
LYMPHATIC
FILARIASIS
INFECTION
& DISEASE:
Control
Strategies

Report of a Consultative Meeting
held at the Universiti Sains Malaysia
Penang, Malaysia
(August 1994)



World Health Organization
Division of Control
of Tropical Diseases
(CTD)

UNDP/World Bank/WHO
SPECIAL PROGRAMME FOR
RESEARCH AND TRAINING
IN TROPICAL DISEASES
(TDR)

<p>LYMPHATIC FILARIASIS INFECTION & DISEASE: CONTROL STRATEGIES</p>
--

EXECUTIVE SUMMARY*

		Page
E-1	The Problem and the Outlook for its Solution	i
E-2	Control of Infection	i
E-2.1	<i>Treatment of the human population: New strategies</i>	i
E-2.2	<i>Reducing the vector mosquito population</i>	ii
E-3	Control of Disease (Morbidity): New Strategies	ii
E-4	Monitoring the Success of Control Programmes: New Techniques	iii
E-5	Management of Control Programmes	iii
E-6	Costs and Cost-Effectiveness of Specific Control Strategies	iv
E-7	Operational Research Needs	iv

*Report of a WHO/CTD/TDR Consultative Meeting held at the
Universiti Sains Malaysia,
Penang, Malaysia, 22-24 August 1994

© World Health Organization 1994

The designations employed and the presentation of the material in this document do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its frontiers or boundaries.

Authors alone are responsible for the views expressed in this document and for the presentation of the material therein.

E-1 The Problem and the Outlook for its Solution

Lymphatic filariasis persists as a major cause of clinical morbidity and a significant impediment to socioeconomic development in much of Asia, Africa and the Western Pacific as well as in certain regions of the Americas. Indeed, the prevalence of this mosquito-borne infection is increasing worldwide, in large part due to the rapid unplanned urbanization in many endemic areas. It is estimated that *at least* 120 million persons are infected, with essentially all manifesting either the overt findings of lymphoedema, elephantiasis, hydrocoele and recurrent infections or the newly recognized, subclinical abnormalities of lymphatic and renal function.

Despite these disappointing numbers, however, simplified, safe, and cost-effective methods to control and potentially eradicate this infection have recently become available. For example, instead of the older 12-day treatment regimens using diethylcarbamazine (DEC), it is now clear that much simpler treatment strategies employing single yearly doses of DEC or even its daily consumption as an additive to common table/cooking salt are equally effective for control programmes and much easier and less expensive to deliver. Indeed, use of these and other techniques have already caused the elimination of lymphatic filariasis from Japan, Taiwan, South Korea and the Solomon Islands; and China too is in the final stages of an exceptionally effective control programme.

Lymphatic filariasis has recently been identified by the International Task Force for Disease Eradication as one of only six "eradicable" or "potentially eradicable" infectious diseases. This fact, coupled with the recognition that appropriate control efforts can be effectively and inexpensively linked with *pre-existing* national and local public health infrastructures, now provides strong impetus to initiate widespread chemotherapy programmes, with concurrent vector control, where possible, aimed at finally controlling

this parasitic infection and the morbidity that it causes in all endemic areas.

E-2 Control of Infection

The two general strategies (which need not be mutually exclusive) to reduce transmission of filarial infection are:

(1) treating the human host to decrease microfilaraemia and (2) decreasing human-vector contact, usually by reducing the density of the mosquito vectors. *Optimal* control strategies will necessarily differ for different endemic countries, since each must take into account the particulars of the local host-vector combination, existing health care infrastructure, and cultural practices.

E-2.1 Treatment of the human population: New strategies

'Mass distribution' programmes should completely replace those based on a 'selective treatment' strategy (i.e., detection of microfilaraemics who are then treated 'selectively'). The recommended regimens for mass treatment would be either of the following:

- (a) DEC-fortified salt (0.2 - 0.4% w/w). Use of DEC-fortified salt for a period of 9-12 months has been shown to be simple, cheap and effective in dramatically reducing or eliminating lymphatic filariasis. It is generally well tolerated, safely used in pregnancy and can be incorporated into iodized salt. It can be utilized in most control programmes but cannot yet be recommended in areas where there is coexisting onchocerciasis or loiasis.
- (b) Single annual or semi-annual mass administration of DEC (6 mg/kg body weight). This regimen appears to be as effective as the older 'standard' 12-day course of DEC, has fewer adverse effects, and results in enhanced population compliance and decreased delivery costs. Adverse

reactions, though greater than those seen with DEC-fortified salt, are well tolerated, but this regimen definitely should not be used in areas where onchocerciasis or loiasis coexists.

If, as anticipated, ivermectin subsequently becomes registered for use in lymphatic filariasis, two additional chemotherapy tools would become available:

- Ivermectin 400 µg/kg given once yearly;
- Ivermectin 400 µg/kg + DEC 6 mg/kg given once yearly.

The single-dose ivermectin regimen appears equivalent to single-dose DEC regimens in efficacy, safety and tolerance, and, in addition, it has the advantage that *it can be used safely in areas where onchocerciasis or loiasis may also coexist*. The combination regimen, however, appears to be superior to either drug alone for long-term reduction of microfilaria density and prevalence, and it would almost certainly become the 'annual-dose treatment' of choice (except in *O. volvulus* and *L. loa* endemic areas) if ivermectin became appropriately registered.

The exact duration for which these various treatment strategies need to be sustained has not been established, though current estimates suggest 5-10 years for yearly-dose strategies and 9-12 months for DEC-salt.

E-2.2 *Reducing the vector mosquito population*

Vector control has played an important supporting role for filariasis control in certain local programmes, and reduction of vector density can be an important contributor to achieving long-term sustainability of transmission interruption. However, filariasis control programmes should not be based on vector reduction alone. Rather, vector control should be implemented whenever feasible as a complementary tool to filariasis control

programmes based primarily on drug administration.

Certain technologies are now emerging that should improve vector control capabilities, though all still require large-scale validation and assessment of their impact on filarial transmission as well as the subsequent clinical effect in the human population. These measures include the following:

- biocides: especially *Bacillus sphaericus* (a toxin-producing bacterium) to control *Culex quinquefasciatus*;
- polystyrene beads: to limit breeding of culicine vectors in specific urban situations with enclosed (e.g. latrines, cess pits) breeding sites;
- insecticide-impregnated bed nets and curtains: to limit host-vector contact;
- indoor spraying of long-lasting, residually active pyrethroids: especially for the adult-stage of *Culex* and *Mansonia* mosquitoes;
- community participation in integrated vector management: difficult to sustain in the urban setting, but successfully used in controlling rural *Mansonia*.

E-3 **Control of Disease (Morbidity): New Strategies**

Dramatic advances in our understanding of the pathogenesis of lymphatic filariasis, especially recognizing the importance of local microbial superinfection in exacerbating lymphatic pathology and recognizing the appreciable subclinical pathology in the lymphatics of 'asymptomatic' microfilaraemic individuals, have led to specific, on-going clinical trials that appear likely to yield the following treatment recommendations:

- (a) for adenolymphangitis (ADL): treatment (and possibly prophylaxis) with antibiotics, since the majority of these acute episodes appear to be of bacterial aetiology;

- (b) for lymphoedema/elephantiasis: rigorous local hygiene with/without local antibiotic and anti-fungal agents to prevent ADL episodes and permit the reversal of existing lymphoedema;
- (c) for asymptomatic microfilaraemia: early treatment to prevent further lymphatic and renal damage; in the absence of specific data, the long-standing "standard" courses of DEC (6 mg/kg/day for 12 days [*W. bancrofti*] or for 6 days [*B. malayi*]) remain appropriate.

For other clinical syndromes associated with lymphatic filariasis (e.g. tropical pulmonary eosinophilia, chyluria, etc.) there is no new information available to change the current recommendations for their extended treatment with DEC.

E-4 Monitoring the Success of Control Programmes: New Techniques

Surveillance of potential transmission or established human infection in an unsurveyed population is necessary to determine where control efforts should be initiated, how effective they are, and when they may be discontinued. There is a major need to replace night blood surveys as the primary method for determining the level of endemicity in a community. Evaluation of antigenaemia rates in daytime, finger-prick blood specimens from children or other selected cohorts of the population has proven to be a workable alternative to night blood surveys, and analysis of infection rates in mosquito vectors with entomologic or DNA-based techniques shows equal promise. 'Rapid assessment' techniques, such as review of existing health reports and hospital records or clinical examination of adult males for hydrocoeles to assess the prevalence of infection, are also being developed as 'tools' for identifying endemic communities in previously unsurveyed areas.

Mathematical models have provided increasingly powerful tools for analysis,

prediction and evaluation of control strategies in other parasitic infections, and such models should be particularly valuable for lymphatic filariasis because of the complexity of the interactions among the vector, human and parasite populations and because of the long time-scales involved in filarial infection and disease. Models that can serve as cost-effective tools for studying the population dynamics of transmission and for assessing the consequences of control interventions and their relative cost-effectiveness are under development.

E-5 Management of Control Programmes

The new control strategies based on anti-filarial chemotherapy do not require complex management structures.

The strategy requiring the least management input is DEC-fortified salt distribution. While specific inputs are required for production, advocacy and community empowerment, the distribution itself can use existing (health or non-health) delivery systems. Additionally, this approach can take advantage of inherent cost recovery through consumer purchasing and, thus, might require no sustained financial input.

Single-dose, annual or semi-annual mass treatment also removes the need for the complex management structures necessary for detecting individual cases, and it provides the opportunity for integration into existing Primary Health Care systems for delivery implementation.

Morbidity control, too, can be effected with only minimal management input other than training the community in the importance of local hygiene to affected limbs or organizing self-help support groups among patients and their families.

