proportionally consistent with other endemic areas in other countries. Recently, Njenga et al. (2007) observed an even higher prevalence of hydrocele (34.4 %) in adult males – with around 55.3% in those over 50 years of age. The prevalence of lymphoedema in the latter area was 12.6% in adult males and 5.7% in adult females.

Malawi

Malawi is a country where the prevalence of LF disease – at least from published information – is lower than seen in Tanzania and Kenya. Studies in adults by Ngwira et al. (2002) revealed a prevalence of some 11.7% of hydrocele and 1.0-3.7% of lymphoedema in areas of 28-58% antigen positivity. Nielsen et al. (2002b), studying populations with an overall endemicity of around 20% microfilaraemia (63% antigenaemia), found that there was 1.3-3.7% lymphoedema and 13-18% hydrocele present among the adults.

Uganda

The work of Onapa and colleagues (2001b) indicates that Uganda does have areas with significant levels of lymphoedema (greater than 4.5%) and

up to 28% hydrocele – interestingly in areas with only comparatively moderate antigenemia prevalence (18-30%). This situation deserves further attention to determine the factors at play in this focus.

Other countries

There is little recent data available on LF morbidity from Madagascar (Champetier de Ribes et al., 1996, 2000) where a major LF program is now in place, or from the Comoros where parasitological surveys have documented high infection prevalences (Charafoudine and Pesson, 1986; Blanchy and Benthein, 1989). Nor is there much confirmed data from Ethiopia, Burundi, Rwanda, Zambia, Zimbabwe or Mozambique; these latter six countries have all initiated national LF efforts or at least have expressed a strong wish to do so.

The approaches to morbidity reduction

Naturally, approaches to reduction in morbidity of LF will take different forms in different countries depending on the local situation. Although opinions differ about the pathogenesis of the disease, particularly for the acute attacks and the different forms of lymphoedema/elephantiasis, there are several important activities that a programme should try to incorporate (Figure 3).

These different components to a morbidity programme should in most cases be linked directly to the MDA activities – this ensures use of the case improvement to advocate for the MDA programme and assist in obtaining high coverage. People understand why they need to take MDA drugs if they can see direct benefits on those affected with the disease in their communities.

Aspects of the morbidity that have not perhaps to date been given the emphasis they deserve include 1) the psychological impact of the disease on patients and their families, 2) the patients' need to be reintroduced to the community's activities, and 3) the patients' need to regain the ability to earn a fair and necessary income. These are particularly important in younger patients. One important area that should see major improvements in the near future is that of the management of the wounds which often develop in severe cases of lymphoedema. Given the recent advances in the understanding of healing, and the great improvements in wound care today, these new approaches will hopefully be used more frequently in LF cases.

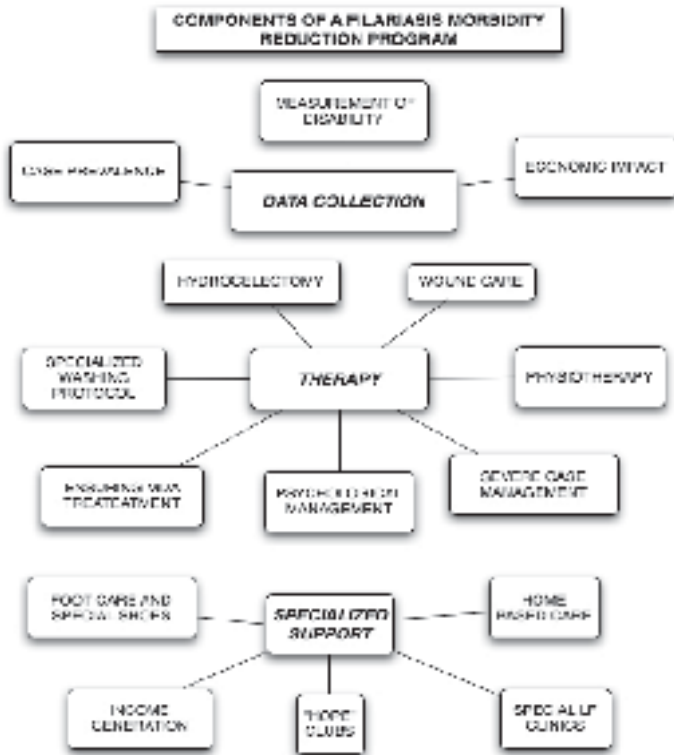


Figure 3. Components of a filariasis morbidity reduction programme.

The needs for the future

The Global Programme for Elimination of LF is often described as having "two pillars": firstly drug distribution for the breaking of transmission and secondly morbidity reduction activities. The success of the MDA-based transmission interruption activities will in the final instance be measured by the actual elimination of LF disease – thus LF patients themselves are central in all the many tremendous efforts currently underway in many countries across the world. Patients are the reason these programmes began

and are being carried out. It is therefore vital to put more effort into the patient pillar of the Global Programme. It is fair to say that, to date, the drug distribution efforts have been given greater focus than morbidity reduction activities.

The activities needed cover a wide range – from basic research (such as better infection detection systems), through improved procedures for treatment of the medical conditions seen in LF, to the various social and economic issues. An obvious and relatively straight forward need is to better identify the cases of hydrocele and increase the number of surgical procedures available to alleviate these cases. As lymphoedema/elephantiasis and hydrocele are especially personal conditions and are generally not fatal, LF has usually been given a back seat to a country's expenditure on diseases such as HIV/AIDS, tuberculosis and malaria.

It is important in the development of MDA programmes in a country that all the affected patients be given medical attention upon request or when identified. As a country's MDA programme is expanding this often means that patients from endemic areas not yet included in the programme require medical attention and instruction. In Tanzania a special "filariasis clinic", common in Asian LF programmes, was put in place early in the development of the MDA programme; this facility serves as an advocacy tool, cares for those not yet receiving the benefits of a local MDA programme, and in fact serves as a learning platform for management of such patients.

Visible improvement in LF patients under the effects of an active MDA has been seen in Tanzania to be a major, positive advocacy tool for the LF programme as a whole (Mackenzie et al., 2008), and has encouraged many non-complying residents to become involved in the programme. Improved ways to reach all affected patients – through home-based care programmes, LF clubs and the like – is essential to the overall success of a MDA programme.

It is important that in future more emphasis is placed on understanding the social and economic impact of this disease, particularly in the Eastern and Southern African setting. The extensive use of tools to measure disability and economic impact must be integrated into standard programme protocols. This is vital to eventual success, and especially for funding advocacy. In this era of integration of control and elimination of different parasitic diseases (grouped as "neglected tropical diseases") it becomes particularly important to keep each disease, and its specific impact on patients, in high focus.

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Chapter 5



LF vectors

Vectors of lymphatic filariasis in Eastern and Southern Africa

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Abstract

A review of studies on vectors and transmission of lymphatic filariasis in Eastern and Southern Africa, with an emphasis on studies carried out after 1970, is presented. The vectors in this region are all members of a species complex or group: the Anopheles gambiae complex, the An. funestus group and the Culex pipiens complex. The methods for identification of vectors have advanced considerably in later years, and the current status is given. Studies on vector incrimination, transmission and vector efficiency are also outlined. The field studies on lymphatic filariasis vectors have mainly been undertaken in Kenya and Tanzania, but also in Uganda, Madagascar and the Comoros. Vector control studies from this region, aiming at reducing the transmission of lymphatic filariasis, are also reviewed.

Introduction

The discovery in 1877 by Patrick Manson of the role of mosquitoes in transmission of lymphatic filariasis (LF) stimulated intense interest in blood-feeding insects and their significance in disease transmission (Sasa, 1976). Other pathogens were also shown to be insect transmitted, and towards the turn of the century Ronald Ross demonstrated developing stages of malaria parasites in mosquitoes. These discoveries resulted in a profound need for tools for the identification of mosquitoes, and in the remaining part of the 19th and first part of the 20th century research in mosquito taxonomy developed rapidly and many new species were described. Whereas 110 mosquito species were known in 1900, this figure

had increased to over 1100 in 1922 (Edwards, 1922). At this time *Culex quinquefasciatus* was regarded by far the most important filarial vector globally, and *Anopheles gambiae* had been incriminated as filarial vector in West Africa. The vector in Egypt was not yet known, and there was contradictory information concerning the role of *Mansonia sp.* as filarial vectors in Africa (Edwards, 1922).

Intensive taxonomical investigations led to the publication of a series of comprehensive keys for identification of African mosquitoes between 1938 and 1952: 'Mosquitoes of the Ethiopian Region I-III' (Evans, 1938; Edwards, 1941; Hopkins, 1952), some of which are still used in supplement with more recent publications (Gilles and Coetzee, 1987; Service, 1990; Jupp, 1996). In 1959, African filariasis vectors had still only been incriminated at very few locations (Tanzania, Kenya and Sierra Leone) (Manson-Bahr, 1959). The number of locations increased substantially during the following years, and in 1976 the situation was summarized as follows (Sasa, 1976): Mosquitoes of the *An. gambiae* and *An. funestus* groups are widespread and main vectors of *Wuchereria bancrofti* in the tropical and sub-tropical regions of Africa. In coastal areas of East Africa, *Cx. quinquefasciatus* is also involved. Transmission in Madagascar is by *An. gambiae*, *An. funestus* and *Cx. quinquefasciatus* (but the latter appears less efficient). *Cx. quinquefasciatus* is the main vector on other Indian Ocean islands such as Mauritius, the Comoros, the Seychelles and the Maldives.

This review provides an update on the research carried out on LF vectors in Eastern and Southern Africa. It has an emphasis on the period after 1970, as the earlier period was covered comprehensively by Sasa (1976).

Vector taxonomy and identification

The vectors of LF in Africa are all members of a species complex or group: the *Anopheles gambiae* complex, the *Anopheles funestus* group and the *Culex pipiens* complex. Identification to the species complex or group is based on morphological characters, whereas the further identification within the complex or group is more complicated and laborious, and still offers some unresolved taxonomic challenges. The nomenclature and taxonomical status used below is based on Knight and Stone (1977) with supplements from Knight (1978) and Ward (1984, 1992).

The Anopheles gambiae complex

This is the most comprehensively investigated of the complexes/groups. *An. gambiae* was initially described as one species, but was later recognized as a complex of sibling species with five members (Davidson and Jackson, 1962; Davidson, 1964; Paterson, 1964). These were two saltwater species (*An. merus* and *An. melas*) and three freshwater species (provisionally designated A, B, and C). Davidson and Hunt (1973) presented evidence for a new species from Uganda, which was provisionally called D. Species A, B, C and D were later assigned the scientific names *An. gambiae s.s.*, *An. arabiensis*, *An. quadriannulatus* and *An. bwambae*, respectively (Mattingly, 1977; White, 1985). Recently, yet a new species was recognized and was given the provisional name *An. quadriannulatus* species B (Hunt et al., 1998).

Despite a great deal of efforts, identification based on morphological characters has only been useful to partially separate the *An. gambiae* sibling species (Gillies and Coetzee, 1987). The golden standard for identification has been cytotaxonomy based on differences in banding patterns of the polytene chromosomes (Coluzzi et al., 1979; Green, 1982; Coluzzi, 1984; White 1985; Gillies and Coetzee, 1987). Such cytotaxonomical identification is time consuming and cumbersome and demands highly trained personnel, and is therefore not suitable for the identification of a large number of specimens. Most recently, a polymerase chain reaction (PCR) based technique has been developed which can separate the members of the complex (Scott et al., 1993; Townson and Onapa, 1994; Fanello et al., 2002; Fettegne et al., 2002). This technique is sensitive, simple to use and suitable for identification of large numbers of specimens.

The *An. gambiae s.l.* complex thus at present comprise the following seven sibling species: *An. gambiae s.s.* Giles, *An. arabiensis* Patton, *An. quadriannulatus* (Theobald), *An. quadriannulatus* species B, *An. bwambae* White, *An. melas* Theobald and *An. merus* Dönitz (Gillies and De Meillon, 1968; Knight and Stone, 1977; Knight, 1978; Gillies and Coetzee, 1987; Ward, 1992; Hunt et al., 1998). Of these, *An. gambiae s.s.*, *An. arabiensis*, *An. merus* are principal vectors of LF in Eastern and Southern Africa. (White, 1989; Zagaria and Zavioli, 2002). *An. melas* is a vector in West Africa, but is not found in Eastern and Southern Africa. *An. quadriannulatus* is not considered a vector as it feeds mainly on animals, and the vector status of *An. bwambae*, which has only been found at one locality in Uganda, is unknown (Gillies and Coetzee, 1987; Gibson, 1996).

The Anopheles funestus group

This group consists of nine species, of which the first four belong to the Funestus subgroup: *Anopheles funestus* Giles, *An. parensis* Gillies, *An. aruni* Sobti, *An. vaneedeni* Gillies and Coetzee, *An. confusus* Evans and Leeson, *An. lesoni* Evans, *An. rivulorum* Leeson, *An. brucei* Service and *An. fuscivenosus* Leeson (Gillies and De Meillon, 1968; Knight and Stone, 1977; Ward, 1984, 1992; Gillies and Coetzee, 1987).

Identification based on morphological characters is difficult and time consuming, and the four species of the Funestus subgroup have identical morphology in all life stages (Gillies and de Meillon, 1968; Gillies and Coetzee, 1987). The chromosome banding pattern allows unequivocal identification of wild caught females of *An. funestus*, *An. parensis*, *An. confusus*, *An. lesoni* and *An. rivulorum* (Green, 1982; Koekemoer et al., 1999). A PCR technique has recently been developed for identification of *An. funestus*, *An. vaneedeni*, *An. parensis*, *An. lesoni* and *An. rivulorum* and has been recognized as a simple and effective method for identifying these five members of the complex (Koekemoer et al., 2002; Weeto et al., 2004)

An. funestus is the dominant member of the group, both in numbers and distribution (Gillies and De Meillon, 1968). The principal LF vector from the group in Africa is *An. funestus* (White, 1989). Several of the other group members have been found resting indoor with human blood meals (Coetzee and Fontenille, 2004) and their role in transmission of LF should be investigated.

The Culex pipiens complex

This complex includes five species and forms: *Culex pipiens* Linnaeus, *Cx. quinquefasciatus* Say, *Cx. quinquefasciatus* form *pallens* Coquillett, *Cx. globocoxitus* Dobrotworsky and *Cx. australicus* Dobrotworsky and Drummonds (Knight and Stone, 1977; Knight, 1978; Ward, 1992; Service, 1993; Harbach, 1999 pers. comm.). The taxonomy of the complex is by no means settled, and the species appear to differ mainly in their behaviour and biology (Service, 1993). The species status of *Cx. quinquefasciatus* is still discussed, and some regard the complex as one polytypic species with different subspecies (Mattingly, 1967; Barr, 1981; Subra, 1981; Ishii, 1992).

The members of the complex differ in minor morphological details (Ishii, 1992). The shape of the male genitalia is by many experts regarded as the only reliable morphological character which can be used to distinguish *Cx. pipiens* and *Cx. quinquefasciatus* (Barr, 1967, 1981). Cytotaxonomy is of

little use for distinguishing the species (Service, 1993). Enzyme electrophoresis combined with morphological examination was recently used to demonstrate hybridisation between *Cx. pipiens* and *Cx. quinquefasciatus* in Madagascar (Urbanelli et al., 1995).

Studies using PCR technique have supported the view that *Cx. quinquefasciatus* should be degraded to a subspecies of *Cx. pipiens* (Crabtree et al., 1997; Bourguet et al., 1998). Recently, Smith and Fonseca (2004) developed a rapid PCR based assay, which identify some of the members of the *Cx. pipiens* complex.

The principal LF vector from the *Cx. pipiens* complex in Sub-saharan Africa is *Cx. quinquefasciatus* (White, 1989). In Egypt, where there are no *Cx. quinquefasciatus*, *Cx. pipiens* is the vector (Farid et al., 1991).

Overview of vector biology studies in Eastern and Southern Africa

This section summarizes by country the studies on LF vector biology carried out in Eastern and Southern Africa since 1970, with a focus on vector incrimination, transmission and vector efficiency. In the late 1960s, *Cx. quinquefasciatus* had become a very common mosquito in most urban and semi-urban areas of Africa. It was known to be a vector of LF in Eastern and Southern Africa but not in Central and West Africa. The background for this was not understood, and its vectorial status was regarded as complex and changing (Hamon et al. 1967).

Tanzania

White (1971a) was one of the first to investigate the relative importance of *Cx. quinquefasciatus*, *An. gambiae* and *An. funestus* as vectors of LF in a locality where all three vectors were present (Tanga Region). The two anophelines were noted to have substantially higher infectivity rates than *Cx. quinquefasciatus*, and *An. funestus* delivered more than four times as many infective bites per year than *Cx. quinquefasciatus*, despite the number of bites were less than half (Table 1). It was also demonstrated that *Cx. quinquefasciatus* was the only vector in urban Tanga.

Magayuka and White (1972) investigated hybrid compatibility and susceptibility to *W. bancrofti* of laboratory reared populations of *Cx. quinquefasciatus* from six Tanzanian and Kenyan localities. They found no

incompatibility and uniformly high susceptibility and suggested that the *Cx. quinquefasciatus* found throughout Kenya and Tanzania was one strain.

Table 1. Infectivity rate (percent of vectors with infective larvae), annual biting rate (ABR; number of vector bites per person per year) and annual infective biting rate (AIBR; number of infective bites per person per year) for the three main vectors of *Wuchereria bancrofti* in Muheza, Tanzania (data from: White, 1971). The infectivity rates are based on collection of indoor resting mosquitoes by pyrethrum spray catch. Infectivity rates in brackets have been converted by White to values expected with human landing catch, and these values were used for calculation of AIBR.

Vector	Infectivity rate	ABR	AIBR
<i>Cx. quinquefasciatus</i>	0.36% (0.54%)	3,058	17
<i>An. gambiae s.s.</i>	1.27% (2.41%)	2,971	72
<i>An. Funestus</i>	1.38% (6.07%)	1,591	97

Magayuka (1973) examined wild caught *An. coustani*, *An. ziemanni*, *An. pharoensis*, *An. tenebrosus*, *Mansonia africanus* and *M. uniformis* from the Tanga area for filarial infection. No L3s of *W. bancrofti* were found. Newly emerged mosquitoes of all six species were fed on a microfilaraemic donor, but only *An. tenebrosus* supported development of L3s. That none of the wild caught *An. tenebrosus* had L3s of *W. bancrofti* was explained by its exophilic night biting behaviour.

Crans (1973) infected laboratory reared *An. gambiae s.s.* and *Cx. quinquefasciatus* with *W. bancrofti* and found that the latter took up more than three times as many microfilariae and a much larger proportion harboured L3s after 14 days than the former. He suggested that this rather surprising result was due to the laboratory rearing and the highly inbred mosquito colonies used.

Krafsur and Garrett-Jones (1977) investigated the survival of *W. bancrofti* infected *An. funestus* in wild caught mosquitoes. They found that the age specific parasite density did not vary significantly between days three and fifteen after infection. There was no evidence that the high worm burdens affected the survival of the mosquitoes.

Mosha and Magayuka (1979) examined wild caught and experimentally infected mosquitoes and summarized comprehensively

earlier work on vectors in East Africa. Nine wild caught species were dissected in numbers above 40. Only *Cx. sitiens* had infective *W. bancrofti* larvae (Table 2). Eight of the nine species were experimentally infected and dissected. *An. pharoensis*, *Cx. sitiens* and *Aedes aegypti*, supported development of *W. bancrofti* L3s. The zoophilic and exophilic behaviour of the three species and the day biting behaviour of *Ae. aegypti* could account for the insignificant numbers of infective wild caught specimens.

Table 2. Dissection of wild caught and experimentally infected mosquitoes for infective larvae of *Wuchereria bancrofti* (data from: Mosha and Magayuka, 1979)

Mosquito species	Number mosquitoes infective/dissected	
	Wild caught	Experimentally infected
<i>An. pharoensis</i>	0/42	70/167
<i>An. tenebrosus</i>	0/625	0/5
<i>An. coustani</i>	0/122	0/3
<i>Cx. sitiens</i>	2/809	15/98
<i>Ae. aegypti</i>	0/715	7/145
<i>Ae. pembaensis</i>	0/977	0/9
<i>Ma. uniformis</i>	0/824	0/92
<i>Ma. africanus</i>	0/324	0/40

Comprehensive investigations on the epidemiology of LF were carried out in four coastal villages (Machui, Kwale, Tawalani and Moa) near Tanga from 1973 to 1976 by the team of John McMahon (McMahon et al., 1981). Longitudinal entomological baseline studies on mosquito density and transmission were performed, and the villagers were examined for clinical manifestations and microfilaraemia (Table 3). The examinations continued after application of intervention measures. The vectors in order of importance were found to be *An. gambiae*, *Cx. quinquefasciatus* and *An. funestus*. Ten other species of mosquitoes were examined for infection, but only one *Cx. sitiens* contained a L3 of *W. bancrofti*. Transmission by the *An. gambiae* complex was seasonal (mainly during and after the long rains), whereas by *Cx. quinquefasciatus* it was throughout the year. The

estimated number of infective bites per person was highest in the village with highest prevalences of clinical manifestations and microfilaraemia and lowest in the village with the lowest prevalences. The average number of L3s found per infective mosquito in spray catch and human landing catch collections were compared.

Bushrod (1979) showed in one of the study villages above (Kwale) that *An. gambiae s.l.* and *Cx. quinquefasciatus* were the vectors and that they had similar infectivity rates. The anopheline vectors were exophilic and antropophagic, and appeared to be *An. merus*, which probably accounted for their comparatively low vector efficiency.

Bushrod (1981) examined further the role of the *An. gambiae* complex in LF transmission in another coastal village. The mosquitoes were identified with a combination of morphological and cytotaxonomic methods considered reliable to draw conclusions regarding *An. gambiae s.s.* and *An. merus*. The latter was predominant during the drier periods, whereas both species were present in similar numbers during rainy periods. *An. gambiae s.s.* was endophilic whereas *An. merus* was highly exophilic. *An. merus* appeared to be an important vector of LF in the area.

McGreevy et al. (1982) examined experimentally the uptake of *W. bancrofti* microfilariae in Tanga by laboratory reared local *An. gambiae* and *Cx. quinquefasciatus*, and the further development to L3s was studied in *Cx. quinquefasciatus*. The proportion of *Cx. quinquefasciatus* that became infective and the number of L3s per infective mosquito increased as the microfilarial density of the donors increased, but a large proportion of the ingested microfilariae failed to develop into L3s. Even at very low microfilarial densities, unlikely to be detected with standard diagnostic techniques, *Cx. quinquefasciatus* supported development of L3s. Earlier work by McGreevy and co-workers on East African material had demonstrated a lethal effect of *An. gambiae* cibarial and pharyngeal armatures on microfilariae (McGreevy et al., 1978).

Curtis et al. (1981) compared the susceptibility of Liberian and Tanzanian *Cx. quinquefasciatus* to Tanzanian *W. bancrofti*. The two strains of mosquitoes had almost similar susceptibility, which was significantly higher than the susceptibility to Liberian *W. bancrofti*. It was concluded that the Liberian strain would not be useful as a source of genes for breeding of a refractory mosquito for transmission control in East Africa.

Matola (1985) surveyed the Lower Rufiji Basin for malaria and LF in order to later evaluate the impact of a planned dam further upstream. The

Table 3. *Wuchereria bancrofti* infection and transmission in four villages in coastal Tanzania (Tawalani, Moa, Machui and Kwale) before and after intervention (data from: McMahan et al., 1981 and Kolstrup et al., 1981). The table shows the prevalence of microfilaraemia (Mf%) in the human populations before and one year after intervention, the infectivity rate (L3%), mean L3 load (L3/inf), annual biting rate (ABR), and annual infective biting rate (AIBR) for the three main vectors *An. gambiae* (*An. g.*), *An. funestus* (*An. f.*) and *Cx. quinquefasciatus* (*Cx. q.*) during the pre-intervention year, and the percent reduction in ABR (ABR red%) and AIBR (AIBR red %) during the post-intervention year. Mosquitoes were collected by indoor human landing catch.

Vector species	Tawalani			Moa			Machui			Kwale		
	An. g.	An. f.	Cx. q.	An. g.	An. g.	Cx. q.	An. g.	An. g.	Cx. q.	An. g.	An. g.	Cx. q.
Mf%	28.3			24.2		18.5						15.6
L3 %	1.5	1.4	0.6	0.7	0.8	0.4	0.7	0.4	0.7	0.7	0.4	0.0
L3/inf	2.14	1.25	2.16	1.0	1.89	3.33	2.0	3.33	2.0	2.0	3.33	0.0
ABR	10500	2350	24350	1100	2300	3600	2650	3600	2650	2650	3600	900
AIBR	152	37	179	8	25	16	24	16	24	24	16	0
Intervention measure	DEC			Vector control			DEC			Vector control		
Post intervention year												
Mf%	0.8			-	3.9							-
ABR red%	-	-	91.2	92.3	-	-	85.7	-	85.7	-	-	83.9
AIBR red%	91.5	100.0	94.2	75.0	100.0	100.0	62.5	100.0	62.5	100.0	100.0	-

three well known East African LF vectors were present, and the vector densities and filarial infection rates (but not infectivity rates) were recorded before and after the long rains.

Minzava and Kilama (1986) examined the distribution of the *An. gambiae* complex in Tanzania. *An. merus* was most common along the coast whereas *An. arabiensis* dominated in dryer inland areas. *An. gambiae* dominated or was the only species in humid coastal and lacustrine areas.

Minzava et al. (1989) investigated differences in transmission of LF between members of the *An. gambiae* complex and *An. funestus* while at the same time testing a biochemical method for identification of members of the *An. gambiae* complex. They observed significant differences in infection rates between *An. gambiae s.s* and *An. funestus* and between *An. arabiensis* and *An. funestus* but no differences in infectivity. Only few *An. merus* were dissected and none were infective. It was thus difficult to interpret the results in terms of LF transmission.

Lines et al. (1991) compared human landing catch of *An. gambiae s.l.*, *An. funestus* and *Cx. quinquefasciatus* to that of catch by light traps set close to occupied untreated bed nets. They found that on average three light traps caught about the same number of mosquitoes as a team of two human catchers. Light traps have since been used widely in Southern and Eastern Africa for collecting vector mosquitoes.

Mboera et al. (1997) reported on a longitudinal study in a highly endemic village near Tanga. Mosquitoes were collected with light traps in six houses each fortnight for a year. *An. funestus* and *An. gambiae s.l.* were caught in high and almost equal numbers, whereas there were only few *Cx. quinquefasciatus*. The *W. bancrofti* infectivity rate was highest in *An. funestus* and slightly lower in *An. gambiae s.l.* No infections were found in *Cx. quinquefasciatus*.

Pedersen et al. (1999) compared the status of LF in three urban/semi-urban communities on Pemba Island to the status seen 15 years earlier. The overall prevalence of microfilaraemia had decreased, but clinical manifestations were seen at remarkably similar prevalence. Mosquitoes were collected by light traps and dissected for L3s. During the period of investigation the great majority was *Cx. quinquefasciatus*, supplemented by a few *An. gambiae s.l.*, and L3s were only found in the former. *Cx. quinquefasciatus* thus appeared to be the predominant vector, as also seen on Zanzibar (Maxwell et al., 1990) and other Indian Ocean islands (Brunhes, 1975).

Gasarasi (2000) examined the distribution of *W. bancrofti* L3s in experimentally infected *Cx. quinquefasciatus* and *An. gambiae* before and after a bloodmeal from a membrane feeding apparatus. In *Cx. quinquefasciatus* the proportion of L3s in the abdomen increased after the blood meal, while it decreased in the head and mouthparts. A similar pattern was seen in *An. gambiae*. The overall loss of L3s was much larger in the former than the latter vector species. The background and implications of this observation is unclear.

Kenya

From 1973 to 1975 the team of Dirk Wijers carried out LF surveys in two highly endemic villages in coastal Kenya, Mambui and Jaribuni. Vectors and transmission were monitored for one year in both villages (Wijers and Kiluu, 1977). Mambui was a densely populated seaside village where *Cx. quinquefasciatus* was the main vector and was breeding in pit latrines and cess pits. Considerable differences were encountered in vector biting densities between the different collecting sites, probably mainly because of differences in distance to breeding sites and because mosquitoes were more attracted to poorly built than to well-built houses. In this village transmission peaked during the long rains (June-July). Jaribuni was a more inland rural community with a scattered population, where *An. funestus* was the main vector breeding in a nearby river and *An. gambiae s.l.* played a minor role. The distance to the river appeared to be the main factor determining the intensity of transmission. In this village transmission peaked just after the short rains (December-January). Infectivity rates of the three vector species were similar, but infective *Cx. quinquefasciatus* carried more L3s than the other species (Table 4). It was concluded that *Cx. quinquefasciatus* can be an efficient vector in East Africa, with a vector potential comparable to that of *An. funestus* and *An. gambiae*.

Mosha and Petrarca (1983) examined three sibling species of the *An. gambiae* complex (*An. merus*, *An. gambiae s.s.* and *An. arabiensis*) for *W. bancrofti* infection on the coast of Kenya. The infectivity rate was considerably higher for *An. gambiae s.s.* than for *An. merus*. The latter appeared to be restricted to a narrow margin along the coast and to be a relatively poor vector compared to the former.

Mwandawiro et al. (1997) studied the main vectors of LF in three endemic villages near the Kenyan coast. Mosquitoes were collected by human landing catch and pyrethrum spray catch in four houses in each village for a year. The study demonstrated that *Cx. quinquefasciatus* could

be an important vector also in rural areas of Kenya. The fact that this was the case even in villages without conspicuous breeding sites such as wet pit latrines suggested that the role of this mosquito species as a vector of LF may be expanding to more rural areas.

Table 4. Infectivity rate, mean L3 load (number infective larvae per infective mosquito), annual infective biting rate (AIBR) and annual transmission potential (ATP; number of infective larvae to which one person is exposed per year) for the three main vectors of *Wuchereria bancrofti* in two villages in Kenya (data from: Wijers and Kiluu, 1971). *Cx. quinquefasciatus* was the main vector in the coastal Mambui village and *An. funestus* was the main vector in the more inland Jaribuni village. There were very few *An. gambiae s.l.*, and these were only dissected in Jaribuni. Mosquitoes were collected by human landing catch.

Vector	Infectivity rate	Mean L3 load	AIBR	ATP
<i>Cx. quinquefasciatus</i>	0.97%	3.4	46	155
<i>An. funestus</i>	0.99%	1.4	}155	226
<i>An. gambiae s.l.</i>	1.1%	2.6		

Muturi et al. (2006) investigated concomitant infections with malaria and *W. bancrofti* in mosquitoes on the coast of Kenya. *An. gambiae s.l.* and *An. funestus* were collected by pyrethrum spray catch. Sporozoite rates and filarial infection and infectivity rates were determined. Multiple infections appeared to reduce vector survival thereby making simultaneous transmission of both infections a rare event.

Tanzania and Kenya

Rwegoshora et al. (2005) carried out intensive monitoring of LF vector abundance and transmission in a high and a low endemicity village in the coastal belt of Tanzania and Kenya, respectively. Mosquitoes were collected with light traps in 50 randomly selected houses in each village once a week for a year. Transmission intensities were significantly different in the two villages (Table 5). *An. funestus* had the highest infectivity rates in both villages followed by *An. gambiae* and *Cx. quinquefasciatus*. The study convincingly showed that the vector species contributing most to

transmission varied with locality and season. Highest transmission intensity was generally seen during and immediately after the long rains. A low infectivity rate in *Cx. quinquefasciatus* could be explained by its shorter life length (as assessed from a lower parity rate, and from a lower proportion of infected mosquitoes becoming infective than for the anophelines). Fitting of the data from the two villages to a mathematical model (Michael et al., 2001) demonstrated a profound effect of transmission intensity on infection and chronic disease patterns in the human populations. The effect of mass drug administration with diethylcarbamazine (DEC) on transmission in the two villages was reported later (Simonsen et al., 2004).