While vector control generally requires a separate management structure, it often provides the opportunity for an increased level of community participation.

Opportunities also exist for integration with existing vector-based control programmes for other diseases (e.g., malaria).

E-6 Costs and Cost-Effectiveness of Specific Control Strategies

The affordability of filariasis control is particularly important because of the relatively low priority often accorded it by health planners.

DEC-fortified salt requires the least resource input since it relies on existing community purchasing practices. There is, however, some increase in purchasing cost to the consumer, with recent experience in India suggesting that high quality, re-crystallized DEC fortification will add US \$0.80 per year per adult to the average bill for purchase of salt.

The replacement of active case detection and courses of multi-dose treatment of the population by use of single-dose mass treatment provides the opportunity for *increasing coverage without additional cost* through reallocation of existing resources.

E-7 Operational Research Needs

Though *currently available information is sufficient for immediate initiation of large-scale filariasis control or elimination programmes*, there are still certain issues which, if resolved, would enhance programme design and implementation; specifically, these are:

- (a) more precise estimates of the global, regional and national burden of illness caused by lymphatic filariasis, and rapid assessment techniques to help make these estimates;
- (b) a control strategy that can be used safely and effectively in areas where bancroftian filariasis might coexist with onchocerciasis or loiasis (i.e., one based on ivermectin delivery or use of DEC-fortified salt, if proven

safe for patients with onchocerciasis and loiasis);

- (c) detailed, comparative, cost-effectiveness analyses (CEA):

- between mass-delivery and fortified-salt approaches to controlling lymphatic filariasis (including how the delivery of anti-filarial medication can be integrated with other health and non-health delivery systems);
- for vector control - not as a stand-alone option for filariasis control, but as a potential adjunct to chemotherapy-based strategies;
- of surveillance and rapid assessment procedures under actual conditions of implementation - in particular, comparing DNA-based techniques and mosquito dissection for detection of vector infectivity, and comparing blood antigenaemia detection with microfilarial detection by microscopy and clinical or recall techniques for determining prevalence of infection in a community;

- (d) identification and quantification of the economic and social costs of filarial disease, including costs both to individuals and to the national health care budget for management of elephantiasis, hydrocoele and adenolymphangitis;

- (e) further definition of the clinical consequences of 'asymptomatic' microfilaraemia, with its newly-recognized accompanying abnormalities of lymphatic and renal function, and an estimation of their contribution to the social and economic burden of filarial disease;

- (f) evaluation of the personal and social psychology of compliance with annual mass drug treatment or long-term use of fortified-salt, and of decision making in the personal-choice use of fortified salt;
- (g) development of predictive models which provide the kinds of information required by managers for planning and monitoring control programmes;
- (h) uniform surveillance, clinical assessment and monitoring techniques so that *types* of site-specific control strategies can be defined, as well as those areas where total eradication of infection will be most readily achieved.

LYMPHATIC FILARIASIS INFECTION & DISEASE: CONTROL STRATEGIES

Report of a WHO/CTD/TDR Consultative Meeting held at the
Universiti Sains Malaysia,
Penang, Malaysia, 22-24 August 1994

	Page
1. Global Prevalence, Distribution and Disease Burden of Lymphatic Filariasis	1
1.1 <u>Prevalence</u>	1
1.2 <u>Geographical Distribution</u>	2
1.3 <u>Patterns of Infection and Disease</u>	2
1.4 <u>The Global Burden of Disease</u>	3
1.4.1 <i>Disability</i>	3
1.4.2 <i>Economic</i>	4
1.4.3 <i>Research priorities</i>	4
2. Current National Control Strategies	4
3. New Research Findings Giving Rise to New Control Strategies	7
3.1 <u>Infection Control (Chemotherapy)</u>	7
3.1.1 <i>Drug regimens available for filariasis control - Comparative efficacy</i>	7
3.1.2 <i>Adverse reactions</i>	9
3.1.3 <i>Macrophilicidal activities of DEC and ivermectin</i>	9
3.2 <u>Morbidity control</u>	10
3.2.1 <i>Adenolymphangitis and lymphoedema/elephantiasis</i>	10

	Page
3.2.2 <i>"Asymptomatic" microfilaraemia</i>	10
3.3 <u>Vector control</u>	11
3.4 <u>Programme development/oversight</u>	12
3.4.1 <i>New tools for diagnosis and epidemiological assessment and monitoring</i>	12
3.4.2. <i>Predictive models</i>	14
3.4.3 <i>Social and economic issues in control programmes</i>	14
3.4.3.1 Socioeconomic findings	14
3.4.3.2 Community participation	14
4. Conclusion	15
4.1 <u>Recommended Control Strategies</u>	15
4.2 <u>Operational Research Needs</u>	15
Tables	17
References	23
List of participants	27

STRATEGIES FOR CONTROL OF LYMPHATIC FILARIASIS INFECTION & DISEASE

A meeting was held at the Universiti Sains Malaysia, in Penang, Malaysia from 22-24 August 1994 (list of participants appended). The purposes of this meeting were to define as precisely as possible the current understanding of the epidemiology and global impact of lymphatic filariasis; to review current control efforts in selected endemic countries; to identify the dramatic recent advances in clinical understanding, therapeutic options and assessment techniques of potential value to control programmes; and then to determine specific control strategies that can be recommended for immediate implementation in endemic countries.

1. Global Prevalence, Distribution and Disease Burden of Lymphatic Filariasis

1.1 Prevalence: Information about distribution and prevalence is an obvious prerequisite for any meaningful discussion of the public health importance of a disease. For lymphatic filariasis, caused by *Wuchereria bancrofti*, *Brugia malayi* and *B. timori* parasites, estimates of global prevalence have been made previously by WHO (1,2), with the latest published figures (2) indicating infection of some 72.8 million people with *W. bancrofti* and 5.8 million with *B. malayi* or *B. timori*. These figures are based largely on reports by member states to the WHO Expert Committee on Filariasis, except for the countries of Sub-Saharan Africa where most estimates were derived from much earlier surveys (3). Although the WHO estimates have proved important in indicating the numerical scale of the problem, they provide less information relevant to the public health importance of these infections since separate estimates of disease are not available. A more recent detailed assessment of available information has attempted to correct for age, gender, and disease-specific biases in the earlier figures, and it estimates that approximately 119.1 million individuals are now infected with lymphatic filariasis worldwide, 106.2 million having bancroftian filariasis and 12.9 million having brugian

filariasis (table 1; refs. 4,5). The number with *overt* physical disabilities from their infections is approximately 43 million, with bancroftian filariasis accounting for almost all (40 million) of these cases.

These recent estimates (4,5) were based on all published and unpublished quantitative data from the last 20 years that was retrievable from the open literature, from the WHO regional offices and from individual countries. 'Corrections' to this broad dataset were undertaken in two steps. The first step consisted of estimating age-specific rates of infection and disease (hydrocoele in males and lymphoedema for both sexes) in each study, with data recorded to the nearest age-class when available. Age-specific rates for studies that provided only crude overall infection and disease rates were derived as follows: first, age-specific rates from all studies in a region providing such information were combined to produce standard regional age-prevalence curves; then, these curves were applied to the 'crude overall rates' given in studies in that region to derive the corresponding age-specific infection and disease rates for the study community. Similarly, sex ratios of infection and disease prevalence, and, in the case of males, the ratio of hydrocoele to lymphoedema were calculated from studies providing the required data in each region and then used to generate gender- and disease-specific estimates in those instances when only composite overall prevalences were reported.

In the second 'corrections' step the direct and derived age-specific rates from these studies were then combined to obtain national and regional burdens. First, age-estimates from each study in a particular country were averaged to obtain the corresponding national gender-specific, age-prevalence curves. Then, with available demographic data, these curves were converted to numbers of individuals afflicted in a particular country by sex and age-class. Wherever possible, WHO estimates of the size of the national populations living in

endemic regions (derived from information reported by Member States) were used in these calculations. The exception is China, where some recent estimates (6) have ignored the populations of provinces having infection prevalences below 1%. For the present estimates, however, populations of all provinces where infection is present have been considered as the exposed, endemic population. For global estimates, the total number of country or regional cases were summed, and average prevalence (expressed in percentages) calculated using the total endemic population as the denominator (Tables 1a,1b).

The new estimate of the world burden of 119.1 million cases of lymphatic filariasis is higher than the 1992 WHO estimate of 78.6 million but, given the difference in the methods of estimation, not very remarkably so. Indeed, the similarity encourages the belief that the true burden lies in the vicinity of these figures, and probably closer to the more recent estimate, since most available figures tend (for technical reasons) to underestimate both microfilarial and disease prevalence; also 'cryptic' infections (i.e., not manifested by either overt lymphatic pathology or microfilaraemia are not taken into consideration at all in these calculations because of the difficulty in diagnosing them objectively and with certainty).

1.2 Geographical Distribution

The 1992 report of the WHO Expert Committee on Filariasis (2) indicates that brugian infection is endemic in 8 countries in Asia, while *W. bancrofti* occurs in 7 countries in the Americas, 4 in the Eastern-Mediterranean region, 8 in South-East Asia and 8 in the Western-Pacific region; an additional 38 countries lie within the *W. bancrofti* endemic areas of Sub-Saharan Africa. The prevalence estimates in Table 1a indicate that India, with 45.5 million cases and Sub-Saharan Africa, with 40 million cases, have very similar burdens of *W. bancrofti* infection. Individually these regions account for about 38% and 34% respectively of the total world burden, a conclusion contrasting with that from previous estimates which suggested that the majority of filarial

infection and disease was confined to India. In fact, in terms of prevalence, (Table 1a), slightly higher infection and disease rates are observed for the Sub-Saharan African region than for India. Given the public health significance of this finding for Africa, it is clear that there is an urgent need for more precise information on infection prevalence in this region, including information to quantify current at-risk population sizes or, at least, to identify all endemic countries. The region with the third highest number of cases (14.5 million) and prevalence (1.83%) of bancroftian filariasis is Asia (excluding China and India) and the Pacific islands, followed by China with a total burden of 5.46 million cases. Though focally important, only low burdens of infection and disease are observed for 'Latin-America and the Caribbean' and for the 'Middle Eastern Crescent'.