Rwegoshora et al. (2007) subsequently analysed the house-to-house variation in LF vectors and transmission in the high endemicity village. The variation in biting rate was considerable (Figure 1) and appeared to be affected by the distance to the breeding sites, differences in the quality of house construction, and number of inhabitants per household. The number of inhabitants per household was significantly higher in houses with high than in those with low transmission. Household annual biting rates (ABR) correlated positively with household annual transmission potentials (ATP). Intriguingly, however, the human filarial infection status did not differ significantly between households with high and low ABR or ATP. Possible reasons for this could be the long time required for *W. bancrofti* to establish in humans, human behaviour affecting exposure, the sharing of mosquito populations in the village and differential susceptibility of humans to infection.

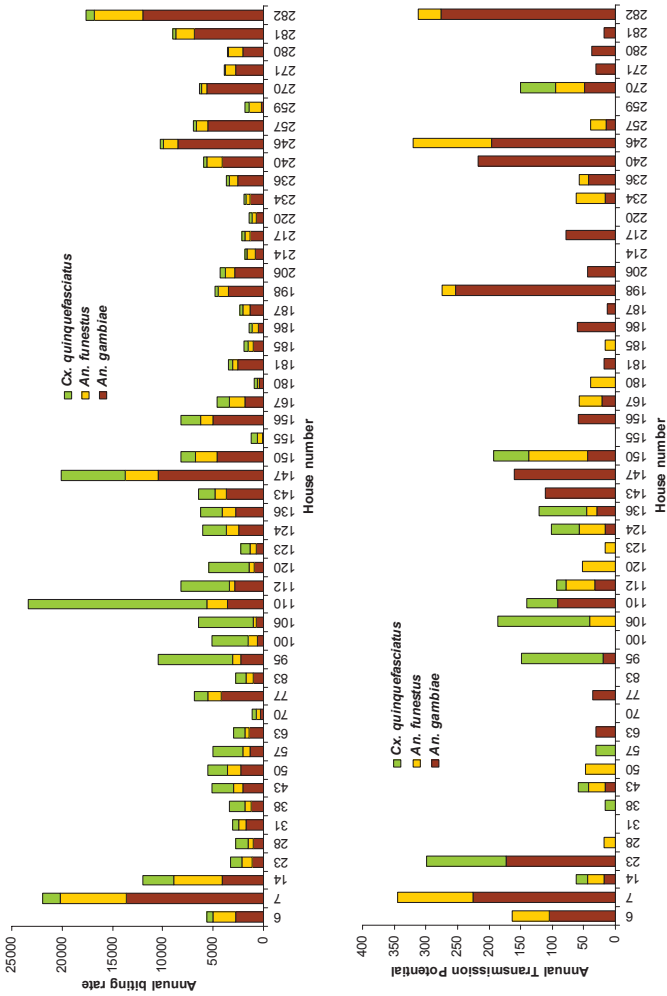
Uganda

Baseline epidemiological investigations on LF were conducted for the first time in Uganda by Onapa et al. (2001). Three communities north of Lake Kyoga were examined. Prevalences of microfilaraemia and clinical manifestations were high. Mosquitoes were collected with light traps and pyrethrum spray catch. *An. gambiae s.l.* (mainly *An. gambiae s.s.*) and *An. funestus* were common in all three communities (Table 6) and *W. bancrofti* L3s were recovered from both species upon dissection. It was concluded that LF is highly endemic in these comparatively high-altitude areas of Uganda, with *An. gambiae s.l.* and *An. funestus* being the main vectors.

A thorough investigation of the possible role of *M. uniformis* as vector of *W. bancrofti* in Uganda was carried out by Onapa et al. (2007). Outdoor

Table 5. *Wuchereria bancrofti* infection and transmission in two East African coastal villages, Masaika in Tanzania and Kingwede in Kenya (data from: Rwegoshora et al., 2005). The table shows the prevalence of microfilariemia (mf %), and the parous rate, infectivity rate, annual biting rate (ABR) and annual transmission potential (ATP) for the three main vectors. Mosquitoes were collected weekly for one year by light traps in 50 houses per village.

Vector species	Masaika (mf % = 24.9)			Kingwede (mf % = 2.7)				
	Parous rate	Infectivity rate	ABR	ATP	Parous rate	Infectivity rate	ABR	ATP
<i>An. gambiae s.l.</i>	81.5	0.83	3050	55.2	80.0	0.26	200	0.8
<i>An. Funestus</i>	80.6	1.22	1200	21.6	85.6	0.40	550	3.0
<i>Cx. quinquefasciatus</i>	46.0	0.32	1900	16.1	71.8	0.06	900	2.6
Total	-	-	6150	92.9	-	-	1650	6.4



Figur 1. Annual biting rates (upper) and annual transmission potentials (lower) for individual households in Masaika village, Tanzania (data from: Rwegoshora et al., 2007).

biting peaked early in the evening, while indoor biting peaked around midnight. By far the majority of indoor resting *M. uniformis* had taken their blood meals on humans. Both biting and feeding behaviour were therefore compatible with a potential for transmission. Dissection of experimentally fed *M. uniformis* showed that the larvae accumulated in the thorax and very few developed further. Large numbers of wild caught *M. uniformis* were dissected but none had L3s of *W. bancrofti*. *M. uniformis* did therefore not appear to play a role as vector of LF under natural conditions.

Table 6. Average infection and infectivity rates for the vectors of *Wuchereria bancrofti* in villages in Uganda (data from: Onapa et al., 2001). The mosquitoes were collected by light traps.

Mosquito species	No. collected	No. dissected	No. infected (%)	No. infective (%)
<i>An. gambiae s.l.</i>	6,439	1,051	40 (3.8)	15 (1.4)
<i>An. funestus</i>	5,689	594	33 (5.5)	11 (1.8)
<i>Mansonia sp.</i>	3,203	0	-	-
<i>Other culicines</i>	649	0	-	-

Malawi

Merelo-Lobo et al. (2003) were the first to incriminate the vectors of LF in a Malawian focus. *An. gambiae s.s.*, *An. arabiensis* and *An. funestus* all had L3s of *W. bancrofti*, and *An. funestus* appeared to be the predominant vector. No *Cx. quinquefasciatus* were caught during the investigation season.

Ethiopia

McConnel and Smith (1973) investigated the vectors of LF in Ethiopia. Mosquitoes were collected by pyrethrum spray catch and light traps, and by human landing catch for *Mansonia sp.* Upon dissection, L3s of *W. bancrofti* were found in both *An. gambiae* and *An. funestus*. No filarial infections were found in several other mosquitoes species dissected, and no *Cx. quinquefasciatus* were caught. *An. gambiae* and *An. funestus* thus appeared to be the principal vectors of LF.

Indian Ocean islands

In Madagascar, studies by Brunhes (1975) indicated that *An. funestus* and *An. gambiae s.l.* were the main vectors of *W. bancrofti*. When present in equal density these two species made the same contribution to transmission. *An. gambiae* was distinctly exophilic and slightly exophagic. *Cx. quinquefasciatus* was not observed in the LF endemic areas. However, experimental studies showed that this species was able to support development of the parasite, but it was less efficient in this respect compared to the anophelines. Other studies showed that *M. uniformis* in Madagascar was refractory to *W. bancrofti* (Brunhes et al., 1972; Brunhes and Brunhes, 1972).

The first all year longitudinal study in the Comoros showed the main vectors to be *An. gambiae s.l.* and *Cx. quinquefasciatus*, with the latter being the most efficient (Brunhes, 1975). *Cx. quinquefasciatus* was also the most frequent mosquito in most of the villages studied. A later survey of the Comoros confirmed the dominant vector role of *Cx. quinquefasciatus* (Sabatinelli et al., 1994).

Summary of vector biology in Eastern and Southern Africa

The principal vectors of LF in Eastern and Southern Africa belong to the *An. gambiae* complex (*An. gambiae s.s.*, *An. arabiensis*, *An. merus*), the *An. funestus* group (*An. funestus*) and the *Cx. pipiens* complex (*Cx. quinquefasciatus*).

An. gambiae and *An. arabiensis* breed in freshwater in open sunlit muddy pools with little organic pollution and high oxygen content. *An. merus* is saltwater tolerant and can breed in tidal swamps and pools, but it has recently also been found breeding in freshwater (Gillies and de Meillon, 1968; Gillies and Coetzee, 1987; Coetzee et al., 1993). *An. funestus* breeds in clear freshwater sites which are more vegetated than those of *An. gambiae/An. arabiensis*, and it also tolerates slow water movements (Gillies and de Meillon, 1968). *Cx. quinquefasciatus* is a freshwater breeder very tolerant to pollution with organic matter, low oxygen levels and a wide pH range. It occasionally also breeds in natural clean freshwater (Mattingly et al., 1951; Subra, 1981). These breeding preferences make *Cx. quinquefasciatus* the urban and peri-urban vector of LF in Eastern and Southern Africa, *An. gambiae*, *An. arabiensis* and *An. funestus* the rural vectors and *An. merus* a vector along the seashore.

The LF vectors in this region are all night-biting, predominantly endophagic and endophilic. They are anthropophilic but differ in their

readiness to feed on other hosts when not feeding on humans. *An. gambiae* and *An. arabiensis* are highly anthropophilic, but when alternative mammalian hosts are available *An. arabiensis* shows a greater tendency to feed on these than *An. gambiae* (Gillies and Coetzee, 1987). *An. merus* is more exophilic and prefers feeding on cattle when these are present, but nevertheless frequently feeds on man (Gillies and de Meillon, 1968; Bushrod, 1981; Gillies and Coetzee, 1987). *An. arabiensis* is generally found in drier savanna habitats than *An. gambiae*, which is considered originally a forest species (Coluzzi et al., 1979).

An. funestus is one of the most anthropophilic mosquitoes known and has a consistently high human blood index. It is highly anthropophilic and the only indoor man-biting species of the *Funestus* group. The other group members appear to be zoophagic, but bite man readily outdoors in the absence of other hosts (Gillies and de Meillon, 1968; Gillies and Coetzee, 1987).

Cx. quinquefasciatus, like many other *Culex* species, are ornithophilic when not biting man. They vary in the degree of ornithophagy (Mattingly et al., 1951). *Cx. quinquefasciatus* predominantly bites man but readily shifts to bird feeding when deprived of access to human blood (Bøgh et al., 1998).

The average adult life span of mosquitoes in hot tropical climate is generally only 1-2 weeks (Service, 1993). The longevities of *An. gambiae* and *An. arabiensis* were studied in detail in coastal Tanzania (Gillies, 1988). The mean duration of the gonotrophic cycle was determined by recapture of marked mosquitoes and by the number of oviposition scars on the ovary. Average life spans of 1.5 weeks for *An. gambiae* and 1.3 weeks for *An. arabiensis* were observed. Based on studies on parity and survival rates, *An. gambiae s.s.* and *An. funestus* appear to be equally long-lived, whereas *An. arabiensis* lives slightly shorter (Gillies, 1988). *An. merus* is regarded relatively short-lived (McMahon et al., 1981). *Cx. quinquefasciatus* generally does not live as long as *An. gambiae* and *An. funestus*.

Summary of vector efficiency in Eastern and Southern Africa

As seen from the studies summarized above, and as discussed by Southgate (1992), *Cx. quinquefasciatus* generally has lower LF transmission efficiency than the anopheline vectors. This is despite the larger size, the larger uptake of microfilariae and the lack of cibarial armature. A main reason appears to be the shorter life span of *Cx. quinquefasciatus*, but midgut barriers might also play a role.

Within the *An. gambiae* complex the freshwater species *An. gambiae s.s.* and *An. arabiensis* are regarded as more efficient transmitters than the

saltwater species *An. merus*, mainly due to the shorter life span and higher degree of zoophily of the latter (Southgate, 1984). Hence Mosha and Petrarca (1983) found three times greater infectivity of *An. gambiae s.s.* than of *An. merus*. Bushrod (1981) found equal infectivity in the two species in an area where non-human blood-meals were not freely available to the mosquitoes. *An. arabiensis* is slightly more exophilic than *An. gambiae s.s.*, and in some areas also more zoophilic, which make it as good a vector in some areas and less efficient in others.

An. funestus is as long-lived and anthropophilic as *An. gambiae s.s.* and would be expected to be equally efficient in transmitting *W. bancrofti*, as also observed by White (1971a). However, there are not much field data available comparing the vector efficiency of these two species. It is interesting that *An. quadriannulatus*, which is considered to be non man-biting and not a vector of LF, experimentally is fully susceptible to *W. bancrofti* and feeds with equal frequency on humans and cattle (Hunt and Gunders, 1990; Pates et al., 2001).

Vector control studies

Vector control studies in Eastern and Southern Africa, aiming at reducing the transmission of LF, have included a range of intervention measures. The investigations reported since 1970 are summarized below.

Insecticidal control and environmental management

White (1971b) discussed the importance of *Cx. quinquefasciatus* as a vector of LF in East Africa, and summarised knowledge and experience on its control. He moreover reported on tests with organophosphorous granules, chlorfenvinphos (Birlane), against this vector. As the tests performed well, this measure was recommended.

Bushrod (1979) applied larval control measures in a village near Tanga, where the main vectors were *An. gambiae s.l.* and *Cx. quinquefasciatus*. All freshwater breeding sites seen during the long rainy season within a one km radius from the village were treated weekly with temephos (Abate). Brackish water pools were treated regularly with paraffin with 1% Castor oil added, oil drums used for domestic water storage were treated with temephos (Abate) and pit latrines were treated with chlorpyrifos (Dursban). The measures resulted in a 95 % reduction of mosquito numbers.

The four villages investigated by McMahon et al. (1981) were exposed to different LF control measures (Kolstrup et al., 1981). Vector control was implemented in two of the villages (Table 3). In Moa, the main vector *Cx. quinquefasciatus* bred in pit latrines. Treatment of the latrines with chlorpyrifos (Dursban) resulted in a considerable reduction in the annual infective biting rate for this mosquito. In Kwale, various larval control measures were implemented, with results as reported above by Bushrod (1979). It was recommended to apply larvicides against *Cx. quinquefasciatus* when this species has focal breeding, to apply larvicides combined with simple environmental measures against *An. gambiae s.l.* when its breeding sites are not too extensive, and to consider residual house spraying at other places where *An. gambiae s.l.* and *An. funestus* are vectors.

Polystyrene beads

Maxwell et al. (1990) carried out an extensive study in Makunduchi town, Zanzibar, with expandable polystyrene beads as a vector control measure. In this place, wet pit latrines provided the breeding place for the vector, *Cx. quinquefasciatus*. After a year of baseline data collection polystyrene beads were expanded in boiling water and applied to form floating layers on all infested pits. The adult mosquito population subsequently declined remarkably. To retain control, surveillance for new wet pits and treatment of these continued. Mass treatment of the population with DEC reduced the microfilarial intensities. The mosquito population was reduced by 98%, and the combined effect of the vector control and mass treatment reduced the number of infective bites per person per year by more than 99%.

A follow-up study (Maxwell et al., 1999) showed that the measures implemented in Makunduchi over the following five years reduced the microfilarial prevalence even further. In another control town in Zanzibar, where the inhabitants had received DEC treatment but no vector control, the microfilarial prevalence also decreased immediately after treatment, but five years later it had increased almost to the initial level. The polystyrene bead measure had apparently prevented re-infection of the successfully treated individuals.

Vector control with polystyrene beads in combination with application of *Bacillus sphaericus* to open breeding sites was tried in the bigger and more complex environment of Zanzibar town (Maxwell et al., 1999). The results were less convincing than in Makunduchi, partly because treatment of breeding in drains and marches with the *B. sphaericus* had “disappointingly” little effect, and partly because of the more complex and much larger setting.

Charlwood (1994) used expanded polystyrene beads in partly open septic tanks at a hospital compound in Ifakara and showed that they effectively reduced the biting population of *Cx. quinquefasciatus*.

Investigations in Dar es Salaam (Chavasse et al., 1995a, 1995b) combined the use of expandable polystyrene beads in closed *Cx. quinquefasciatus* breeding sites with insect growth regulators in open breeding sites. The mosquito population only partly decreased. The insect growth regulators worked well and persisted long in some sites, but many mosquitoes caught after the intervention had invaded from outside the study area and others came from undiscovered (and therefore untreated) sites within the study area.

Curtis et al. (2002) summarised the experiences from Tanzania and India on the use of polystyrene beads for control of *Cx. quinquefasciatus*, and they recommended this measure for other appropriate areas.

Insecticide impregnated bed nets

Insecticide treated bed nets generally have a substantial killing effect on anopheline mosquitoes. Many studies have shown that they significantly reduce the anopheline mosquito biting rate as well as malaria morbidity and mortality (Hill et al., 2006). Since the treated bed nets have been noted to only give a very limited reduction in the number of indoor resting *Cx. quinquefasciatus* and only kill very few (Magesa et al., 1991; Curtis et al., 1996), it was questioned whether the nets can effectively reduce *Cx. quinquefasciatus* transmission of *W. bancrofti*.

The effect of pyrethroid impregnated bed nets on LF transmission was therefore investigated in 12 villages on the coast of Kenya (Mukoko, 2000; Mukoko et al., 2004). Indoor resting mosquitoes were collected by pyrethrum spray catch at weekly intervals during three months before and three months after half of the villages had been provided with permethrin impregnated bed nets (Bøgh et al., 1998). The number of indoor resting *An. gambiae* and *An. funestus*, but not of *Cx. quinquefasciatus*, declined significantly after intervention (Figure 2). Examination of the blood meals showed that the intervention made the *Cx. quinquefasciatus* shift from feeding nearly exclusively on man to taking most of the blood meals on birds (probably chicken) (Figure 3). This suggested that the impregnated bed nets significantly reduced the transmission of *W. bancrofti* to man. That this actually happened was confirmed by all year transmission studies (Figure 4)

which showed a reduction in ATP by 92% in the intervention villages (Pedersen and Mukoko, 2002).

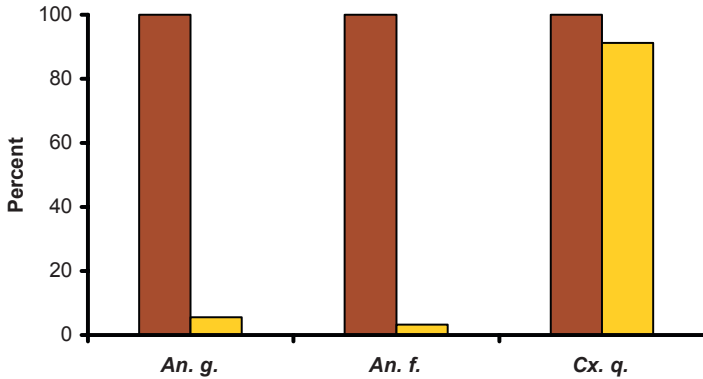


Figure 2. The relative indoor resting mosquito density before (brown bars) and after (yellow bars) intervention with permethrin impregnated bed nets (data from: Bøgh et al., 1998). *An.g.* = *Anopheles gambiae*, *An.f.* = *Anopheles funestus*, *Cx.q.* = *Culex quinquefasciatus*.

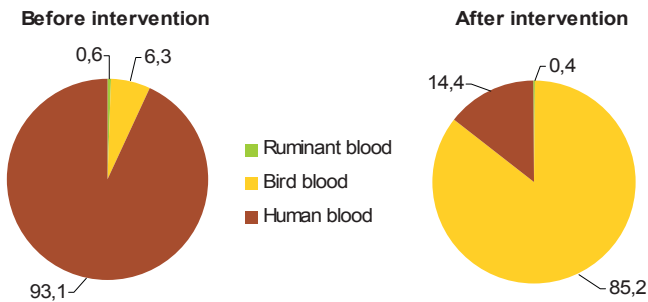


Figure 3. The source of blood meal for indoor resting *Cx quinquefasciatus* before and after intervention with permethrin impregnated bed nets (data from: Bøgh et al., 1998).

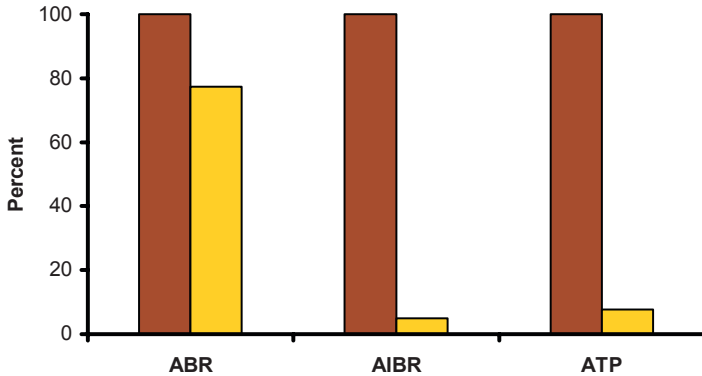


Figure 4. The relative transmission indices of *Wuchereria bancrofti* before (brown bars) and after (yellow bars) intervention with impregnated bed nets (data from: Pedersen and Mukoko, 2002). ABR = annual biting rate, AIBR = annual infective biting rate, ATP = annual transmission potential.

Vector control as a supplement in LF control programmes

One of the principal goals of the Global Programme for Elimination of Lymphatic Filariasis is to interrupt LF transmission. The main measure recommended for achieving this goal is regular mass administration of drugs to the entire endemic populations. Whether this measure is enough to do the job within a reasonable time frame also in areas with low treatment coverage and/or high endemicity has been questioned (Burkot and Ishimori, 2002), and mathematical modelling has shown that it will be difficult to reach the goal in such areas without considerably prolonging the treatment and/or adding of other measures such as vector control (Michael et al., 2004).

The above examples from Eastern and Southern Africa clearly demonstrate that vector control can have a significant impact on the transmission of LF, especially when implemented in combination with mass drug administration. For example, impregnated bed nets considerably reduced transmission in areas of both anopheline and culicine transmitted LF, and application of expanded polystyrene beads to enclosed breeding

sites reduced transmission in areas of culicine transmitted LF. Vector control with polystyrene beads amplified and prolonged the effect of drug treatment. Examples from other parts of the world have moreover shown that vector control alone or in combination with other measures can have dramatic effects on LF transmission, and have played a major role in the success of earlier control programmes (Burkot et al., 2006). More studies are urgently needed to evaluate and define the role for supplementary vector control in the current efforts to stop transmission in the different epidemiological settings where LF prevails.

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Chapter 6



LF control

Implementation and management of lymphatic filariasis control and elimination programmes: the Tanzanian experience

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Abstract

The Tanzania Lymphatic Filariasis Elimination Programme was launched in 2000 and is now functional in 27 Districts of five Regions. More than 7.4 million people have received the annual mass drug administration of ivermectin (Mectizan®) and albendazole. This paper describes the history of control programmes in Tanzania, the setting up of the present Lymphatic Filariasis Elimination Programme, its goals and principles, as well as details of the implementation of the programme. It also addresses the key components of setting up the Tanzanian programme: social mobilization and advocacy, political will, training mechanisms, delivery mechanisms and strategies, funding, as well as monitoring and evaluation. The discussion also includes the need to address financial sustainability and describes how Tanzania has managed with its meagre resources to support programme implementation. Current approaches to implementing the programme in conjunction with other mass treatment efforts for infectious disease are also described in brief.

Introduction

Lymphatic filariasis (LF) is a disease that has probably been in existence for thousands of years and is proposed from archaeological images in Egypt to have been present in the time of the Pharaohs. The devastating and debilitating nature of the disease is well known, even in non-scientific circles; however in contrast, details of the disease, its pathogenesis and its

distribution are less well known. In recent years the development of more easily used field tests for detection of the presence of infection have allowed for more extensive assessment of the epidemiology of *Wuchereria bancrofti*. This has revealed a much higher distribution of infection in many countries throughout the world (Mackenzie et al., 2002).

Although the disease was for many years generally ignored in endemic countries, a number of groups have long maintained research into LF and in some cases were carrying out focal control programmes; in the case of China even a countrywide elimination program. In Africa, the research centre in Tanga, Northern Tanzania, has been the leading centre for research and treatment activities for more than half a century (McMahon et al., 1979, 1981; Meyrowitsch et al., 1995, 1996; Simonsen et al., 2004; Rwegoshora et al., 2005); other countries such as Kenya and Uganda, have also had longstanding LF investigation programmes. One of the reasons that Tanzania has been prominent in African LF research is the high prevalence in this country compared to other countries in the continent.

A major boost to LF programmes came in 1997 with the passage of Resolution 50.29 by the World Health Assembly, the official approval of a proposal to eliminate LF from the world. Thus, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) was born. This programme, which is in effect one of the largest mass distributions of drugs ever attempted, will distribute anti-filarial drugs annually to over 1.8 billion people in over 80 countries around the world. This global effort to eliminate the infection has provided a huge boost to the discipline of filariasis and has increased the amount of research into this poorly understood condition, and also brought greater awareness of the disease to the public both nationally and internationally.

Lymphatic filariasis control in Tanzania: a historical perspective

The presence of lymphatic filariasis in Tanzania was recorded as early as 1911 (Engeland and Manteufel, 1911), and since then a number of countrywide studies have been carried out to delineate the extent and magnitude of the disease in the country (Dunderdale, 1921; Mansfield-Aders, 1927; Hawking, 1940a, 1940b, 1943; Jordan, 1953, 1954, 1955, 1956a, 1956b, 1960; Smith, 1955; White and Magayuka, 1969; Menu and Kilama, 1974; Maxwell et al., 1990). Based on these studies, three main and two minor foci of LF were identified in Tanzania. The three main foci are the coastal belt, the Indian Ocean offshore islands (Zanzibar, Pemba

and Mafia), and the area surrounding Lake Victoria. The minor foci are located in the Morogoro lowlands and in an area around Lake Nyasa in Southern Tanzania (Minjas and Kihamia, 1991). Early attempts to control LF were localized and carried out more with a research bias than with a public health end-point. These studies were carried out on Ukara Island (Jordan 1958), and at different periods in Tanga (Kolstrup et al., 1981, Meyrowitsch et al., 1996) and on Zanzibar Island (Maxwell et al., 1990).

Recently the rapid epidemiological assessment exercise carried out by the National LF Elimination Programme, which covered the whole country using the Immunochromatographic Card Test (ICT) for circulating antigen, has shown that LF is more endemic than was previously thought; this exercise showed that in fact LF is present in the entire country. These new maps clearly show that LF is highly endemic along the coastal belt and decreases as one goes further inland. This has created not only a new understanding of the epidemiology of LF in Tanzania but also a need to define how this infection can be controlled countrywide, a much greater challenge than controlling focal areas of the disease.

Initiation of the LF Elimination Programme in Tanzania

The turning point in LF control worldwide was precipitated by the World Health Assembly Resolution that stressed the elimination of LF as a public health problem by the year 2025. Following on from this there was the declaration by Smith Kline and Beecham to provide albendazole for the treatment of LF and an additional declaration by Merck to expand its donation of ivermectin (Mectizan®) to cover the treatment of LF for as long as it took to eliminate LF as a public health problem. Following the announcement of the GPELF, the Tanzanian Authorities quickly joined the effort and began planning for a National LF Elimination Programme. The planning embraced the goals of the GPELF and discussed the best way to achieve these in the Tanzanian context. The goals of the Tanzanian Programme are shown in Figure 1.

The Strategic Plan for Tanzania developed by local experts and partners focused on mapping the distribution of LF in the country, mobilizing the community to be aware of LF as a public health problem, and the all-important step of the community distribution of ivermectin (Mectizan®) and albendazole. A national task force was set up in the Ministry of Health, a director of the National Programme appointed, and a

Central Programme Office developed as an independent entity within the National Institute of Medical for Research. The major activity for the LF Programme in these early years was the rapid epidemiological mapping of the country to determine those Regions and Districts that fall under the GPELF criteria for implementation; namely that >1% of the population in a District (known as the Implementation Unit) is positive for LF circulating antigen.

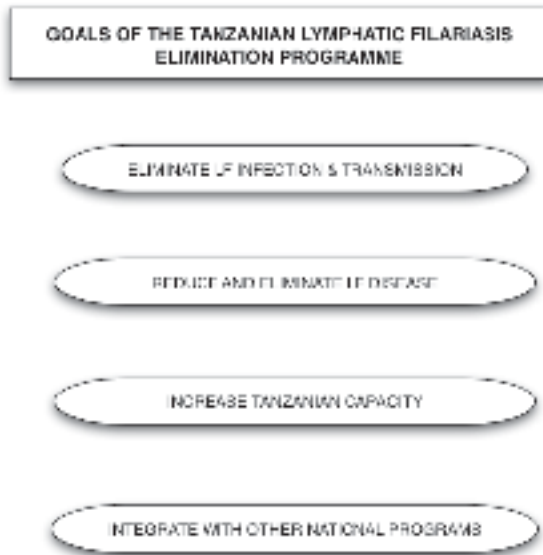


Figure 1. The goals of the Tanzanian LF Elimination Programme.

The Programme chose to focus its first year of MDA implementation in the single island district of Mafia; this decision was driven by the need to define the optimal approach to the various components of MDA, and by financial constraints. In 2000 - after a number of base line studies that included KAP interviews, studies on the disease prevalence, the ICT prevalence in sentinel sites, and the testing of educational material - the first official mass drug administration (MDA) began, after a celebratory launch event. The LF Programme was launched officially on Mafia Island on October 1st 2000 by the then Permanent Secretary in the Ministry of Health; that year 38,000 inhabitants of Mafia received the Programme's

ivermectin (Mectizan®) and albendazole. The knowledge gained from this first effort in Mafia formed the basis of the “LF Programme Package” that has been used for all the MDA activities as the National Programme expanded each year over the last seven years. The package comprised of the following major components: training, social mobilization and advocacy and implementation.

In the countrywide plan set by the National Taskforce it was agreed that the MDA should be scaled up on a regional basis - as and when finance was available. During the first year of the Programme major funding support was acquired from the Bill and Melinda Gates Foundation, and this allowed the expansion to encompass Pwani Region in the second year of the Programme (2001). Further support was given from DFID (U.K.) that allowed for the inclusion of Mtwara Region (in 2002) and Lindi Region (in 2003). Perhaps the most significant financial supporter has been the Tanzanian Ministry of Health itself; their direct financial support allowed expansion to Tanga Region (in 2004) and Dar es Salaam (in 2005), and the overall achievement of reaching a total population of 7.4 million people. Presently the Ministry of Health is the major supporter of all the various MDA activities in the LF Programme.

Evaluation of the MDA activities in its many facets is also a vital aspect of the Programme and has been, at times, difficult to carry out due to financial restraints. It has been important to carry out as wide an assessment profile as is possible, and to acquire a range of data from the obvious, such as the basic parasitological indicators, to the less obvious clinical parameters, such as the presence of new cases and improvements in the psychological status of LF patients.

Key factors in programme implementation

The experience of the past seven years has identified a number of factors that were crucial to the Programme’s successful implementation. One of the most important issues that are extremely important in promoting implementation was “political will”. The Tanzania local government system is highly decentralized and it was important to ensure ownership at the various levels and to ensure that all the different groups understood the Programme and would design “local” approaches to ensuring the MDA was functional. Initially political will was gained by national Programme officers personally visiting the personnel in the Regions. However, recent

years political support has been achieved by holding annual planning meetings. These planning meetings bring together the main regional and district officials – i.e. the District Commissioners, District Treasurers, District Development Directors - with those of the medical system – i.e. the District Medical Officer and their staff. Other personnel involved in the planning meetings are from the Regional level, and include the Regional Commissioner, Regional Administrative Secretary and the Regional Medical Officer.

Thus the approach to management of the implementation of the Programme has moved from simply an activity run by the health sector (where all the activities were carried out by the District Health Management Team) to a more broad-based development approach focused on a multidisciplinary approach to running the activities. The main output from these meetings include an annual implementation plan for all activities related to LF, with a clear indication of the district contribution to each of the Programme components.

Effective social mobilization and advocacy was also a key component to effective MDA. This took on a variety of forms and methods as knowledge was gained as to the most effective methods and understanding of specific issues in different geographic areas. Radio spots, television segments, posters and newspaper articles were all used to inform of upcoming events. Locally, at the time of the actual distribution of the drugs (or assessment activities), mobile megaphones, film shows, poetry and musical groups, were all important mobilization activities. It was essential that the key messages were understood, and delivered in the local context.