The regional estimates for brugian filariasis (Table 1b) indicate that China (32%) and India (20%) account for half of the global burden, with the South-East Asian countries of Indonesia, Thailand, Malaysia, Philippines, Viet Nam and South Korea accounting for the rest.

1.3 Patterns of infection and Diseases

The global age-specific estimates seen in Tables 2a,2b indicate the markedly age-dependent nature of lymphatic filarial infection and disease. Numerically, the largest number of cases (microfilaraemia and disease) for both parasite genera occurs in the 15-44 year age-group, but the prevalences of microfilaraemia and disease are highest in the 45-60+ age-group. Gender-specific estimates indicate a male bias for microfilaraemia, apparently 10% more cases in bancroftian filariasis and 25% more cases in brugian filariasis. Chronic disease due to bancroftian filariasis also appears to be more prevalent among males, largely because of the large number of hydrocoele cases (26.79 million). When the numbers of lymphoedema cases are compared, the bias actually appears to be in the opposite direction, with significantly greater (about 18% more) disease among females (7.81 million) than males (5.36 million cases). For brugian filariasis both microfilaraemia (males: 6.52 million

cases, females: 3.84 million cases) and lymphoedema (males: 1.8 million cases, females: 1 million cases) appear to be higher among males.

There is less quantitative information on acute disease manifestations, but these appear to be less obviously age dependent than do chronic manifestations (7), although the frequency of adenolymphangitis (ADL) episodes in individuals does appear to increase with age and the severity of chronic disease manifestations (8). The frequency of acute episodes is believed to be related to the progression to chronic disease, but it is not known whether the episodes are determined by intercurrent microbial infection, immunological mechanisms or exposure to infective mosquito bites (8).

1.4 The Global Burden of Disease

1.4.1 *Disability*

The 1993 World Bank Development Report (WDR) uses Disability Adjusted Life Years (DALYs) as a standardized metric for comparing the public health impact of different diseases and conditions (9). The global burden of lymphatic filariasis was estimated at 850,000 DALYs lost, which represents only 0.23% of the global burden of parasitic and infectious disease. If this current value is seen as a serious underestimate, then it may equally be appreciated as illustrating the current lack of appropriate information and the need for more quantitative data from which new estimates can be derived. Such data requirements fall into two categories: (i) estimation of disease incidence, and (ii) estimation of the disability level associated with each disease category.

Current estimates of disease incidence, necessarily through lack of data, focus on the more gross chronic manifestations. How justified this limited focus may be is debatable, but what is certainly true is that such a narrow definition significantly reduces the estimate of disease incidence, not only because acute disease is likely to be many times more prevalent than chronic (8), but also because acute disease occurs in the younger age classes which are positively

weighted in the calculation of DALYs and which constitute the majority of the population of endemic countries. This age-effect is likely to be particularly important in Africa where almost no information on incidence of acute disease exists.

Another important factor in estimating incidence of disease is gender. The WDR estimates (9) suggest that the burden in women is approximately half that in men (presumably reflecting the differential occurrence of hydrocoele). Since acute disease appears similarly prevalent in both sexes (7), there is the likelihood that much disease in women has been overlooked.

The *disability* associated with chronic disease is largely unquantified but is currently under investigation in a series of WHO-sponsored studies. Anecdotal evidence suggests (10) that the impact of disability may be both economic (e.g. lost employment opportunities) and social/psychosocial (e.g. stigmatisation and reclusion). Studies in a wide range of endemic countries will be required to define such impacts since social and economic consequences are likely to be highly culture-specific.

The disability associated with acute disease is even less well understood and has largely been ignored. ADL appears to occur from adolescence onwards as well as in the young adult age-groups where chronic disease manifestations are rare. A study of chronic-disease patients in India (8) indicates that the duration of each ADL episode (mean of 4.1 days) is largely independent of age but that the frequency (mean of 4.2 episodes per year) increases with both age and disease chronicity. The study indicates that while some individuals may suffer 'filarial fever' much more often, the average for middle-aged lymphoedema patients is 30 days a year; and the figures suggest significant additional disability for those with pre-existing chronic disease. While social and economic consequences of acute episodes are also largely undetermined, the existence of specific local names (e.g. *Yanakkalu jwara* in Tamil, and *homa ya mitoki* in Kiswahili) suggests that the condition is sufficiently obtrusive to be commonly recognised.

Calculation of the disability associated with acute disease would likely have an appreciable effect on estimates of the disease burden of lymphatic filariasis. Indeed, not only might the disability be additive for those with chronic disease, but it might also appear as a new source of disability prominent in the younger age classes which, as stated before, are weighted more heavily in the estimate of DALYs and which make up a larger proportion of the population of developing countries. Thus, it is clear that the accurate estimation of the global health burden of lymphatic filariasis is crucially dependent on obtaining a more detailed epidemiological understanding of acute disease. Furthermore, the newly recognized existence of very substantial amounts of 'subclinical' pathology in essentially all microfilaraemic individuals (11-13) argues that estimates of the global health burden of filariasis must find ways to include the health consequences of this type of pathology as well.

1.4.2 *Economic*

Establishing an economic case for the control of lymphatic filariasis will certainly assist the promotion of filariasis control, as review of this complex area has recently indicated (10). While both indirect costs and direct costs to the household and to the health care system appear large, they are as yet unquantified. WHO is currently sponsoring studies in this area to complement the efforts of others to estimate global disease burden.

1.4.3 *Research priorities*

For the emergent strategies for filariasis control to be adopted by endemic countries, the best case (health, social, economic) for controlling this disease needs to be made. The following areas are identified as priorities for providing the necessary data:

(a) adoption of standardized methods (including rapid assessment techniques) for collecting, presenting and interpreting epidemiological data on infection and disease;

- (b) estimation of the incidence of infection and disease in Africa;
- (c) definition of the epidemiology of acute disease;
- (d) assessment of disease in women;
- (e) estimation of disability attributable to chronic 'subclinical' disease;
- (f) estimation of the economic impact of the infection and disease.
- (g) assessment of the psychosocial impact of the infection and disease.

Such information will permit more accurate estimations of the global economic and health burden attributable to lymphatic filariasis; without it, "lymphatic filariasis will continue to struggle to compete with more prominent diseases for scarce health resources..." (10).

2. **Current National Control Strategies of Selected Countries**

Official representatives or other knowledgeable individuals from 11 countries endemic for lymphatic filariasis described the policies for filariasis control in these countries. Specific problems, successes and current directions of these programmes were reviewed as follows (see also Table 3).

China (14): Efforts to control lymphatic filariasis have been intensive and concerted since the first National Programme began in 1956, and the results have been remarkable. From a prevalence of 31 million cases in 1956, diligent use of DEC-fortified salt and mass treatment programmes with standard 2-week courses of DEC have brought the number of filariasis cases to an estimated 1.58 million. Indeed, in almost all of the originally endemic provinces prevalence is now less than 1%. Current efforts at controlling filariasis are focused on the use of DEC-fortified salt for periods of 6-9 months in communities where filariasis still remains.

Egypt (15): Despite early success at controlling bancroftian filariasis through DEC

delivery and mosquito/environmental control efforts, after the control programme was relaxed in 1965 the problem of bancroftian filariasis began to return. Currently the peri-Cairo, rural and semi-urban area of the Nile delta have foci where the prevalence of bancroftian filariasis is greater than 20%. A division of the Ministry of Health responsible for filariasis, malaria and leishmaniasis control oversees filariasis control in Egypt, and this control is based primarily on identifying microfilaraemic individuals in night-blood surveys and treating them with standard courses of DEC. Additionally, limited mosquito control efforts relying on insecticides, *Bacillus thuringiensis* and insecticide-impregnated bednets are also utilized in some areas.

French Polynesia (16): During the 1950s lymphatic filariasis was a public health priority in French Polynesia, as 30% of the population was microfilaraemic and 10% suffered from lymphoedema. Mass chemotherapy with various regimens of DEC was initiated, the schedule ultimately becoming 6 mg/kg delivered in single doses twice yearly to the entire population. Prevalence levels fell dramatically (to 2% by 1982), but after the control programme was replaced in 1982 by a passive system of DEC availability and health education, infection rates returned progressively towards pre-control levels. In 1993, the Ministry of Public Health re-initiated the mass chemotherapy programme, with DEC (3 mg/kg) being given every 6 months.

India (17): The National Filaria Control Programme (NFCP) is a division of the National Malaria Eradication Programme in the Ministry of Health. The NFCP budget is approximately 30 million rupees per year (approximately US \$1,000,000), and primary control strategies include larviciding and environmental control measures for mosquito reduction in urban areas, as well as screening urban populations by night blood surveys and treating with DEC (6 mg/kg/day x 12 days) those found either to be microfilaraemic or to have lymphoedema. Almost 4 million blood films were reported on during 1992. A small number of programmes using DEC-fortified cooking/table salt to control bancroftian

filariasis are also currently underway. Though 75% of the population at risk lives in rural areas, all filariasis control efforts are confined to urban areas. No assessment of the impact of these control efforts is routinely carried out.