These key factors that have emerged from the initial surveys and from the experience of seven years of MDA implementation can be translated into a set of “Programme Principles”. These are shown in Figure 2. These Principles can be grouped as a) those associated with communication and advocacy, b) those associated with the Programme’s specific knowledge of the problem being addressed and any changes as the Programme develops, and c) the necessary supportive activities; in addition, there are d) general management approaches which are important to keep in mind.

Tanzanian successes

There have been a number of successes in the programme over the last seven years. The importance of involving the political establishment in the early stages of planning has promoted success in the Programme; the

successful realization of this factor was important to planning and implementation.

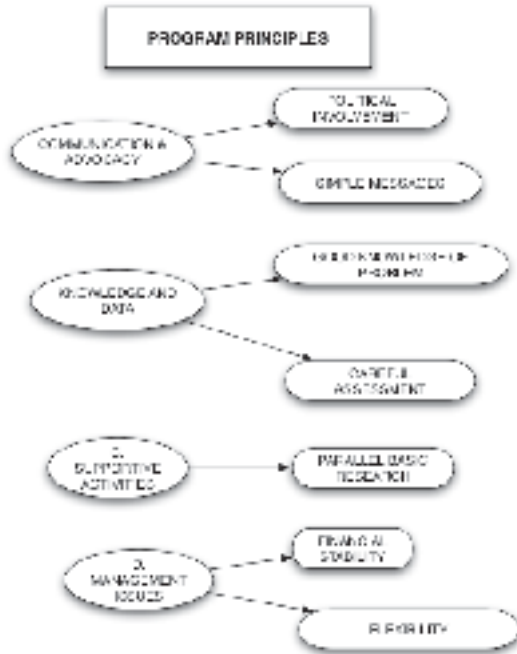


Figure 2. Principles of the Tanzanian LF Elimination Programme.

More obvious successes include the reduction in microfilaremia from 40-50% to around 1% after 6 years of the Programme, the universal improvement in the clinical condition of patients suffering from elephantiasis, and the performing of over 2000 hydrocelectomies. During the time that the Programme has been in place over 1200 medical personnel have been trained in LF and this has helped to raise the awareness of the disease and the presence of a Programme that will alleviate the clinical manifestations and break transmission in millions of people. Another success has been the training of over 15,000 village health workers who are the frontline Programme implementers.

An unexpected success is the improvement in the patients with lymphoedema, in particular the reduction and in many cases the elimination of acute attacks in these individuals. In fact, a number of early stage lymphedema patients have returned almost completely to normal. This has instilled great confidence in the Programme from both District residents and from the medical staff who implement the activities.

There have been differences in effectiveness, measured in terms of drug coverage, between different Regions and Districts. The reasons for these regional differences include the infrastructural and geographic differences between Regions – some districts are vast in area and residents are extremely dispersed making it difficult to distribute drugs. Differences in the abilities of local administrators also have an effect on the efficiency of the MDA programme and its assessment. In addition, a high level of personal commitment from the local administrators and health personnel to the Programme is important for the optimal running of the MDA activities.

An important aspect of an active MDA programme is that, as a whole, it has beneficial ancillary effects on a number of components of the health system. For example, that it encourages collaboration between the different arms of the health system and the successes that are seen in the positive responses from the residents promotes trust in the national health system. The contribution of the MDA programme to the improvements of the lives of many, many patients, through hydrocelectomy and through the effects of the hygiene and drug administration programme, has been very instrumental both in encouraging good coverage and in boosting the reputation of the national health system.

The government contribution to the Programme is a very significant factor in its success. Initially, donor funds were the predominant source of funding. The government funding however has increased steadily from 16,000 USD in 2001 to 400,000 USD in 2007. This coupled with contributions from the districts through their comprehensive health plans has been an important step towards building the sustainability of the Programme.

New opportunities: Neglected Tropical Diseases programmes

In recent years there has been a move to encourage joint implementation of diseases that are targeted for preventive chemotherapy. These diseases as defined by WHO (2006) are LF, onchocerciasis, schistosomiasis, soil transmitted helminths and trachoma. The aim of this is to enhance delivery

of interventions whilst decreasing cost. It also looks to improving efficiency as the same village health workers deliver all interventions. This has led to the Tanzanian LF Elimination Programme carrying out co-implementation with the onchocerciasis programme in the regions of Tanga and Morogoro. Recently, Tanzania has developed a strategy to integrate the delivery of drugs for LF, trachoma, schistosomiasis, onchocerciasis and soil transmitted helminths. It is envisaged that co-implementation will be the future delivery strategy for the LF Elimination Programme.

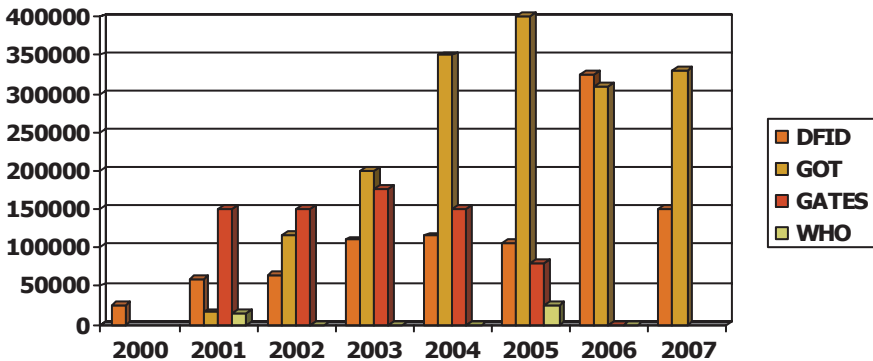


Figure 3. Annual financial contributions to the Tanzanian LF Elimination Programme from different sources in USD. DFID = Department for International Development (U.K.); GOT = Government of Tanzania; GATES = Bill and Melinda Gates Foundation; WHO = World Health Organization.

Comment

Many of the lessons learnt and principles defined over the past seven years of implementing a national LF Elimination Programme in Tanzania will, in all likelihood, be applicable to many other countries in Africa and beyond. Although each country will have their own specific characteristics and needs to observe as they develop and enact their new Programmes there are likely to be common themes in them all. These will include, amongst others, understanding and communication at the village level, attention to patient's needs, financial stability and inventive ways of communicating simple strong messages to all levels of the Programme and the public.

Another important factor is good leadership, which we have noted to be the key distinguishing factor between district programmes that perform extremely well, and those that under-perform.

The successes achieved in Tanzania have not come easily and without at times a degree of disappointment and temporary panic. Nevertheless the possibility of achieving the overall goals of the Programme, together with the encouragement given by the political and public acceptance, and by the visible improvements in disease, have all provided energy to the Programme. The ultimate goal of elimination of LF still remains a great challenge but for Tanzania, this target is now clearly closer.

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Chapter 7



LF bibliography

Lymphatic filariasis bibliography for Eastern and Southern Africa

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Abstract

A search was made for scientific publications on lymphatic filariasis in Eastern and Southern Africa. 279 publications, covering the period from 1901 to 2007, were identified and are listed. The publications report on studies from eleven endemic countries (Angola, Comoros, Ethiopia, Kenya, Malawi, Madagascar, Mozambique, Tanzania, Uganda, Zambia, Zimbabwe). No publications were identified from three suspected endemic countries (Eritrea, Burundi, Rwanda), or from the four countries located in the most southern part of the region (Lesotho, Namibia, South Africa, Namibia).

Introduction

Since the beginning of last century, numerous important scientific investigations on lymphatic filariasis (LF) have been undertaken in Eastern and Southern Africa. The peer reviewed publications originating from this research are listed in the following bibliography. The countries covered are those which during the Bagamoyo LF Workshop in November 2007 were documented to be endemic (Angola, Comoros, Ethiopia, Kenya, Malawi, Madagascar, Mozambique, Tanzania, Uganda, Zambia, Zimbabwe) or suspected to be endemic (Eritrea, Burundi, Rwanda) for LF. The remaining countries in the region (Lesotho, Namibia, Republic of South Africa, Swaziland) have never reported LF, and it is likely that the environment is unfavourable for transmission and that LF is not a public health problem.

The articles are divided into two groups, based on the year of publication. The first group covers the articles from 1901, when LF was

first reported from this part of Africa (Cook, 1901; Daniels, 1901), until 1974. Much of the knowledge from this historical period was summarized in the authoritative reviews by Sasa (1976) and Hawking (1977). The second group covers the articles from 1975 until the present day. These articles generally report on work carried out in present-day institutions and by researchers many of which are still active. The articles thus also provide an overview of the current institutional and individual resource base on LF in this part of Africa.

The search for articles from the early first period took a starting point in the two mentioned reviews by Manabu Sasa and Frank Hawking. The reference lists in the articles referred to by these two authors were scrutinized for other references, as were the articles collected for preparation of a review on the global prevalence and distribution of LF (Michael et al., 1996). PubMed searches were moreover carried out with the terms ‘Filariasis’ or ‘Elephantiasis’ pair-wise combined with the individual countries in the region.

The search for articles from the second period was based on our private collection of research articles compiled during many years of research on LF in the region. The reference lists in these articles were examined for other relevant references, and this was finally supplemented with PubMed searches with the terms ‘Filariasis’ or ‘Elephantiasis’ pair-wise combined with the individual countries in the region.

To provide a systematic overview, the endemic countries in the region from which articles were identified have been divided into four groups based on environmental and geographical characteristics, as follows:

- Ethiopia
- Kenya, Tanzania & Uganda
- Angola, Malawi, Mozambique, Zambia & Zimbabwe
- Comoros & Madagascar

Results

A summary of the number of articles on LF recorded during the early and late search period in each of the surveyed countries is shown in Table 1. It is noteworthy that the highest number of articles have emerged from studies in Tanzania (49.5%) followed by studies in Kenya (19.7%) and Madagascar (12.5%). No articles were found from Eritrea, Burundi or

Rwanda. The combined publication activity for the region based on LF articles per year is shown in Figure 1. The peak seen during 1955-1964 is mainly due to the work by Peter Jordan in Tanzania, whereas that seen during 1975-1979 is mainly due to the work of the research teams of Dirk J. Wijers and John E. McMahon in Kenya and Tanzania, respectively. This period was followed by years of less productivity. However, the period since 1995 shows the highest publication activity ever for the region, due to the combined efforts of many dedicated researchers. The publication activity by country for the overall period is illustrated in Figure 2.

Table 1. Number of publications by country and period.

Country*	Number of publications in period	
	1901-1974	1975-2007
Angola	5 ^o	0
Comoros	7	10 [#]
Ethiopia	4	5
Kenya	13	42 [§]
Malawi	3 [□]	3
Madagascar	26	9 [#]
Mozambique	3 ^o	1
Tanzania	51	87 [§]
Uganda	3	3
Zambia	3 [□]	5
Zimbabwe	3	2
Total	118	161

*) No publications from Eritrea, Burundi or Rwanda found.
 o) Two of these are included both under Angola and Mozambique; □) One of these is included both under Malawi and Zambia; #) One of these is included both under Madagascar and Comoros; §) Five of these are included both under Kenya and Tanzania

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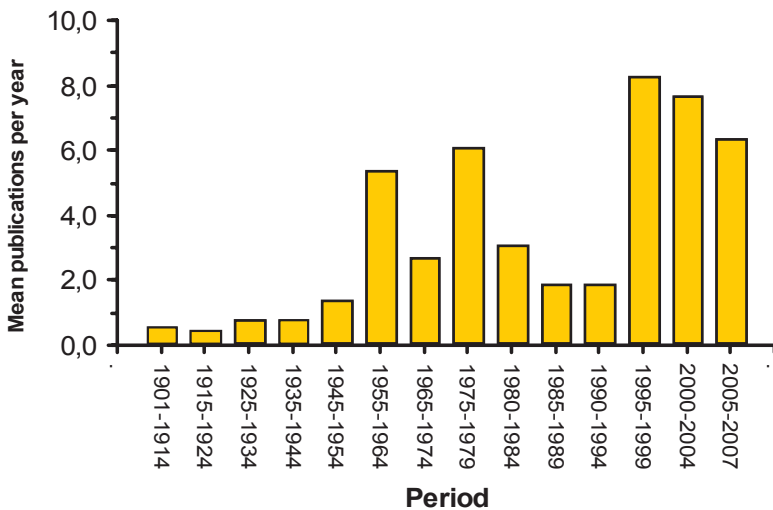


Figure 1. Lymphatic filariasis research activity in Eastern and Southern Africa, expressed as mean number of scientific publications per year for the periods.

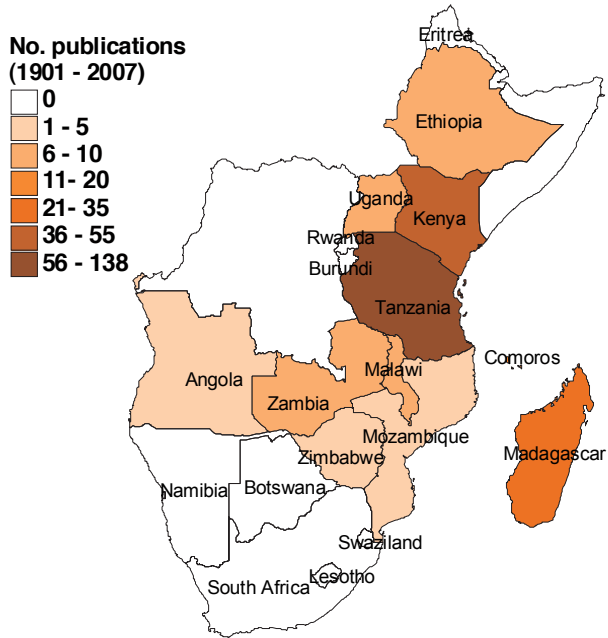


Figure 2. Map showing the number of publications on LF by country in Eastern and Southern Africa during the period 1901-2007.

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Appendix



LF workshop abstracts

Abstracts from the workshop on ‘Lymphatic filariasis research and control in Eastern and Southern Africa’ held in Bagamoyo, Tanzania, 13-16 November 2007

**ABSTRACT No. 1
Keynote Lecture**

Lymphatic filariasis elimination programmes in Eastern and Southern Africa: The AFRO perspective

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Implementation of the global programme for elimination of lymphatic filariasis as a public health problem in the WHO Africa Region started in 2000. Tanzania, among the nine (9) LF endemic countries of the Eastern and Southern Africa sub-region was among the first four countries to conduct mass drug administration in the same year. Programme implementation commences with identification of the population at risk and determination of the disease distribution. This mapping exercise has now been carried out in all the 9 endemic countries of the sub-region, although it remains incomplete in Mozambique and Zambia and mapping results still require validation in Zimbabwe as the pattern obtained from results of the national surveys is questionable. The distribution pattern shows high disease endemicity along the coastal areas, which is reducing and absent when moving towards the non-endemic countries in the extreme south of the continent. Cumulatively, five of the nine countries have progressed to mass drug administration of which only Comoros has reached national scale. The number of rounds conducted in these countries is as follows: Tanzania (6 rounds since 2000), Comoros (4 rounds since 2001), Kenya (3 rounds since 2002), Uganda (3 rounds since 2002), Madagascar (2 rounds since

2005). The total number treated in mass drug administration in these countries to date is approximately 8.2 million, this forms 11.7% of the total identified population at risk (n = 69.8 million) in this sub-region. Cumulatively, 28.7 million treatments have been given in the five programmes since 2000. Constrained financial resources to the programme continue to be a major challenge hindering scaling up of programmes. This has resulted in some countries in failure to sustain annual rounds of MDA in communities where these were started, notably in Comoros, Kenya and Uganda. Impact of mass drug administration has shown to lead to the target of interrupting transmission as demonstrated in the Zanzibar and Comoros programmes. There is still a challenge in determination of end-points for mass drug administration.