Indonesia (18): Indonesia is the only country with all three species of lymphatic filarial parasites, with both periodic and sub-periodic *B. malayi* (feline and primate reservoir hosts), and with transmission by five different mosquito genera and a plethora of individual species. A National Filariasis Control Programme was established in the early 1970s, and much pioneering work on 'spaced' low-dose DEC, with appreciable community participation and involvement of the primary health care system, was carried out subsequently (19). The current strategy is based on mass distribution of low-dose DEC (100 mg for an adult, 50 mg for a child less than 10 years old) given weekly for 40 weeks by primary health care workers in endemic communities where mf prevalence is greater than 1%. This strategy has proven very successful in bringing down both microfilarial rates and the incidence of lymphoedema when they have been monitored. Efforts to identify additional villages in which this strategy can be initiated are currently in progress. It is felt that the control of lymphatic filariasis is possible using DEC as the mainstay of the control strategy.

Malaysia (20): A formal and systematic Filariasis Control Programme for Malaysia was started in the early 1960s, with current control activities incorporated under the Vector-Borne Diseases Control Programme of the Ministry of Health. With an annual incidence of 3-5 cases of microfilaraemia per 100,000 population, 17 control teams are dispersed throughout the endemic areas to carry out geographical reconnaissance, night blood surveys, treatment of cases with DEC for 6 days, follow-up evaluation and health education. These activities are concentrated in the areas of the country with the highest endemicity levels (Kedah, Perak, Kelantan, Terengganu, Pahang and Sabah).

Papua New Guinea (21): Though no formal national surveys have been carried out, areas

of heavy endemicity with very high rates of both microfilaraemia (up to 98%) and lymphatic pathology have been documented. Similarly, no national control programme yet exists for controlling lymphatic filariasis, but Ministry of Health-approved mass treatment campaigns with DEC have been undertaken both in Western Province and in the East Sepik region with external (Australia, WHO) funding and assistance.

Philippines (22): The Filariasis Control Programme is currently part of the Communicable Disease Control Service in the Philippines. Distribution of lymphatic filariasis (both bancroftian and brugian) is widespread, and the true prevalence and distribution of these infections are not completely defined. A survey in the 1960s indicated that 42 of 56 surveyed provinces were endemic for lymphatic filariasis. Control activities (treating diagnosed cases with standard DEC regimens) currently operate at a low level because of the meagre financial and personnel resources available.

Sri Lanka (23): No new cases of brugian filariasis have been reported after 1968. It is currently estimated that there are 7.5 million persons at risk of *W. bancrofti* infection along the coastal areas of the country. Until 1987, approximately 1 million blood films per year were examined for microfilariae; more recently about 2/3 of that number are examined yearly. Although thought to be an underestimate (because of inadequate sample size), the prevalence of microfilaraemic persons in these areas was 0.36% in 1993. All microfilaraemic individuals are given DEC (150 mg twice daily for 2 weeks, with an additional course of treatment one month later). The programme is administered through a governmental Anti-Filariasis Campaign (AFC) established in 1947. A major part of the control activities has now become the responsibility of the Ministries of Health of the newly constituted Provincial Councils. The national AFC is responsible for coordinating this activity and also effecting control measures outside of the 'classical' endemic areas.

Tanzania (24): Bancroftian filariasis with significant clinical disease is endemic in

coastal Tanzania and in areas near Lake Victoria and Lake Malawi. At present, there is no national programme or implemented policy for control of either morbidity or transmission; rather, there is an 'indirect' programme whereby externally supported vector control programmes to reduce malaria morbidity also help to control filariasis by using both sprayed insecticides and pyrethroid impregnated bednets. Polystyrene beads and *Bacillus sphaericus* are also used for vector control of *Culex quinquefasciatus*. These limited control efforts exist primarily in the urban areas of Dar es Salaam and Tanga, and there are no broadly applied control efforts in rural areas of the country. The political will is present, as well as the necessary expertise, but funding for filariasis control is not available except for projects sponsored by outside agencies.

Thailand (25): A Filariasis Control Programme was instituted in 1961; it is now integrated into the basic health service programme but supervised by a distinct filariasis division. No large-scale vector control measures are in effect, though use of impregnated bednets and repellents is encouraged; DEC chemotherapy is the sole control strategy employed, with various schedules being used to treat asymptomatic microfilaraemic persons and clinical cases of both bancroftian filariasis (found along the Myanmar border and thought to be imported by refugees from that country) and brugian filariasis (endemic in southern Thailand). Surveillance is performed in index areas once every two years. The overall objective is to reduce microfilarial carrier rates to at least 0.6% in all endemic areas and then to interrupt both transmission and the occurrence of lymphoedema/elephantiasis.

3. New Research Findings Giving Rise to New Control Strategies

3.1 Infection Control (Chemotherapy)

Currently there is but one available drug, diethylcarbamazine (DEC), registered for use in treating lymphatic filariasis (reviewed in ref. 26). However, a second drug, ivermectin (the current mainstay for controlling morbidity in onchocerciasis [27]),

has been evaluated extensively in recent years against lymphatic filariasis (reviewed in ref. 28), and though not yet registered for such use, it seems destined eventually to become another important tool for the control of both bancroftian and brugian filaria infection. Furthermore, despite this relative paucity of drugs for controlling lymphatic filariasis, remarkable findings about optimal ways in which DEC and ivermectin can be used (alone and in combination) have been made in recent years (29). This information has spawned the development of both new control strategies and renewed optimism that control programmes can be successful.

DEC and ivermectin are primarily microfilaricidal drugs, though it is clear that for DEC (and possibly for ivermectin) there is macrofilaricidal activity as well (26). Moreover, even if these drugs had only microfilaricidal effects, success should still be anticipated in control programmes where they are used, both because prolonged clearance or decrease of microfilariae from the blood helps to reduce transmission of infection, and because reduced transmission and decreased levels of microfilaremia in a community have long been recognized to have a positive 'clinical effect' on infected subjects (i.e., decreased frequency of ADL attacks which lead to decreased incidence of clinical lymphoedema [30]), and thus enhanced compliance in community treatment programmes.

3.1.1. *Drug regimens available for filariasis control - Comparative efficacy*

- (i) 'Standard' 12-day (*W. bancrofti*) or 6-day (*B. malayi*) courses of DEC administered repeatedly - often at one year intervals - as mass treatment to affected communities have commonly formed the basis of anti-filarial control programmes (26). Such regimens, however, have proven to be expensive and difficult to administer both because of the drug's causing rapid parasite death that leads to fever and malaise ('systemic adverse reactions'), local inflammatory reactions ('localized adverse reactions') or gastrointestinal symptoms (the major

DEC pharmacological 'side effect') in many who were initially microfilaraemic but entirely asymptomatic (31). Indeed, it is largely because this therapeutic regimen was so unpopular that alternative treatment regimens have been sought. Furthermore, while these same 'standard courses' of DEC have also been used in treatment programmes focused on 'selective chemotherapy' where only microfilaraemic individuals were treated, this strategy, too, has proven to be cumbersome and unworkable both for the reasons affecting mass treatment programmes and because of the additional resources necessary to carry out diagnostic procedures on the entire population in order to identify the microfilaraemic individuals requiring treatment. Thus, 'standard-course DEC' *can* be effective for mass chemotherapy but at a cost in resources, health personnel and patient compliance that makes it impractical for most control programmes.

- (ii) Single-dose ('spaced dose') DEC given at weekly, monthly, 6-monthly or yearly intervals has been enthusiastically advanced for many years by workers especially in the Pacific Islands and Indonesia (19,32-34); more recently, numerous controlled clinical trials have reaffirmed the efficacy of such regimens (29). While more frequent single-dose DEC (usually weekly or monthly) regimens are effective in decreasing microfilarial prevalence and density, their advantage over yearly or 6-monthly DEC may not be great enough to warrant the increased expense of more frequent drug delivery (33). For bancroftian filariasis the largest experiences with control programmes using single-dose yearly DEC have been those carried out in Tahiti (n = 50,000; [32]) and Fiji (n = 7,600; [33]) where 4 or 5 yearly-administrations of single-dose DEC resulted in decreases in microfilarial prevalence of 57% and

86% respectively, and decreases in microfilarial density of 78% and 97% respectively. Similarly, for *B. malayi* a control programme in Kerala, India (n = 22,700 [35]) with 2 annual administrations of single-dose DEC resulted in a decrease in microfilarial prevalence of 75% and in microfilarial density of 81%. It is impressive that these community trials, even though lacking complete coverage of the population at each round of treatment, yielded reductions in microfilarial densities that approximate those seen when individuals have been treated with single doses (or with the 12-day 'standard course') of DEC and followed sequentially for 12 or more months (reductions in microfilarial density of 92-96% at 1 year [29,36-38]).

- (iii) Single-dose ivermectin has not yet been used in large-scale community control programmes for lymphatic filariasis, but its effectiveness against microfilariae of both *W. bancrofti* and *B. malayi* has been evaluated in individual patients for periods of 12-24 months after drug administration. Numerous earlier studies had examined the effectiveness of lower ivermectin dosages, but it is clear now that a dose of 400 µg/kg yields definitely superior microfilaricidal activity (29,39). While microfilarial prevalence fell by only 36-70% at 12 months post-treatment, this dose decreased microfilarial densities by 86-99% for 12-24 months post-treatment in both *W. bancrofti* and *B. malayi* infections. Thus, since single yearly (or even 2-yearly) doses of ivermectin appear equally effective as similar dosing with DEC, ivermectin alone would be a valuable alternative control tool for use in endemic communities, especially where the use of DEC is contraindicated (as in areas where onchocerciasis or loiasis co-exists).

- (iv) The combination of single doses of DEC and ivermectin appears to be significantly more effective than either drug alone (29). Again, no community studies have been carried out, but at 12 and 24 months post-treatment 3 published studies (38,40-42) comprising a total of 33 *W. bancrofti* infected patients receiving an ivermectin/DEC combination showed a fall in microfilarial prevalence of 45-70% and a decrease in microfilarial density of 96-99+%. Furthermore, the dose of ivermectin used in these studies was only 20 µg/kg (with 6 mg/kg DEC), not the 400 µg/kg ivermectin dosage now felt to be optimal. In on-going trials a similar number of patients receiving the combination regimen of 6 mg/kg DEC and either 400 µg/kg ivermectin (in French Polynesia or 200 µg/kg (in India) also showed superior responses one year after treatment (>98% microfilarial reductions) compared to single doses of ivermectin or DEC alone (approximately 90% reductions). Thus, while data on this combination given at yearly or 2-yearly intervals are still preliminary, the potential value of the 'IVER/DEC' combination for use as a chemotherapeutic control tool appears most promising.

- (v) DEC-fortified salt (with DEC concentrations ranging from 0.1-0.6%) can be used as a substitute for normal cooking and table salt since DEC is chemically stable. When consumed for periods of 6-9 months it has regularly decreased microfilarial prevalence by 70-100% in both bancroftian and brugian filariasis (43). DEC-fortified salt has been used as a mainstay for control programmes in very large populations in China, Taiwan and India, with excellent results that substantiate observations made on patients followed individually and in whom prevalence of *W. bancrofti* microfilaraemia has been shown to decrease by 97% after 4 months of DEC-salt usage and

whose microfilarial densities fell even more dramatically, by greater than 99% (44). Though this strategy of DEC-salt usage does appear both workable and highly effective, essentially all of the communities in which it has been employed thus far have only had access to salt supplies that were strictly controlled by health care authorities.

3.1.2 *Adverse reactions*

The adverse reactions (both systemic and localized) developing after DEC and ivermectin treatment (even single doses) have been extensively reviewed (31,45). The systemic reactions are likely the manifestation of host inflammatory responses to parasite antigens liberated by rapid death of the microfilariae, while the localized adverse reactions are probably induced by death of the adult parasites. Such reactions are almost unavoidable, but they can be reasonably well tolerated by individuals or populations, especially if it is not necessary to have the 'long-term' compliance required to complete the 6-12 day 'standard-courses' of DEC.

Interestingly, however, not all of the chemotherapeutic control regimens described above induce the same degrees of adverse reaction. Without question, the regimen causing fewest adverse reactions is DEC-fortified salt usage, most individuals having no adverse reactions at all (43). Similarly, a recent study comparing the adverse reactions induced by different DEC regimens confirmed earlier anecdotal findings that greater 'adverse reactivity' is seen following 'standard course' 12-day DEC administration than after single-dose DEC (31). Finally, when adverse reactions of single-dose DEC and single-dose ivermectin have been compared, the degree of reactivity has generally been similar and clinically very acceptable for both drugs, though the character of the reactions (greater systemic reactions with ivermectin and more frequent localized reactions with DEC) differs somewhat (31,38,46).

3.1.3 *Macrofilaricidal activities of DEC and ivermectin*

Evidence that DEC can kill adult worms as well as microfilariae is both indirect (long-term absence of microfilariae from the blood post treatment, clearance of parasite antigen from the blood) and direct (development of inflammatory nodules containing dead parasites post-treatment, observed cessation of activity of adult worms by ultrasound techniques [26,47,48]). What is also clear, however, is that not all adult worms are killed by a single dose (or single course) of DEC and that long-term or repeated treatment is necessary to eradicate infection (26,48). The reasons for this only-partial macrofilaricidal effect of DEC are not known.

Still less certain is the degree of macrofilaricidal activity that ivermectin has, some recent studies suggesting similar levels of macrofilaricidal activity for ivermectin and DEC on *W. bancrofti* parasites (49) and others suggesting complete absence of macrofilaricidal activity for ivermectin (50).

3.2 Morbidity control

3.2.1 *Adenolymphangitis and lymphoedema/elephantiasis*

The potential for morbidity control has been greatly advanced in recent years by increased understanding of the pathogenesis of both lymphoedema and acute adenolymphangitis (ADL) in patients living in filariasis endemic areas (8,51,52). ADL episodes are characterized by pain, lymphadenitis, lymphangitis, and inflammation in the affected limb or scrotum, that are usually accompanied by fever, chills and other systemic symptoms. Although ADLs have long been recognized as regularly associated with filarial disease, their aetiology has remained uncertain, sometimes being ascribed to parasite toxins, sometimes to host immunologic responses, and sometimes to bacterial infection. Recent evidence, both from astute clinical observations and from immunohistological and bacteriological studies of tissue from lymphoedematous limbs of affected patients, has suggested that

bacterial or fungal superinfections of limbs with compromised lymphatic function play the primary role in triggering most episodes of ADL (8,51,52), which, themselves, actually cause or exacerbate the elephantiasis changes in affected patients.

A major implication of this new understanding is that *simple measures of hygiene*, coupled with *local (or in severe cases, systemic) antibiotics* given prophylactically, can have profound effects in preventing these damaging episodes of ADL and even in allowing the host to repair and recover from some or all of the overt damage caused by filarial infection and subsequent superinfections (8,51,52). Trials are in progress to determine the optimal regimens for managing such patients, but it is clear that diligent attention to local hygiene of the affected limbs will have markedly positive benefits. Preliminary evidence also suggests that community-based *patient self-help groups* work extremely effectively to stimulate and maintain personal compliance with the vigorous hygiene regimens required for this morbidity control; and this newly enunciated strategy is clearly one that can be exploited worldwide, because nowhere are such patients lacking in the intense desire to rid themselves of their debilitating and ostracizing deformities. Further validation and utilization of this approach should lead to dramatic decreases in the morbidity caused by filariasis that should, in turn, have profound socio-economic impact in endemic countries.

3.2.2 "*Asymptomatic*" microfilaraemia

The second new approach to controlling the morbidity of lymphatic filariasis derives from now recognizing the urgency of treating patients with 'asymptomatic microfilaraemia'. The ability of such individuals to remain asymptomatic probably relates to their immunologically down-regulated state (53), but two sets of recent observations have revealed that this being clinically 'asymptomatic' in no way implies freedom from 'morbidity'. First, it was recognized that most of these microfilaraemic individuals have haematuria and/or proteinuria that reflects low-grade renal damage which does appear generally to be

reversible after treatment (11). Second, and even more dramatic, were the observations by several groups of investigators using lymphoscintigraphy to visualize by radioisotope tracer techniques the functional anatomy of the lymphatic vessels (12,13). What was seen was quite surprising, as almost all of these infected individuals, even though asymptomatic, had markedly abnormal, dilated lymphatics and markedly abnormal patterns of lymph flow. Though reversibility of these lymphatic abnormalities with treatment has not yet been demonstrated, it is clear that the asymptomatic microfilaraemic state is not so benign as initially believed, and such patients should probably be treated as early as possible to prevent or limit irreversible damage to the lymphatic and renal systems.

Finally, the further recognition from lymphoscintigraphy studies that lymphoedema is not always the result of occlusion of lymphatic channels but can also occur when there are extensive collaterals (12,13) confirms the expectation that alternative lymph flow patterns can be established through lymphatic collaterals. Again, such findings have important practical implications for morbidity control, since they suggest that even the so called 'burnt-out' cases with gross lymphoedema and elephantoid changes can be helped. The treatment of such cases should be aggressive and should employ the most appropriate tools available, be they foot care, antibiotics, other drugs or even, in those special cases where indicated, surgical shunt procedures (54). Not only do the treated individuals themselves benefit tremendously from the reversal of such morbidity, but community control programmes also become more successful, since these 'visible' improvements can be appreciated by all in the endemic communities.

3.3 Vector control

Vector control has played an important supporting role for filariasis control in many local programmes, and the reduction of vector density can be an important contributor to sustained interruption of transmission. However, control programmes based entirely on vector reduction have rarely been continued long enough to decrease the

prevalence of filarial infection in human populations, and experience suggests that for its greatest impact vector control should be implemented within the framework of an integrated filariasis control programme based on drug administration.

Certain new technologies are now available to improve vector control efforts, though all still require further assessment of their long-term impact on infection in the human population. These include the following:

(i) **Biocides:** The toxin-producing bacterium *Bacillus sphaericus* is the most promising new biocidal candidate for controlling larvae of *Culex quinquefasciatus*, the main vector of lymphatic filariasis in many endemic areas of the world (55), and even for controlling the *Mansonia* vectors of brugian filariasis in certain regions (56). Appropriate formulations of this microbial agent have shown significant residual activity against *Cx. quinquefasciatus* and *Cx. pipiens* in highly polluted breeding habitats, and this bacterium has the potential to persist and recycle under field conditions for up to 3 months. It is environmentally safe and suitable for integrated control programmes with community participation. The estimated cost for vector control programmes using *B. sphaericus* has been estimated as less than US \$0.5 per person per year in areas where breeding habitats of mosquito vectors are very common. In recent large-scale field trials in north Cameroon, Brazil, India, Sri Lanka and Tanzania a remarkable impact of *B. sphaericus* use has been observed in reducing vector biting density by 80% through bi-monthly treatment of mosquito larval habitats; in addition, there was a significant decline in the proportion of *Culex* carrying filarial infective larvae. Thus *B. sphaericus* (alternated with *B. thuringiensis*) may prove to be the selective mosquito-control agent of choice for use against *Cx.*

quinquefasciatus in integrated control programmes.

(ii) **Polystyrene beads:** Control of mosquito vector breeding in closed water systems (pit latrines and cesspits) through use of expanded polystyrene beads has been extremely effective in certain urban areas with endemic filariasis (57).

(iii) **Insecticide-impregnated bednets and curtains:** Use of insecticide-treated bednets has been successfully employed in numerous countries to control the anopheline vectors of malaria (58). The value of these methods for filariasis control must still be determined, but preliminary findings from Papua New Guinea are promising.