ABSTRACT No. 2
Keynote Lecture

**Integration of interventions for disease prevention and control:
A strategic approach to the intensified control
of Neglected Tropical Diseases (NTDs)**

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Integration is the creation of linkages within existing programmes for the purpose of improving their performance. The resources available to each individual programme are pooled and used to facilitate a multidisease prevention and control programme. This approach should accelerate the achievement of the overall goal of improving the health status of the population to a level that enables them to lead a productive life. However, it is important that the goals and objectives of the individual programmes do not lose identity as a result of integration. The comparative advantages of the individual programmes should be used to promote complementarity and maximum benefit. The integrated approach to disease prevention and control should therefore, seek, at the macro level, to promote the comparative advantages of the individual programmes and create mechanisms for maximum complementarities. In the case of NTDs, it is necessary to develop packages for their prevention and control using the integrated approach. One such package could be for programmes that use wide-scale chemotherapy as the main strategy for disease prevention, control and/or elimination. Linkages of this package with other wide-scale interventions, such as immunization, should then be explored and harnessed. This will, inevitably result in several benefits for the individual programmes, the health workers involved and the beneficiary communities.

**ABSTRACT No 3
Communication****The current status of lymphatic filariasis and its control in Kenya**

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Nationwide mapping of lymphatic filariasis (LF) in Kenya was completed in 2005; defining distribution of the disease to be restricted to the Coastal region of the country. In the defined LF endemic region all the approximately 3 million people were at risk of infection, with estimated one million already afflicted by the disease. Currently LF control in Kenya is based on the Global Programme to Eliminate Lymphatic filariasis (GPELF), which targets interruption of transmission through mass drug administration (MDA) to all endemic communities once annually, repeated for 4–5 years. The first MDA in Kenya was implemented in 2002 with initial support from the Global Alliance to Eliminate LF (GAELF) through WHO. This covered only one implementation unit (District) with a population of 590,000. The second MDA of 2003 included 2 addition IUs bringing the total population covered to about 1.4 million (50% of total population at risk). The 2004 MDA was postponed to early 2005 and covered the same IUs as in 2003. No MDA was implemented in 2006 due to unavailability of funds. The first MDA (2002) covered 81% of the population in Kilifi District. The second MDA (2003) covered 75%, 85% and 77% of the population in Kilifi, Kwale and Malindi respectively; the third MDA (2005) covered 72%, 71% and 76% of the population in Kilifi, Kwale and Malindi respectively. The apparent impact of MDA and the problems in sustainability of the elimination programme in Kenya's context will be discussed.

**ABSTRACT No 4
Communication****Establishment of a mass drug administration programme for lymphatic filariasis in Tanzania and assessment of its success: Case study of Mafia Archipelago**

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Mafia Island was selected as a pilot area for establishing a Mass Drug Administration (MDA) programme for eliminating Lymphatic Filariasis (LF) in Tanzania. A strategy of ivermectin and albendazole combination treatment was used. Different steps were taken before implementation of the MDA. Consultations were held with leaders at different levels as well as with the communities, on issues to be followed to reach a successful, acceptable, replicable and sustainable programme. Studies on knowledge and beliefs in the communities regarding the cause of LF disease and transmission were carried out. Patients suffering from clinical manifestations of LF were trained on how to take care of the manifestations, and patients with hydrocoele were educated and convinced to go to the district hospital for hydrocelectomy. Health officials, politicians and village health workers took a leading role in educating communities on the disease, and on the importance of participating in the MDA and taking the drugs. The communities accepted the programme and participated in the MDA. The treatment coverage in year one was 73%. It dropped in years two and three, but following community mobilization and some change in strategies, it increased to 79% and 65% in years four and five, respectively. Monitoring and evaluation was an important component of the programme. This was done after three and five rounds of treatments. The effect of the MDA's was clearly seen. People with clinical manifestations of LF reported improvements of skin conditions and reduction in frequency of filarial attacks. Antigen levels and microfilaria loads decreased considerably, but there was still a substantial level of infection after five rounds of MDA. More than five rounds of MDA are therefore necessary to eliminate LF from high endemic areas. As the initial phase of the programme was successful in Mafia, it was decided to start similar MDA activities in the other five districts of Coastal Region in the year 2001, and later on in all the regions of the coastal belt of Tanzania (Mtwara, Lindi, Tanga and Dar es Salaam). Despite of many constraints met (especially related to finances and infrastructure), the programme is determined to move on and to expand activities to cover all endemic areas.

ABSTRACT No 5 Communication

Mapping the geographical distribution of lymphatic filariasis in Mozambique

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Lymphatic filariasis (LF) was first documented in Mozambique in the 1950's. Nevertheless, information about LF and its distribution in the country long remained scanty. Only a few surveys were carried out in the northern part of the country based on clinical manifestations and presence of microfilariae in the blood. In order to obtain relevant information for mapping the LF distribution in Mozambique, a study was carried out in all districts from February 2005 to July 2006. An administrative post was selected randomly in each district. At each site 50 or 100 individuals of both sexes above 15 years of age, living in a 25 km radius from the selected site for at least 10 years, and who had not left the place for more than 6 months in the last 10 years, were included in the study on a voluntary basis. Blood samples were collected and tested by using Now[®] ICT Filariasis, a rapid test for detection of antigen of *Wuchereria bancrofti*. In districts with a prevalence of less than 2%, a second site was selected and tested. Longitude and latitude were also collected by using GPS at each investigated site. Validation of results was done by carrying out night surveys in 6 districts: 2 highly endemic, 2 with moderate endemicity and 2 with low endemicity by using ICT in addition to examination for microfilariae by using Giemsa stain technique. A total of 11.150 individuals in 128 districts were tested in the first phase of the survey and 413 in 5 districts were tested for validation of the results. 103 of the 139 surveyed districts (75%) had above 1% individuals infected with *W. bancrofti*, and were therefore considered endemic for LF. A high prevalence was registered in the northern coastal provinces of the country: Nampula, Cabo Delgado and Zambézia. A relatively high prevalence was also registered along the Zambezi River.

ABSTRACT No 6 Communication

The current status of lymphatic filariasis and its control in Zanzibar

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The Zanzibar campaign against LF started in 2001 following the Global initiative. The Ministry of Health and Social Welfare – Programme for Elimination of Lymphatic Filariasis (MOHSW–PELF) has been very successful in conducting LF Mass Drug Administration (MDA) campaigns, with the objective of interrupting transmission, for six years using a combination of ivermectin and albendazole. A house to house drug distribution strategy and a very intensive social mobilization campaign resulted into attaining the highest drug distribution coverage in the

country. In December 2006 the sixth round of MDA was carried out, with praziquantel as an additional drug to the schistosomiasis endemic areas in the country. The decision to include praziquantel was taken after a successful triple therapy pilot study, using ivermectin, albendazole and praziquantel, conducted in two schistosomiasis endemic sites, which monitored the adverse effects associated with co-administration of the three drugs. Several surveys conducted in both sentinel sites and spot check sites to assess the impact of MDAs showed a remarkable success in the reduction of the prevalence of LF. In the Kizimkazi sentinel site before the first MDA, the mf prevalence was 17.8% and mf density 356 mf/ml. In the Kwahani sentinel site, the mf prevalence before first MDA was 7.2% and mf density 323 mf/ml. In surveys done post fourth MDA round in Kizimkazi the mf prevalence had decreased to 1.0% while in Kwahani it was zero. However, in surveys done ten months after the fifth MDA round to determine the mf prevalence, the result was zero in both Kizimkazi and Kwahani. The programme is planning to carry out a study using different sensitive diagnostic tools, the results of which will be used to decide whether to continue with more rounds of MDAs or to stop. With the morbidity control which is another main objective of LF programme, 625 LF lymphoedema patients have received trainings in Home Based Care lymphoedema management and a decline in frequency of ADL as well as improvements of the general condition of most patients are reported.

ABSTRACT No 7 Communication

Overview of filarial infections in Zimbabwe

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Information on the general distribution of filarial infections in Zimbabwe is scanty, outdated and was initially obtained largely from incidental findings in blood films collected in the course of routine malaria surveys. In one of the surveys conducted in the Zambezi Valley in 1958 the prevalence of *Wuchereria bancrofti* was 34.6 % and that of *Mansomella perstans* was 50 % whilst the prevalence for mixed infections was 15.3%. None of these cases showed any elephantoid reaction although 3 of the cases had suffered for long periods with genito-urinary pathology. A similar survey in 1971 at Kanyemba in the Zambezi Valley recorded a prevalence of *W. bancrofti* of 17 %. Clinical symptoms observed among the study subjects were hydroceles and elephantiasis. A detailed survey on the distribution of

M. perstans indicated that the parasite was restricted to the basin of the Zambezi River system in forest and semi-forest areas of the middleveld where surface water was plentiful. Its occurrence was less frequent in the lowveld and was absent in the highveld. Many of the isolated cases recorded around Zimbabwe could be due to imported labour. Studies conducted in two districts showed an overall prevalence of 61 % (Lomagundi district) and 20 % (Lupane district). The majority of cases of *M. perstans* were found to be symptomless. Where symptoms occurred the most frequent complaints were extreme tiredness, pains in the joints and neurological symptoms. It was assumed that in only 20 % of Zimbabwe can the population be said to be at risk. The insect vector for *M. perstans* was presumed to be a species of the *Culicoides* of which many species occurred in Zimbabwe but this was yet to be demonstrated. Further research should be done to determine the actual vector species responsible for *M. perstans* and *W. bancrofti* transmission. More information need to be collected to map the distribution of all filarial species currently present in Zimbabwe and ascertain the degree of severity of the disease in the population at risk.

ABSTRACT No 8 Communicaiton

Lymphatic filariasis in Ethiopia

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The first indication of lymphatic filariasis (LF) in Ethiopia was in the 1930s, when Luder reported the presence of *W. bancrofti* microfilariae in a urine sample from a patient. However, the patient was residing in an area endemic for onchocerciasis, thus diminishing the reliability of the report. There were several other reports by different investigators, such as Schaller and Kuls, about various forms of elephantiasis (vulval, scrotal, breast, etc.) in the southwestern parts of Ethiopia, but these were not substantiated with appropriate parasitological evidences and most cases probably had a non-filarial cause (podoconiosis). The occurrence of LF in Gambella, western Ethiopia, was first described in the early seventies by McConnell and Schmidt, and was later confirmed by McConnell et al. Most recently (1995), two Ethiopian researchers, Jemaneh and Kebede, came up with additional evidence of LF in the same region. The lack of data on the distribution and occurrence of LF has necessitated nationwide survey and mapping activity. As a result, the Federal Ministry of Health of Ethiopia in collaboration with WHO, The

Carter Center and the Medical Faculty of Addis Ababa University has finalized preparations to conduct a national survey for LF. In this activity, which is expected to be launched very soon, four major areas in western and southwestern Ethiopia are targeted for initial mapping. The survey areas include Gambella, Benishangul-Gumuz, Western lowlands of Oromia, southwestern localities of the SNNPR, and North Gondar Zone of Amhara Region. These localities are either within or proximate to previously reported LF endemic foci. With a successful implementation, it is expected that data will be available for use as a benchmark for the launching of a National Lymphatic Filariasis Elimination Program. Moreover, this national survey becomes very timely due to the massive scale up of insecticide treated bednets (20 million LLINs) being distributed to all malaria endemic and at risk villages (free of charge) all over the country. The rapid mapping activities will involve cross-sectional surveillance by active case detection of LF and detection of filarial antigenaemia (with ICT card tests). The currently recommended mapping method, i.e., a combination of administrative unit sampling with elements of the RAGFIL (Rapid Assessment of the Geographical Distribution of Bancroftian Filariasis) approach, will be used for selection of survey sites. This method will quickly identify the priority areas for MDA. The proposed work also includes a survey of the clinical features of the disease in Ethiopia, where lymphoedema and elephantiasis can also be caused by podoconiosis, thought to be related to certain soil types.

ABSTRACT No 9 Communication

Lymphatic filariasis mapping in Zambia

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Lymphatic filariasis (LF) is presumed to be rare in Zambia as very few isolated cases have been reported. In response to the World Health Assembly decision in 1997 to eliminate LF as a public health problem, Zambia undertook a mapping exercise from 2003 to 2005 in order to determine the prevalence and geographical distribution of the disease in the country. The surveys were conducted by determining *Wuchereria bancrofti* circulating filarial antigen (CFA) by the use of immunochromatographic test cards (ICT, Binax Inc., USA). Fourteen (14) districts

in eight provinces of Zambia were selected as the implementation units (IU) for the LF surveys. A total of 4177 volunteers above the age of 15 years participated in the survey. Three thousand nine hundred and fifty four (3954) ICT test cards produced valid results. Of these, 444 (11.23 %) from a total of 11 districts (in 7 provinces) were positive for LF circulating filarial antigen. Kalabo District in Western Province recorded ICT prevalences of 50.62 to 53.95 % and Luangwa District in Lusaka Province recorded prevalences of 23.75 to 40.47%. The results indicate that LF is indeed endemic in Zambia and may be an important public health problem that needs more attention than it is presently receiving.

ABSTRACT No 10
Communication

Lymphatic filariasis mapping in Malawi

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Mapping the distribution of lymphatic filariasis (LF) is a prerequisite for planning national elimination programmes. Results from a nation wide mapping survey for LF in Malawi are presented. Thirty-five villages were sampled from 23 districts excluding three districts (Karonga, Chikwawa and Nsanje) that had already been mapped and Likoma, an Island, where access was not possible during the time frame of the survey. Antigenaemia prevalence (based on ICT cards) ranged from 0 to 35.9 %. Villages from the western side of the country and distant from the lake tended to be of lower prevalence. The exception was a village in Mchinji district on the Malawi-Zambia border where a prevalence of 18.2 % was found. In contrast, villages from lake shore districts [Salima, Mangochi, Balaka and Ntcheu (Bwanje valley)] and Phalombe had prevalences of over 20 %. A national map is developed which incorporates data from surveys in Karonga, Chikwawa and Nsanje districts, carried out in 2000. There is a marked decline in prevalence with increasing altitude. Further analysis revealed a strong negative correlation ($R^2 = 0.7$; $p < 0.001$) between altitude and prevalence. These results suggest that the lake shore, Phalombe plain and the lower Shire valley will be priority areas for the Malawi LF elimination programme. Implications of these findings as regards implementing a national LF elimination programme in Malawi are discussed.

ABSTRACT No 11
Keynote Lecture

Diagnostic techniques for lymphatic filariasis and their role in programmes for elimination of lymphatic filariasis in Eastern and Southern Africa

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Lymphatic filariasis is endemic in more than 80 tropical and subtropical countries of which several are within the Eastern and Southern Africa Region. For a long time, LF remained uncontrolled in most endemic areas due to lack of treatment regimens. Recent advances in chemotherapeutic strategies have led to the optimism that the disease can be eliminated from all areas of endemicity. The ambitious Global Programme to Eliminate Lymphatic Filariasis (GPELF) is primarily based on mass drug administration (MDA) of annual rounds of antifilarial treatment. Diagnostic techniques are very crucial to the success of GPELF since they are required for identification of sites for MDA, measurement of the impact of MDA, determining endpoints for MDA and monitoring resurgence of transmission post MDA. Available diagnostic techniques for filariasis and their role in the regional GPELF are discussed.

ABSTRACT No 12 Communication

The current status of lymphatic filariasis in Uganda and its control

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The first epidemiological surveys for lymphatic filariasis (LF) in Uganda were performed in communities in the north and east of the country (Onapa et al., 2001). The surveys reported overall microfilarial prevalences of 9-20%, overall circulating filarial antigen (CFA) prevalences of 18-30%, hydrocele prevalences in adult males of 7-28%, and limb elephantiasis prevalences in adults of 4-9%. The main vectors were observed to be *An. gambiae sl* and *An. funestus*. These surveys were followed by countrywide mapping of LF (Onapa et al., 2005). Among 31 identified endemic sites CFA rates in primary school children ranged from 0.4% to over 31%, while in some of the areas rates in adults were over 50%. Mapping showed marked

geographical variation in distribution, with major foci in north, east and northwestern Uganda. Most of central, southwest and western areas were found free from LF. LF was not found at altitudes above 1300m. Further analysis of mapping data showed that more than 10 million people live in areas with $\geq 1\%$ CFA prevalence. Activities directed at the elimination of LF commenced in 2002 in two districts (Lira and Katakwi) with a combined population of about 1.1 million. In 2003, there was no treatment due to insecurity. In 2004, five districts with a population of 2.5 million were covered, and in 2005, ten districts with a population of 4.9 million were covered. Hydrocelectomies are performed in all hospitals, but they are expensive and beyond the means of the ordinary rural folks. There is virtually no lymphoedema management in any health facilities. However, recently health workers and village health teams in two districts were trained in LF disability management. Uganda has embarked on integrated control of neglected tropical diseases (NTDs). Control is through the NTD Control Programme of RTI International and is funded by USAID.

ABSTRACT No 13
Communication

Consequences of exposure to *Wuchereria bancrofti* transmission in Tanzania among expatriates originating from non-endemic areas

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A study was carried out to assess the consequences of exposure to *Wuchereria bancrofti* transmission among expatriates from non-endemic areas. Consenting expatriates aged 5 years or older, originating from areas of Europe, America, Australia or Asia without transmission of *W. bancrofti*, who had lived for at least one year in areas in Tanzania endemic for *W. bancrofti* transmission, were invited to participate in the study. The recruited individuals were interviewed about history of stay and other relevant personal information, and they were immediately examined for *W. bancrofti* specific circulating filarial antigen (CFA) with the Rapid Now ICT card test. A venous blood sample was thereafter collected for further serological testing. Serum was prepared from the blood and was later analysed quantitatively for CFA (by TropBio Elisa) and specific IgG1 and IgG4 antibodies. 146 individuals were included in the study, representing a total of 1252 years of exposure to *W. bancrofti* (8.6 years in average). None of the examined individuals were positive for CFA,

neither in the ICT card tests nor in the TropBio Elisa tests. Prevalence and level of filarial specific IgG1 and IgG4 showed a non-significant increase with increasing lengths of stay in the endemic areas. The antibody results indicate that expatriates are exposed to *W. bancrofti* transmission when they live in endemic areas, but the CFA results suggest that such exposure rarely leads to the establishment of (adult worm) infection. The possible reasons will be discussed.

ABSTRACT No 14
Communication

Impact of two rounds of mass treatment with diethylcarbamazine plus albendazole on *Wuchereria bancrofti* infection, and sensitivity of ICT test, in Malindi, Kenya

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Annual single dose mass treatment of endemic populations with albendazole plus diethylcarbamazine (DEC) or ivermectin (Mectizan[®]) is recommended as the mainstay of lymphatic filariasis elimination programmes. The aim of the present study was to assess the impact of two rounds of annual mass chemotherapy with a combination of DEC and albendazole on bancroftian filariasis and to compare the performance of the immunochromatographic ICT card test with that of the Og4C3 ELISA before and after the two treatments. Two rounds of single-dose annual mass treatment with the DEC/albendazole combination were given in 2002 and 2003 to four communities under a pilot filariasis elimination project in Malindi District, Kenya. Changes in microfilaraemia and filarial antigenaemia were determined using counting chamber technique and ICT tests, respectively. The study also compared ICT test and Og4C3 ELISA in a cohort of 463 persons. The overall prevalence of microfilaraemia decreased by 65.4% (from 20.5 to 7.1%; $P < 0.001$). The overall prevalence of antigenaemia also decreased significantly by 43.5% (from 35.4 to 20.0%; $P < 0.001$). In comparison with Og4C3 ELISA, the sensitivity of the ICT test decreased by 34.0% from 89.9% at baseline to 59.3% after the two mass treatments. The results indicate high effectiveness of mass treatment using DEC/albendazole combination against *Wuchereria bancrofti* infection. However, our study shows that there is a need to identify other sensitive tests for long-term monitoring and to make critical decisions on when to stop mass treatment campaigns.

ABSTRACT No 15
Keynote Lecture**LF drug studies in East Africa – Past experience and future perspectives**Paul E. Simonsen¹ and Dan W. Meyrowitsch²

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Many studies of high quality and importance for the advancement of our understanding of lymphatic filariasis (LF) have been carried out in Eastern and Southern Africa, especially on vectors and transmission, on epidemiology of human infection and morbidity, and on drugs for treatment and control. Here, an overview of the LF drug studies carried out in this region since the late 1940's will be given. All these studies have been carried out in Tanzania and Kenya. By far the majority of studies have focused on diethylcarbamazine (DEC), and these have covered a multitude of aspects from early investigations on pharmacology and dose optimization via efficacy studies to large scale pilot control trials assessing how best to use the drug for controlling the infection in endemic communities. More recent trials have assessed the effect of ivermectin and its combination with albendazole, and a promising effect of doxycycline on the filarial parasites has moreover been documented. Research on LF drugs has thus been intense in East Africa, and the knowledge and experience gained through this research has provided a solid background for starting up control programmes based on mass drug administration programmes. Future perspectives for LF drug studies in support of ongoing control initiatives will be briefly outlined.

ABSTRACT No 16
Communication**Non-specific lymphadenopathy as an early clinical manifestation of lymphatic filariasis in school age children in Rufiji District, Tanzania**Dinah B. Gasarasi¹, R. Mpembeni² and J. Lutare³

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Lymphatic filariasis (LF) in children remains an enigma. Studies utilizing ultrasonography and antigen detection techniques have provided evidence indicating that LF in children is more common than was hitherto believed and presents with sub-clinical manifestations of lymphangiectasia and non-specific lymphadenopathy. The current study undertaken in Rufiji District was designed to assess the epidemiology of LF in school age children, with an aim to systematically describe the early clinical manifestations in this sub-population. The study population constituted of 5300 school age children aged 6–19 years. In a cross sectional morbidity survey, a standard questionnaire was administered to obtain information on social demographic characteristics of the study population and history of signs and symptoms of LF. Each individual was also assessed by clinical examination for the presence or absence of early signs and symptoms and chronic manifestations of LF. Parallel to the clinical survey blood samples were collected for the detection of *Wuchereria bancrofti* circulating antigen using ICT cards. A longitudinal surveillance was undertaken on a sub-sample of 2500 children for a period of 12 months to determine the incidence, duration and severity of ADL. The results show that the incidence of ADL and chronic clinical manifestations of LF were rare. The incidence of ADL was 11.6 per 1000 population and chronic manifestations of LF were prevalent in 1.6% of the respondents. However, multiple site lymphadenopathy was reported and established during clinical examinations. The majority of those examined (53.1%) had enlarged lymph nodes. Of these 30.7% had enlarged inguinal lymphnodes and the rest with decreasing magnitude included; cervical, femoral, axillary and epitroclear lymphnodes and a significant proportion (32%) were positive for *W. bancrofti* circulating antigen. In conclusion the results show that LF infection is common in school age children as evidenced by high levels of *W. bancrofti* circulating antigen and sub-clinical manifestations of non-specific lymphadenopathy.

ABSTRACT No 17
Communication

***Mansonella perstans* infection and LF control**

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Mansonella perstans is a human filarial parasite, which is common in many parts of Uganda and elsewhere in Africa. It is transmitted by tiny biting midges of the genus

Culicoides, and the microfilariae (mf) circulate in the blood. In many areas the distribution of *M. perstans* overlaps with that of *Wuchereria bancrofti*. From our studies on *M. perstans* epidemiology and control in Uganda we have gained some experience on possible implications of *M. perstans* infection to LF control programs and vice versa. First, on the potential for *M. perstans* to interfere with diagnosis of *W. bancrofti*: a. The morphology of mf of the two species in stained blood smears is different, but it requires well trained technicians to distinguish them. b. The counting chamber technique is often used for diagnosis of *W. bancrofti* in Eastern Africa. With this technique, *M. perstans* mf can easily be overlooked or mistaken for artefacts due to their shape and small size. c. We have tested more than 1000 *M. perstans* mf positive individuals from a *W. bancrofti* non-endemic area with ICT cards for *W. bancrofti* circulating filarial antigens. They were all test-negative, and thus *M. perstans* does not appear to cause false positive reactions in these tests. Second, on the potential for LF control to affect *M. perstans* infection: A randomized double blind study to assess the effect of ivermectin alone and in combination with albendazole showed only a very minor effect of these regimens on *M. perstans* microfilaraemia. LF control programs based on these regimens are therefore unlikely to have much effect on *M. perstans* infections.

ABSTRACT No 18 Communication

Clinical aspects of lymphatic filariasis and its treatment: any news?

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During the period 1970 to approx. 2003 much research was undertaken providing knowledge on important aspects of immunology, pathogenesis of lymphatic filariasis (LF) and treatment options for the disease affected populations. The use of antigen tests, in stead of parasitological examinations for microfilariae, have in recent studies shown that younger age groups, than previously recorded, are infected and may suffer subtle early pathology as visualized by lymphoscintigraphy. The importance of these early pathological changes for later development of symptomatic disease is not really known, but the findings suggest that early intervention with a macrofilaricidal drug and or infection prevention (e.g. bednets) could be important for prevention of symptomatic disease in later life. As it seems that children get infected at a very young age (although rarely having microfilarial in their blood) the role of interaction (first exposure) between various other helminths might play a role for the pathogenesis. Unfortunately there have

been no advances in developing an effective anti-macrofilaricidal drug and a vaccine was never a real option. Studies on interactions between LF and other helminths and other pathogens e.g. HIV are few and not yet conclusive. Clinical research results are also becoming rare. Control of LF relies on keeping microfilarial levels low in the hope that transmission may be interrupted. Meanwhile there is still a need for clinical and operational research in management of the patients who suffer from hydrocele and lymphoedema as well as acute manifestations of LF.

ABSTRACT No 19
Communication

Filariose lymphatique en l'Union des Comores

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L'Union des Comores est un Archipel de 4 îles (Ngazidja, Ndzuwani, Moili, et Maore), située à l'entrée Nord du canal de Mozambique, à mi - chemin entre la côte Est de l'Afrique et le Nord-Ouest de Madagascar. 2236 km² répartie comme suit: Ngazidja: 1.148 km², Ndzuwani: 424 km², Maoré: 375 km² et Moili: 290 km². La quatrième île Maoré est encore sous administration française. L'élimination de la filariose lymphatique en tant que problème de santé publique a démarrée en 2001 avec une prévalence de 4,3 % mise en évidence, par le professeur Karam de l'OMS avec la technique de la recherche d'anticorps circulant (ICT). Le processus d'élimination a permis de réaliser quatre campagnes de traitement de masse (TDM). Le 4^{ème} campagne a démarré avec 0,24 % de prévalence par technique de GE en 2007. Les données rapportés ont défini également une couverture thérapeutique de 78.4 %. Quant à l'invalidité, une portion importante de la force vive du développement, les femmes, les hommes et les enfants sont touchés par l'éléphantiasis et l'hydrocèle connus respectivement sous les noms de Trende et Pumbu. Plus de 267 cas d'hydrocèles ont été traités par chirurgie de 2005–2007 et les crises liées aux souffrances des inflammations d'éléphantiasis sont soulagés par des soins médicaux traditionnels. La campagne 2007 a connu le meilleur score. Elle a couvert 78.4 % soit 373827 personnes sur 498986 éligibles. La couverture étant disproportionnelle, elle varie de 59,4 % à 91 % dans les unités d'exécution. Les 17 unités d'exécution où opère le système de santé sont tous classées endémiques. Le TDM y a été effectif et atteint une couverture géographique de 100 %. La non réalisation de la couverture par sondage et la recherche des anticorps circulant par ICT, deux indicateurs d'appréciation du statut épidémiologique actuel constituent

les faiblesses du programme au titre de la 4^{ème} campagne TDM 2007. En guise de gain au processus, le pays poursuit avec succès le droit chemin vers l'élimination de la FL d'ici 2008 avec l'appui technique et financier de l'OMS dans la coalition mondiale.

ABSTRACT No 20
Communication

Current status of the programme to eliminate lymphatic filariasis in Madagascar

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As a lymphatic filariasis endemic country, Madagascar is committed to implement the World Health Assembly resolution 50.29. Mapping of the entire country was completed in 2004: 98 out of the total of 111 districts were found to be endemic; with an estimated at-risk population of 15.9 million. The overall prevalence was 8.91 % (range 0 % to 58 %). The first round of MDA (with DEC + albendazole) considered as a pilot phase started in December 2005 in 3 IUs. The second round conducted in February 2007, covered 13 IUs and the reported coverage was 77.18 %. The drug distribution strategies were door-to-door and booth distribution. Community commitment for MDA was observed following a strong social mobilization through aggressive awareness campaigns. Eight sentinel sites were identified to ensure close monitoring of evaluation indicators. Five disability prevention and control projects based on community approaches through village empowerment are undertaken by NGOs in collaboration with the MoH. In the framework of "NTD Initiative" promotion, a plan to integrate PELF activities with other programmes has been initiated since early 2007. PELF financial and technical supports were provided by the Government, WHO, World Bank and LF Support Centre Liverpool. Resource mobilization to secure sustainability of PELF activities remains the main challenge together with demand for incentives by the CDDs, and succeeding in integration approaches. The way forward consists of the implementation of the third MDA round, in 17 IUs in November 2007.

ABSTRACT No 21
Communication

Control of lymphatic filariasis and other NTDs in Burundi

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In Burundi, lymphatic filariasis (LF) control, which is at its beginning, has been included in a large integrated program for Neglected Tropical Diseases (NTD) control. The NTDs are onchocerciasis, schistosomiasis, soil transmitted helminthiases (STH), LF and trachoma. In order to control these different diseases, the integrated program uses the approach of Community Directed Mass Drug Administration (CDMDA), when a disease is endemic in an area. The drugs are administered by Community Drug Distributors (CDD) chosen by the population of the area. Before initiation of drug administration, there are two initial steps:

1. Disease mapping in order to define the endemicity
2. Obtaining of baseline data which will permit monitoring and assessment of the impact of Mass Drug Administration (MDA) or other actions

In the integrated program for control of NTDs in Burundi, we are currently performing mapping of LF, and the other steps will follow when the results of this activity is available.

ABSTRACT No 22
Keynote Lecture

Lymphatic filariasis morbidity in Eastern and Southern Africa

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The aim of the current, extensive global efforts to eradicate *Wuchereria bancrofti* is to prevent the development of new cases of lymphatic filariasis (LF) in all its different painful and disabling forms. However, until transmission is completely blocked and there are no new infections, it is important and necessary that there be a concerted effort to improve the health and condition of those already afflicted with the disease. This arm of the global effort against LF, which runs in parallel with the mass drug administration activities, is generally known as “Morbidity

Programs". National programs have implemented these specific patient-oriented Programs to a varying degree, often tending to focus more on the drug distribution activities as their main efforts. Nevertheless it is important to recognize that the patients themselves, and their improving condition, are often the best advocates for the disease eradication activities and the LF Programs as a whole. This presentation will cover three areas of the morbidity of filariasis, namely the pathogenesis and presentation of the disease, the epidemiology of the disease (including the situation on Eastern and Southern Africa), and finally the current practical approaches to control of individual's disease. The funding of morbidity efforts in the national programs is an important aspect to consider, and suggestions as to successful approaches will be presented and discussed. Likewise management of the morbidity of this disease is a vital component of filariasis control programs worldwide but there is no place where this is more important than Africa. The personal suffering for patients and their families places filariasis as one of the most important chronic diseases on earth deserving of the attention of both the global humanitarian and economic communities.

ABSTRACT No 23
Keynote Lecture

Vectors of lymphatic filariasis in Eastern and Southern Africa, and the prospect for supplementary vector control

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Many important studies on vectors and transmission of lymphatic filariasis (LF) have been carried out in Eastern and Southern Africa. An overview of these will be presented. Emphasis will be on studies performed after 1970, as earlier work was summarized by Sasa in his 1976 book on Filariasis. Vector taxonomy, and especially the methods for identification of vectors, have developed considerably in the period and a status will be given. Studies on vector incrimination, and on transmission and vector efficiency/importance, will be emphasised. Most of the vector field studies have taken place in Kenya and Tanzania, but also to some extent in Uganda, Madagascar and the Comoros, whereas taxonomical and vector identification studies mainly have taken place in South Africa. Vector control studies aiming at decreasing LF transmission will also be reviewed, and the role of supplementary vector control in LF control programmes will be discussed.