(iv) **New formulations of pyrethroids:** Synthetic pyrethroids with long-lasting residual effects (up to one year) can be highly successful in controlling adult mosquitos when used for total indoor spraying in urban settings (59). Furthermore, new repellent formulations (soap with DEET and permethrin as active ingredients) have good efficacy against *Mansonia* adults and residual protection when applied on human skin (60). Among the household insecticide products, mosquito coils that contain knockdown synthetic pyrethroids also give reasonably good protection against *Culex* and *Mansonia* mosquitos.

(v) **Integrated vector management:** Rapid unplanned urbanization is associated with problems of inadequate water supply, poor sewage disposal, insufficient solid waste management and poor water drainage, all of which result in a profusion of breeding habitats for *Cx. quinquefasciatus* and in increased filariasis transmission. While repairing septic tanks and upgrading the quality of pit latrines should be considered important components of vector

control campaigns in urban areas, the joint efforts of high-level policy and decision makers with health authorities and municipal planners are also required. Moreover, linkage with non-health sectors must also occur within municipalities to ensure their involvement through carefully developed intersectoral collaboration. Finally, eliciting and sustaining community interest and participation in mosquito control programmes should be important components of integrated vector management, as clearly indicated in numerous examples of successful community participation in the removal of aquatic plant breeding habitats of *Mansonia* mosquitos and in undertaking commercialization of larvivorous/phytophagous fish culture in such habitats, both of which have contributed greatly to sustainable reductions of mosquito populations (61).

3.4 Programme development and oversight

Though the tools necessary to control lymphatic filariasis may well now be in hand, it is necessary to develop and evaluate appropriate implementation strategies that will not only be economical but also be acceptable to the community and sustainable for long periods. Simultaneous development of appropriate monitoring and surveillance methods is also a prerequisite for successful programme management.

3.4.1 *New tools for diagnosis and epidemiological assessment and monitoring*

Diagnosis of active infection is important for determining the level of endemicity of filariasis and for evaluating the success of control measures. At present, however, the identification of microfilariae in the blood (usually, of necessity, sampled at night) is the only absolute indicator of active infection utilized for large populations, and the problems associated with this diagnostic approach are well recognised (including the

fact that some actively infected patients have no circulating microfilariae). In addition, antibody-based assays, the usual type of immunodiagnostic test used to date, generally cannot distinguish between active and prior infection; they also have significant problems with specificity, since individuals are often concurrently infected by 'cross-reacting' gastrointestinal parasites.

Important new diagnostic tools, however, have recently become available; these are the following:

(i) Assays to detect circulating filarial antigen (CFA)

The most recent and promising immunodiagnostics are circulating antigen assays that can identify patients with either microfilaraemic or occult infections; thus, they are of particular value for determining endemicity of infection and efficacy of control measures. The 'first generation' of such assays detected circulating phosphorylcholine-containing antigens and proved helpful in assessing infection rates in areas where transmission had been altered by insecticide spraying, in evaluating reinfection following administration of DEC, and in determining possible infection in amicrofilaremic persons (62). More recent diagnostic tests have detected protein antigens whose epitopes react with the monoclonal antibodies Og4C3 (63) and AD12 (64). These assays detect circulating antigens in sera from essentially all microfilaraemic and a proportion of amicrofilaremic persons residing in *W. bancrofti* endemic areas. Importantly, the levels of circulating antigen appear constant throughout the day (unlike microfilaraemia) and fall to zero after successful chemotherapy has killed the adult worms. *Unfortunately, no comparable assays exist for B. malayi infections.*

(ii) DNA-detection assays

DNA-based technology can now also be used for diagnosis of filarial infection both in humans and in the mosquito vectors by polymerase chain reaction (PCR)-based assays which provide outstanding sensitivity and specificity. For *B. malayi*, PCR techniques can detect a single L3 in pools of up to 100 mosquitos, a single microfilaria in 1 ml of blood, or the equivalent of 1 µg of DNA in 100 µl of blood (65). Recently a similar PCR assay for *W. bancrofti* has been developed with similar sensitivity (66). It is estimated that one technician can now use these assays to screen up to 3600 mosquitos (36 runs of 100 mosquitos each) or 1,000 blood samples in *one* day. The current cost for materials (primarily for the enzymes required for PCR) is US \$1.00 per run.

The advantages of PCR-based tests include high degrees of sensitivity and species-specificity, their detection of only current infections, and the rapidity with which their results can be obtained (same day). In addition, samples can be preserved at ambient temperature for months and shipped to a central laboratory for assay. The primary drawbacks of this technology are the special training and equipment required, and the need for its performance in a central laboratory with good quality control. In addition, its use in assessing transmission of infection in vectors requires further validation in order to relate the semiquantitative PCR output to the transmission indices in standard use that are based on detection of infective larvae in dissected mosquitoes.

(iii) Rapid epidemiological assessment

In part because lymphatic filariasis is geographically widespread but often focal, rapid epidemiological assessment is essential for mapping

the distribution of infection in order to select appropriate control strategies in specific epidemiological situations.

Currently, night blood surveys are the primary method for determining the level of endemicity in a community, and it is this technique that must be replaced by some more 'rapid assessment' method such as: (a) estimation of disease or mf carrier rates through review of existing health reports and hospital/clinic records; (b) clinical examination of adult males for hydrocoeles, with extrapolation to gauge overall prevalence of infection; (c) analysis of mosquito vectors for infection, using traditional entomologic methods or even DNA-based larval detection, if cost-effective and feasible; (d) evaluation of antigenaemia rates in daytime, finger-prick blood specimens from children or other cohorts of the population.

3.4.2. *Predictive models*

Mathematical models now serve as powerful tools for analysis, prediction and evaluation of control strategies in several parasitic infections (67,68), and development of such models is particularly important for lymphatic filariasis since the overall infection/transmission cycle involves particularly complex interactions among the human, parasite and vector populations (69,70). Furthermore, the very long time scales of the processes of filarial infection and disease also mean that such models can provide cost-effective tools for studying both the population dynamics of transmission and the consequences of control. Indeed, recent experience with the simulation model (ONCHOSIM) developed for the Onchocerciasis Control Programme in West Africa (67) has highlighted the usefulness of such models for aiding the design of control strategies, analyzing the relative efficacy of different intervention strategies and providing precise information on cost-effectiveness of the various approaches.

3.4.3 *Social and economic issues in control programmes*

3.4.3.1 Socioeconomic findings

Because of a dearth of information on both social impact and economic costs of lymphatic filariasis, research studies initiated by WHO/TDR are currently collecting data on these aspects of the disease. The important results of these studies (carried out in India, Ghana, Tanzania and the Philippines) will be available in 1995 and will detail social attitudes towards the disease, the direct and indirect costs of acute and chronic disease, and the extent of disease in women. The results should be useful in quantifying the socioeconomic burden of the disease and in providing indicators for evaluating the success of intervention control strategies.

3.4.3.2 Community participation

Community participation is a recognized prerequisite for successful control programmes based on integrated vector control and filarial disease control (61), but the type and level of community involvement will depend on the characteristics of the target community.

The most frequently encountered barriers to engendering community participation in filariasis control are:

- (i) the perception that filariasis is not serious because it is not a fatal disease,
- (ii) the fact that it has a slow progression to chronic sequelae,
- (iii) the heretofore absence of hope for clinical cure among people with elephantiasis,
- (iv) a lack of awareness of the cause of the disease, and
- (v) the perception, particularly among urban dwellers, that their taxes are sufficiently high that governmental agencies should be able to solve public health problems without further community involvement.

As demonstrated, however, in many of the most successful filariasis control programmes, the characteristics of success in engendering community participation include a 'horizontal' community-based approach, a 'bottom-up' strategy, and, especially, linking the programme with *income-generating* activities (61).

4. Conclusion

Lymphatic filariasis is more widespread and inflicts a very much greater disease burden worldwide than was recognized even three years ago at the time of the last WHO Expert Committee on the Control of Lymphatic Filariasis (2). The availability of new, simplified, effective and affordable control strategies together with the recent designation of lymphatic filariasis as one of only six infectious diseases considered eradicable or potentially eradicable (71) makes this an ideal time to initiate a global programme to control or eliminate this disease from all endemic countries and to assert the optimistic expectation that such a programme will be successful.

4.1 Recommendations for Control Strategies

- (a) The focus of control efforts should be on treating the infection in human populations, with vector control serving a supporting role when feasible and affordable.
- (b) 'Mass-distribution' programmes should completely replace those based on a 'selective-treatment' strategy (i.e., detection of microfilaraemics who are then treated 'selectively').
- (c) Regimens recommended for mass treatment in areas where there is *no* co-existing onchocerciasis or loiasis would be *either of the following*:
 - (i) DEC-fortified salt (0.2 - 0.4%) used in place of regular salt for all cooking and seasoning for a period of 9-12 months;
 - (ii) Single, annual or semi-annual mass administration of DEC (6 mg/kg body weight) for 5-10 years.
- (d) When ivermectin becomes registered for use in lymphatic filariasis, two additional mass treatment regimens will be available:

- (i) ivermectin (400 µg/kg) given once yearly - a regimen safe in areas where onchocerciasis or loiasis might also be prevalent;
- (ii) ivermectin (400 µg/kg) plus DEC (6 mg/kg) given once yearly, *except in areas where onchocerciasis or loiasis co-exists*.

- (e) Adjunctive vector control could include the use of biocides (especially *Bacillus sphaericus*), polystyrene beads, insecticide impregnated bednets and curtains, long-lasting residual pyrethroids, and community supported vector management, as locally appropriate.

4.2 Operational Research Needs

Though *currently available information is sufficient to justify the immediate initiation of large-scale filariasis control or elimination programmes*, there are still important issues which, if resolved, would considerably enhance programme design and implementation; specifically, these issues/needs are the following:

- (a) more precise estimates of the global, regional and national burden of illness caused by lymphatic filariasis, and rapid assessment techniques to help make these estimates;
- (b) a control strategy able to be used safely and effectively in areas where bancroftian filariasis may co-exist with onchocerciasis or loiasis (i.e., one based on ivermectin delivery, on use of DEC-fortified salt if proven safe, or on wide-scale vector control); large areas of Africa would thus be 'opened' for treatment of lymphatic filariasis;
- (c) detailed, cost-effectiveness analyses (CEA):
 - comparing yearly mass treatment and (DEC) fortified-salt approaches to

- controlling lymphatic filariasis, (including ways in which the delivery of anti-filarial medication can be integrated with other health and non-health delivery systems);
- for vector control - not as a single option for filariasis control, but as a potential adjunct to chemotherapeutic strategies based on annual mass treatment or use of DEC-fortified salt;
 - of surveillance and rapid assessment procedures under actual conditions of implementation - in particular, comparing DNA-based techniques and mosquito dissection for detection of vector infectivity, and comparing assessment of blood antigenaemia both with microfilarial detection by microscopy and with clinical or historical techniques for determining prevalence of infection in a community;
- (d) delineation and quantification of the economic and social costs of filarial disease, including the costs both to individuals and to the national health care budget for management of elephantiasis, hydrocoele and adenolymphangitis;
- (e) further definition of the clinical consequences of 'asymptomatic' microfilaraemia (in addition to the newly-recognized lymphatic and renal function abnormalities), as these consequences are relevant to calculating the social and economic costs of filarial disease;
 - (f) evaluation of simple measures such as local hygiene and foot care and the use of antibiotics locally or systemically for preventing or controlling morbidity;
 - (g) evaluation of the personal and social psychology of compliance with annual mass treatment or long-term fortified-salt usage, and of decision-making in the personal-choice use of fortified salt;
 - (h) predictive models, particularly relevant to the kinds of information required by control managers for use as tools for monitoring control programmes;
 - (i) uniform surveillance and monitoring techniques so that *types* of site-specific control strategies can be defined, as well as those areas where total eradication of infection will be most easily achieved.

TABLE 1a

Global burden of bancroftian filariasis by sex and demographic region.

Estimates: upper number = cases in millions; lower number (in brackets) = prevalence (%) in region.

<i>Condition and sex</i>	<i>World</i>	<i>Sub-Saharan Africa</i>	<i>India</i>	<i>China+</i>	<i>Other Asia and islands</i>	<i>Latin America and the Caribbean</i>	<i>Middle Eastern Crescent</i>
Population	4,119.86*	512	850	1,134	793	441	391
<i>Microfilaraemia - Males</i>	40.86 (1.95)	14.74 (5.82)	17.00 (3.87)	2.25 (0.39)	6.54 (1.63)	0.19 (0.08)	0.13 (0.06)
<i>Microfilaraemia - Females</i>	32.41 (1.60)	13.13 (5.07)	12.46 (3.04)	1.80 (0.33)	4.79 (1.22)	0.13 (0.06)	0.11 (0.06)
<i>Lymphoedema - Males</i>	5.36 (0.26)	1.78 (0.68)	2.60 (0.60)	0.06 (0.01)	0.92 (0.23)	0.014 (0.006)	0.027 (0.01)
<i>Lymphoedema - Females</i>	7.81 (0.39)	2.86 (1.10)	3.98 (0.97)	0.05 (0.009)	0.87 (0.22)	0.017 (0.008)	0.029 (0.02)
<i>Hydrocoele - Males</i>	26.79 (1.28)	10.20 (4.03)	12.88 (2.93)	1.68 (0.29)	1.90 (0.48)	0.057 (0.03)	0.06 (0.03)
<i>Total cases - Males**</i>	66.65 (3.18)	24.28 (9.60)	29.43 (6.70)	3.62 (0.62)	8.87 (2.21)	0.246 (0.11)	0.207 (0.10)
<i>Total cases - Females**</i>	39.54 (1.95)	15.74 (6.08)	16.10 (3.92)	1.84 (0.34)	5.59 (1.42)	0.149 (0.07)	0.135 (0.07)

* Total population in regions where significant infection exists. Population figures and regions as given and defined for the World Bank Global Burden of Disease Study.

** Equals sum of the number of patients with microfilaraemia alone plus the number of patients with overt disease (lymphoedema or hydrocoele) less the number with both overt disease and microfilaraemia (estimated at 0.9% for lymphoedema and 22% for hydrocoele [see ref. 5 for details of this estimation]).

+ *N.B.* The figures in this column are based on estimates as calculated in ref. 5. Official Chinese government estimates are different, as follows: Population (in millions) 344; microfilaraemia (males: 0.05; females: 0.05); lymphoedema (males: 0.06; females: 0.06); hydrocoele (male only: 0.42); chyluria (males: 0.24; females 0.23); total cases (males: 0.75; females: 0.33).

TABLE 1b

Global burden of brugian filariasis by sex and demographic region.

Estimates: upper number = cases in millions; lower number (in brackets) = prevalence (%) in region.

Condition and sex	World	India	China+	Other Asia and islands
Population	2,776.35*	850	1,134	793
Microfilaraemia - Males	6.515 (0.45)	1.105 (0.25)	2.235 (0.38)	3.175 (0.79)
Microfilaraemia - Females	3.840 (0.28)	0.692 (0.17)	1.250 (0.23)	1.895 (0.48)
Lymphoedema - Males	1.804 (0.13)	0.582 (0.13)	0.461 (0.08)	0.761 (0.19)
Lymphoedema - Females	1.004 (0.07)	0.282 (0.07)	0.271 (0.05)	0.452 (0.12)
Total cases - Males**	8.159 (0.57)	1.635 (0.37)	2.655 (0.45)	3.869 (0.97)
Total cases - Females**	4.752 (0.35)	0.949 (0.23)	1.496 (0.27)	2.306 (0.59)

* Total population in regions where significant infection exists. Population figures and regions as given and defined for the World Bank Global Burden of Disease Study.

** Equals sum of the number of patients with microfilaraemia alone plus the number of patients with overt disease (lymphoedema or hydrocoele) less the number with both overt disease and microfilaraemia (estimated at 0.9% for lymphoedema and 22% for hydrocoele [see ref. 5 for details of this estimation]).

+ N.B. The figures in this column are based on estimates as calculated in ref. 5. Official Chinese government estimates are different, as follows: Population (in millions) 344; microfilaraemia (males: 0.005; females: 0.005); lymphoedema (males: 0.25; females: 0.22); total cases (males: 0.255; females: 0.225).

TABLE 2a

Global burden of bancroftian filariasis by age-group and sex.
 Estimates: upper number = cases in millions; lower number (in brackets) = prevalence (%).

<i>Condition and sex</i>	<i>Age in years</i>						<i>Total</i>
	<i>0-4</i>	<i>5-14</i>	<i>15-44</i>	<i>45-59</i>	<i>60+</i>		
<i>Population*</i>	551.89	918.36	1,932.49	432.02	285.10		4,119.86
<i>Microfilaraemia - Males</i>	1.44 (0.51)	5.75 (1.22)	24.54 (2.48)	6.15 (2.81)	2.99 (2.18)		40.86 (1.95)
<i>Microfilaraemia - Females</i>	1.21 (0.45)	5.69 (1.27)	18.22 (1.93)	4.55 (2.13)	2.75 (1.86)		32.41 (1.60)
<i>Lymphoedema - Males</i>	0.05 (0.01)	0.28 (0.06)	2.84 (0.06)	1.39 (0.64)	0.79 (0.58)		5.36 (0.26)
<i>Lymphoedema - Females</i>	0.08 (0.03)	0.66 (0.15)	3.61 (0.38)	1.18 (0.85)	1.65 (1.11)		7.81 (0.39)
<i>Hydrocoele - Males</i>	0.06 (0.02)	1.82 (0.39)	15.62 (1.58)	5.65 (2.58)	3.64 (2.66)		26.79 (1.28)

* Total population in regions where significant infection exists. Regions as defined for the World Bank Global Burden of Disease Study.

TABLE 2b

Global burden of brugian filariasis by age-group and sex.

Estimates: upper number = cases in millions; lower number (in brackets) = prevalence (%).

Condition and sex	Age in years						Total
	0-4	5-14	15-44	45-59	60+		
Population*	340.19	578.03	1342.36	308.54	207.21	2776.35	
<i>Microfilaraemia - Males</i>	0.203 (0.12)	0.899 (0.30)	4.05 (0.58)	0.882 (0.55)	0.482 (0.47)	6.515 (0.46)	
<i>Microfilaraemia - Females</i>	0.197 (0.11)	0.552 (0.20)	2.27 (0.35)	0.462 (0.31)	0.348 (0.33)	3.84 (0.28)	
<i>Lymphoedema - Males</i>	0.018 (0.01)	0.047 (0.015)	0.759 (0.11)	0.506 (0.32)	0.472 (0.46)	1.804 (0.13)	
<i>Lymphoedema - Females</i>	0.008 (0.00001)	0.027 (0.01)	0.349 (0.05)	0.299 (0.20)	0.328 (0.31)	1.004 (0.07)	

* Total population in regions where significant infection exists. Regions as defined for the World Bank Global Burden of Disease Study.