ABSTRACT No 24
Communication**Monitoring the effect of the Tanzanian National Lymphatic Filariasis Elimination Programme in a high endemicity area of Tanga Region, Tanzania**

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Tanzania launched a National Lymphatic Filariasis Elimination Programme (NLFEP) in 2000. Tanga Region, located in the north-eastern part of the country, was enrolled in the programme and received the first MDA (ivermectin + albendazole) in October 2004. A study to monitor the effect of the NLFEP in a highly endemic area of Tanga Region was initiated in October 2003 as a collaboration between DBL, NIMR (National Institute for Medical Research, Tanzania) and NLFEP. In order to obtain solid baseline data, continuous transmission monitoring started in a selected community (Kirare village, approx. 1500 inhabitants) one year before the first round of MDA, and is planned to continue until one year after the fifth MDA (i.e. total of six years), by catching and dissecting vector mosquitoes from fifty randomly selected houses on a weekly basis. The community population was examined for microfilaraemia immediately before the first MDA, and this activity will be repeated at yearly intervals. At the same time points, specific circulating filarial antigenemia and antibody responses believed to reflect transmission intensity will be followed in selected individuals (those living in the mosquito collection houses). Clinical examination for chronic filarial disease was carried out immediately before the first MDA, and will be repeated one year after the third and fifth MDA. Treatment coverage is monitored by interviews and by examining the drug distributors' record books. Finally, Standard 1 pupils from eight primary schools located in the same area are examined at yearly intervals for circulating filarial antigens, to monitor for any change in prevalence (as a reflection of a change in transmission). An overview of study design and methodologies, and of findings obtained so far, will be presented.

ABSTRACT No 25
Communication

Comparing PCR and mosquito dissection for monitoring the progress of mass drug administration programs for the elimination of lymphatic filariasis in Tanzania

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Delivery and coverage of mass drug administration (MDA) is vital to the effectiveness of the lymphatic filariasis (LF) elimination effort. Equally important is determining when transmission has been reduced below sustainable levels. Thus, easy, effective and accurate monitoring of infection and transmission levels is critical to the LF elimination programs. This study provides preliminary evidence of effective monitoring using mosquito infection as an indicator and aims to produce a comparison of measures across a longitudinal survey in Kirare Village, Tanzania, before, during and after a treatment program. In addition to monitoring vector infection by dissection of mosquitoes, pools of mosquitoes were tested using the molecular xenomonitoring PCR assay for *Wuchereria bancrofti*. The data from both methods showed a significant decline in the mosquito infection rate after each of two rounds of MDA. As measured by PCR and calculated by Poolscreen v2.02, a decrease of 55% was detected after one drug treatment, and a decrease of 81% after two treatments. Likewise, the dissection method showed a significant decline in the rate of infection in the mosquitoes. As the infection rate in the population declines following repeated rounds of MDA, the dissection method is likely to become less useful since fewer mosquitoes will be harboring parasites. The sensitivity of the poolscreen PCR method may then be of high value to detect the few remaining infections in the mosquito populations. In addition to monitoring the progress of the treatment program in Kirare, this study is important in providing comparisons and evaluations of the monitoring tools available over the course of the entire treatment period.

ABSTRACT No 28
Communication

Evaluation of the effects of three annual mass drug administrations with ivermectin and albendazole on lymphatic filariasis in Mtwara Region, Tanzania

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The effect of three years of Mass Drug Administration (MDA) on LF in Mtwara Region, south Tanzania, was evaluated in two sentinel districts, viz. Tandahimba and Newala. Monitoring was carried out in randomly selected villages within each site: the sites in Newala being Makote/makondeko, Nambungu, Legeza/lekanelo and Chitekete villages, whilst in Tandahimba the sites were Chikongo, Lyenje, Mkoreha and Naputa villages. About 550 people were sampled to determine baseline infection and disease prevalence in both districts. Of these, 161 (28%) were females and 398 (71%) were male. The mean age for the participants was 31 years with standard deviation of 16.4, the minimum age was 5 and maximum was 80 years. Fifteen 15 (3%) of people sampled had hydrocele; 9 from Newala and 6 from Tandahimba. Only 3 (0.5%) people had lymphoedema/elephantiasis; 2 from Newala and 1 from Tandahimba. Five hundred and eighteen 518 (93%) were amicrofilaremic and 41 (7%) had microfilaria in their blood. The mf prevalence in Newala was 9% while in Tandahimba it was 5% ($p = 0.060$). The geometric mean of mf count for both districts was 11.2 with 95% confidence interval [7.5-16.7]. ICT was successfully applied to 550 people; 125 (23%) of the 550 were ICT positive. The ICT prevalence in Tandahimba was 45/261 (17%) while in Newala was 80/289 (28%) with p-value of 0.004. About 550 participants successfully tested for both ICT and microfilaremia; 420 (83%) tested negative for both ICT and mf, 89 (17%) were ICT positive only and 41 were having microfilaria in blood only, 36 (88%) participants tested positive for ICT and microfilaremia (mf) and 5 (12%) were ICT negative but they had microfilaria in their blood ($p=0.000$). Analysis of longitudinal trends in infection showed that after 3 MDA rounds microfilaria prevalence dropped in both districts compared to the baseline data (2002); in Tandahimba district microfilaremia prevalence before the first MDA was 6.8% while it was 14.3% in Newala. Coverage rates between villages and between these sentinel sites and regional averages were comparable at each MDA. The results are discussed in terms of the effectiveness of MDA programmes in eliminating LF infection in Mtwara, the effects of drug coverage on programme effectiveness and the likely cost of MDA programmes for eliminating LF in Tanzania.

ABSTRACT No 29
Communication**Lymphatic filariasis in Kyela and Rungwe districts, south-west Tanzania**

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Cross-sectional surveys were conducted in Kyela and Rungwe districts, southwest Tanzania, between 1989 and 1996. The objective was to determine the prevalence of *Wuchereria bancrofti* infections, and to establish its distribution limits with respect to Lake Nyasa (Malawi) and to onchocerciasis endemic communities. Vector species and their relative abundance were also investigated. Blood examination was by counting chamber technique. Surveys in 1989 (total of 185 examined) recorded high prevalences of *W. bancrofti* microfilariaemia in two villages, Lwangwa-Masoko (29.0%) and Kajunjumele (32.5%). Surveys in 1996 in seven villages (total of 733 examined) recorded microfilarial prevalences from 0.7% to 33.2%. However, the 3 villages located in Rungwe district had low prevalences (mean of 4.5%), whereas the 4 villages in Kyela district had high prevalences (mean of 25.6%). High prevalences were recorded from the lowland villages of Ibanda (33.2%), Kajunjumele (32.5%), Kingili (31.1%) and Lwangwa-Masoko (30.4%), whereas the three villages in Rungwe district had lower prevalences: Kibole (0.7%), Lutete (2.5%) and Ntaba (12.9%). This situation was reverse of that of onchocerciasis, where prevalences were higher in Rungwe than in Kyela districts. The villages of Lwnagwa-Masoko, Lema, Ibanda and Kingili also had individuals with double infections of *W. bancrofti* and *Onchocerca volvulus*. Along the Kiwira and Mbaka river valleys, *W. bancrofti* prevalences were high, even at distances exceeding 35 km away from the lake shores. Wet season (April and May, 1996), indoor all night, human bait mosquito catches were done to determine vector species and assess their relative abundance. A total of 369 mosquitoes were collected from 10 houses in two villages in April; mean density was 36.9 per house. In May mosquitoes were collected from 6 houses in 3 villages, with mean of 181.8 mosquitoes per house. The most abundant species were *Anopheles gambiae* complex (in Ngonga, over 90%) and *Culex quinquefasciatus* (in Tenende over 70%). In Kateela village, *An gambiae* complex was 64.0% while *Cx. quinquefasciatus* was 33.1%. *An funestus* was recorded in small numbers in

both Ngonga and Kateela (about 3.0%), but not in Tenende. Intervention strategies are discussed in relation to other ongoing anti-helminthic measures at national and local level.

ABSTRACT No 30
Communication

Association between a human genetic marker (MBL) and the long-term status of *Wuchereria bancrofti* infection in endemic communities in Tanga Region, Tanzania

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The study assessed the possible association between selected Mannose-Binding Lectin (MBL) allele combinations and *Wuchereria bancrofti* infection status among individuals whose infection status had been monitored for 31 years. A total of 104 individuals from two coastal communities in Tanga Region, Tanzania, who had been examined for *W. bancrofti* infection in 1975, were re-identified and re-examined in 1992, 2001 and 2006. Examinations in 1975 and 1992 were for microfilaraemia, whereas examinations in 2001 and 2006 were for *W. bancrofti* specific circulating filarial antigen (CFA). Individuals who were positive for microfilaraemia and/or CFA in at least one of the surveys were categorised as “filaria positive”, while the remaining were categorized as “filaria negative”. Most individuals were in the same filarial infection status category at all four examination times. Whole blood samples from all individuals were collected in 2006 and were examined for genetic polymorphisms in the MBL-coding gene. This was used to categorize individuals as having either a “normal” or a “deficient” MBL phenotype. Statistical analysis showed a significant association between MBL phenotype and filarial infection category, with individuals who had a “deficient” phenotype being three times more likely to be in the filarial positive category compared to those having a “normal” phenotype (OR=3.0; CI95%: 1.2-7.8). Possible interpretations and implications of this finding will be discussed.

ABSTRACT No 31
Communication**Impact of three rounds of annual Mass Drug Administration (MDA) with diethylcarbamazine and albendazole on *Wuchereria bancrofti* in villages along Sabaki River, Kenya.**Charles S. Mwandawiro¹, Sammy M. Njenga¹ and C. Njeri Wamae¹¹*Kenya Medical Research Institute (KEMRI), Nairobi, Kenya*

Annual single dose mass drug administration (MDA) combining diethylcarbamazine (DEC) (6mg/kg body weight) and albendazole (400 mg) was given three times to communities in 8 villages along the Sabaki River in Kenya between 2002 and 2006. All eligible persons aged 2 years and above received treatment. No vector control interventions were applied, although there is widespread coverage of treated bednets through antimalarial campaigns. Mosquito collection and dissection for filarial infection was done once a month for six months every year. In every collection trip, 8 randomly selected houses in each village were visited once where mosquitoes were collected from inside the houses. After the three MDAs, prevalence of microfilaraemia (diagnosed by counting chamber technique) declined from 20.8 % to 2.6 % whereas prevalence of antigenemia (assessed by ICT test) fell from 34.8 % to 13.5 %. Mosquito infective rates decline from 2.2 to 0.1 and transmission intensity indices from 18.26 to 0.64. The results of this study indicate a relatively high effectiveness of MDA using the DEC/albendazole combination against *Wuchereria bancrofti* infection, and this may be a useful strategy to eliminate lymphatic filariasis in onchocerciasis-free areas.

ABSTRACT No 32
Keynote Lecture**Designing monitoring programmes for evaluating the success of lymphatic filariasis control or elimination**Edwin Michael¹¹*Department of Infectious Diseases Epidemiology, Imperial College School of Medicine, London, U.K.*

Successful monitoring underpins the effective management of any parasite control programme insofar as monitoring serves to track the effectiveness of implemented

interventions, identify if management should be continued or modified, and when management objectives are achieved. Here, we show that the scientific design of an effective monitoring programme for evaluating parasite control should provide support for undertaking each of these management activities, ie. monitoring is essentially used to illuminate and guide management decision making. To be effective within this framework, we demonstrate that parasite monitoring programmes should be based on three primary principles. The first is that it should be founded on a logical framework, which (1) is framed by well-articulated objectives that are closely linked to management goals; (2) have a clear programme theory relating implementation processes and intervention effects; and (3) measure a subset of informative indicators with sampling methods that allow statistically reliable results while minimizing costs and logistical problems. The second principle is to apply the framework for aiding management decision making via: (1) validating that management decisions are having the desired consequences; (2) providing new insights into parasite control dynamics, intervention effects, assumptions, and thresholds, and (3) guiding adaptive modifications of management actions in the light of monitoring results and new knowledge gained regarding control dynamics. The third principle in this framework highlights the need to create a formal plan for learning from monitoring data about effective parasite control management. Specific examples for developing such a monitoring plan for evaluating lymphatic filariasis control based, in part, on experiences gained in Tanzania will be used throughout to illustrate these issues.

ABSTRACT No 34
Communication

Lymphatic filariasis and integration of vertical control/treatment programmes in sub-Saharan Africa: SCI's experience

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Since 2002 when it was founded, the Schistosomiasis Control Initiative (SCI) has focused its efforts on providing treatment for schistosomiasis and the Soil-Transmitted Helminths (STHs) in sub-Saharan Africa to those most at risk of developing severe morbidity. But recently SCI has fully engaged in a larger movement seen throughout the health-related aid community leading towards integration of classically vertical control and treatment programmes. As a consequence, SCI is now targeting seven Neglected Tropical Diseases (NTDs), namely the three STHs and schistosomiasis but also lymphatic filariasis, trachoma and onchocerciasis in Mali, Niger, Burkina-Faso, Uganda, Burundi, Rwanda,

Tanzania and Zambia. An overview of SCI's activities in these different settings will be presented with an emphasis on lymphatic filariasis.

ABSTRACT No 35
Communication

The Lymphatic Filariasis Support Centre for Africa

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The Lymphatic Filariasis Support Centre for Africa (LFSCA) is hosted at the Noguchi Memorial Institute for Medical Research (NMIMR), College of Health Sciences, University of Ghana to deal with issues relating to capacity building and human resources development in African LF endemic countries and support activities that will improve community involvement and participation in disease control measures including morbidity control. The Centre will be available to assist endemic country programmes on request in programmatic and operational aspects within its mandate and resources. The LF Support Centre will also serve as a platform for operational research and general advocacy on the African continent in line with the approach adopted by the Global Programme to Eliminate Lymphatic Filariasis (GPELF). The Centre is currently managed by a Coordinator, a deputy Coordinator and a senior scientist of the Parasitology Department, NMIMR. Activities carried out at the Centre include compilation of a database of LF expertise on the African continent, workshops on programme management, laboratory diagnosis and morbidity management. Some students have been trained with support from the centre and operational research undertaken. Resources for the Centre is from GSK, MDP and Merck and Co.

ABSTRACT No 36
Communication

**Research needs in relation to lymphatic filariasis control in Eastern
and Southern Africa**

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A series of scientific meetings between 2003 and 2006 defined the principal uncertainties in lymphatic filariasis (LF) that require additional research – some in relation to basic biology of the parasite and its interactions with the host and environment, and some related to ensuring successful implementation of the Global Programme to Eliminate LF which began officially in 2000. Since that time, studies have been supported to address some of these research questions by both DBL and other funding agencies – most recently including the Bill & Melinda Gates Foundation through its grant to the Global Alliance for ‘Resolving the Critical Challenges now facing the GPELF.’ LF programs in Eastern and Southern Africa share many of the same research needs of the rest of the GPELF, but because of particular advantages in experience, expertise and opportunity they are uniquely positioned to solve a number of major problems of importance and relevance to all the GPELF, including the following: 1) the pathogenesis of lymphedema and hydrocoele and the effect that different treatment approaches (including MDA) have on them; 2) the role that vector biology can play not only in facilitating the MDA-based efforts to interrupt LF transmission but also as a tool to measure the decreasing transmission in national programs; 3) the most appropriate program end-points that define when MDA programs can be safely stopped; and 4) the geographic overlap of multiple NTDs and the creation of programs that can ‘coordinate’ or ‘integrate’ them effectively and efficiently.

Lymphatic filariasis

**research and control
in Eastern and Southern Africa**

Lymphatic filariasis is a disabling and disfiguring disease which results from a mosquito transmitted parasitic infection. It is a widespread and major public health problem in many developing countries with a warm and humid climate, and it is one of the most prevalent of the neglected tropical diseases. Current estimates suggest that more than 1 billion people live in endemic areas and are at risk of infection, and more than one third of these are in Sub-saharan Africa. In recent years forces have united internationally in the fight against lymphatic filariasis through formation of the Global Programme for Elimination of Lymphatic Filariasis (GPELF). This book is the outcome of a recent regional workshop held to review current knowledge and ongoing control activities in Eastern and Southern Africa. It provides an overview of recent research and control efforts and of the challenges that need to be overcome to successfully control the disease in this region.