TABLE 3

Filariasis control efforts in selected endemic countries

Country*	Estimate of prevalence (millions)	% under Active Control Programme	Yearly operational expenditure for filariasis control (US \$)	Control ** strategy
China	1.58	100%	1,279,000	D
Egypt	0.35	10%	500,000	D, V
French Polynesia	0.02	90%	50,000	D
India	36	10%	1,000,000	D, V
Indonesia	N.A.	N.A.	N.A.	D
Malaysia	0.003	60%	500,000	D
Papua New Guinea	1.0	<1%	90,000	D
Philippines	1.02	32%	27,100	D
Sri Lanka	0.05	60%	300,000	D
Tanzania	1.5	0%	0	V
Thailand	0.62	30%	1,000,000	D

* All data supplied by country representatives in attendance

** D = DEC treatment regimen; V = Vector control programme

N.A. - Not available

REFERENCES

1. WHO Expert Committee on Filariasis. *Fourth Report*. Geneva, World Health Organization 1984 (WHO Technical Report Series 702), pp 1-112.
2. *Lymphatic filariasis: The disease and its control*. Geneva, World Health Organization 1992 (WHO Technical Report Series 821), pp 71.
3. Hawking F. The distribution of human filariasis throughout the world. Part III. Africa. *Tropical Diseases Bulletin* 1977;74:649-679.
4. Michael E & Bundy DAP. The global burden of lymphatic filariasis. In *The Burden of Disease* (eds. CJL Murray & AD Lopez). Geneva, World Health Organization 1995 (in press).
5. Michael E, Bundy DAP & Grenfell BT. Estimating the global prevalence of lymphatic filariasis (manuscript in preparation).
6. Hui-Jun Z. *Geographic distribution and prevalence of lymphatic filariasis: update in the Western Pacific region*. Geneva, World Health Organization 1991 (unpublished document FIL/EC/91/WP.4).
7. Pani SP, Balakrishnan N, Srividya A, Bundy DAP & Grenfell BT. Clinical epidemiology of bancroftian filariasis: effect of age and gender. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1991;85:260-264.
8. Pani SP, Yuvaraj J, Vanamail P, Dhanda V, Michael E, Grenfell, BT & Bundy DAP. Episodic adenolymphangitis and lymphoedema in patients with bancroftian filariasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1995;89: (in press).
9. World Bank *World Development Report 1993. Investing in health (World development indicators)*. 1993; Oxford University Press, New York, pp 1-329.
10. Evans DB, Gelband H & Vlassoff C. Social and economic factors and the control of lymphatic filariasis: a review. *Acta tropica* 1993;53:1-26.
11. Dreyer G, Ottesen EA, Galdino E, Andrade L, Rocha A, Medeiros Z, Moura I, Casimiro I, Beliz R, Coutinho A. Renal abnormalities in microfilaremic patients with bancroftian filariasis. *American Journal of Tropical Medicine and Hygiene* 1992;46:745-751.
12. Witte MH, Jamal S, Williams WH, Witte CL, Kumaraswami V, McNeil GC, Case TC, Panicker TMR: Lymphatic abnormalities in human filariasis as depicted by lymphoangioscintigraphy, *Archives of Internal Medicine* 1993;153:737-744.
13. Freedman DO, Filho PJ, Besh S, Silva M, Braga C, Maciel A: Lymphoscintigraphic analysis of lymphatic abnormalities in symptomatic and asymptomatic human filariasis. *Journal of Infectious Diseases* 1994;170:927-933.
14. Sun DJ. A great success in lymphatic filariasis control in China. *Chinese Journal of Parasitology and Parasitic Diseases* (in press).
15. Harb M, Faris R, Gad AM, Hafez ON, Rawzy R, Buck AA. The resurgence of lymphatic filariasis in the Nile Delta. *Bulletin of the World Health Organization* 1993;71:49-54.
16. Perolat P, Guidi C, Rivière F, Roux J. Filariose de Bancrofti Polynésie Française. Situation épidémiologique et perspectives après 30 ans de lutte. *Bulletin de la Société de Pathologie exotique* 1986;79:78
17. Biswas H, Sharma SP, Das M, Gopala Rao V, Yadava RL and Narasimham MVVL. Filariasis control in rural areas through detection and treatment with diethylcarbamazine. *Journal of Communicable Diseases* 1989;21:272-281.
18. Partono F, Maizels RM, Purnomo. Towards a filariasis free community: evaluation of filariasis control over an eleven year period in Flores, Indonesia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1989;83:821-826.
19. Partono F, Purnomo, Soewarta A, Sri Oemijati. Low dosage diethyl-carbamazine administered by villagers for the control of timorian filariasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1984;78:370-372.
20. Vector Borne Disease Control Programme. *Annual Report 1993*. Kuala Lumpur, Malaysia.
21. (not available).
22. Technical Service Manual, Department of Health, The Philippines.
23. Dissanaiké AS. Filariasis in Ceylon then (1961) and in Sri Lanka now (1990) - 30 years on. *Annals of Tropical Medicine and Parasitology* 1991;85:123-129.

24. Minjas JN and Kihamia, CM. "Bancroftian filariasis". In Mwaluko GMP, Kilama WL, Mandara MP, Murru M and Macpherson CNL (eds) *Health and Disease in Tanzania*. Harper Collins Academic, 1991, London, pp 158-176.
25. Suvannadabba S. Current status of filariasis in Thailand. *Southeast Asian Journal of Tropical Medicine and Public Health* 1993;24:5-7.
26. Ottesen EA. Efficacy of diethylcarbamazine in eradicating infection with lymphatic-dwelling filariae in humans. *Reviews of Infectious Diseases*, 1985;7:341-356.
27. WHO Expert Committee on Onchocerciasis. Geneva, World Health Organization 1995 (WHO Technical Report Series) (in press).
28. Ottesen EA and Campbell WC. Ivermectin in human medicine. *Journal of Antimicrobial Chemotherapy* 1994;34:195-203.
29. Chodakewitz JA. Ivermectin and lymphatic filariasis: clinical update. *Parasitology Today* 1995 (in press).
30. Pani SP, Krishnamoorthy K, Prathiba J and Rao RS. Diethylcarbamazine and supportive measures for the treatment of Brugian filariasis. *The National Medical Journal of India* 1989;2:260-263.
31. Dreyer G, Pires ML, Andrade L, Lopes E, Medeiros Z, Tenorio J, Coutinho A, Noroes J, Figueredo-Silva J. Tolerance of diethylcarbamazine by microfilaraemic and amicrofilaraemic individuals in an endemic area of Bancroftian filariasis, Recife, Brazil. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994;88:232-236.
32. Laigret J, Fagneaux G, & Tura E. Chimiothérapie de masse par la diéthylcarbamazine en doses espacées: effets obtenus à Tahiti sur la microfilarémie à *Wuchereria bancrofti*, var. *pacifica*. *Bulletin de l'Organisation mondiale de la Santé* 1980;58:779-783.
33. Mataika JU, Kimura E, Koroivueta J, Kaisuva JN, Brown M, Tuivaga J, Bikai S, Govind SR. Comparison of the efficacy of diethylcarbamazine between 5 rounds of annual single-dose treatment and an intensive 28-dose treatment spread over 2 years against diurnally subperiodic *Wuchereria bancrofti* in Fiji. *Fiji Medical Journal* 1993;19:2-6.
34. Kimura E, Penaia L & Spears GF. The efficacy of annual single-dose treatment with diethylcarbamazine citrate against diurnally subperiodic bancroftian filariasis in Samoa. *Bulletin of the World Health Organization* 1985;63:1097-1106.
35. Panicker KN, Krishnamoorthy K, Sabesan S, Prathiba J and Abidha. Comparison of effects of mass annual and biannual single dose therapy with diethylcarbamazine for the control of Malayan filariasis. *Southeast Asian Journal of Tropical Medicine and Public Health* 1991;22:402-411.
36. Cartel JL, Spiegel, Nguyen Ngnoc L, Cardines R, Plichart R, Martin PM, Roux JF, Moulia-Pelat JP. Compared efficacy of repeated annual and semi-annual doses of ivermectin and diethylcarbamazine for prevention of *Wuchereria bancrofti* filariasis in French Polynesia. Final evaluation. *Tropical Medicine and Parasitology*, 1992;43:91-94.
37. Shenoy RK, Kumaraswami V, Rajan K, Thankom S and Jalajakumari. A comparative study of the efficacy and tolerability of single and split doses of ivermectin and diethylcarbamazine in periodic brugian filariasis. *Annals of Tropical Medicine and Parasitology* 1993;87:459-467.
38. Dreyer G, Coutinho A, Miranda D, Noroes J, Rizzo JA, Galdino E, Rocha A, Medeiros Z, Andrade LD, Santos A, Figueredo-Silva J & Ottesen EA. Treatment of bancroftian filariasis in Recife, Brazil: Comparison of ivermectin and diethylcarbamazine in a long-term (two-year) study. *The American Journal of Tropical Medicine and Hygiene*, 1994;50:339-348.
39. Moulia-Pelat Y, Glaziou P, Nguyen LN, Chanteau S, Plichart R, Beylier I, Martin PMV, Cartel JP. Ivermectin 400 µg/kg: Long-term suppression of microfilariae in bancroftian filariasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994;88:107-109.
40. Richards FO, Eberhard ML, Bryan RT, McNeeley DF, Lammie PJ, McNeeley MB, Bernard Y, Hightower AW, Spencer HC. Comparison of high dose ivermectin and diethylcarbamazine for activity against bancroftian filariasis in Haiti. *The American Journal of Tropical Medicine and Hygiene* 1991;44:3-10.

41. Addiss DG, Eberhard ML, Lammie PJ, McNeeley MB, Lee SH, McNeeley DF and Spencer HC. Comparative efficacy of clearing-dose and single high-dose ivermectin and diethylcarbamazine against *Wuchereria bancrofti* microfilaremia. *The American Journal of Tropical Medicine and Hygiene* 1993;**48**:178-185.
42. Kazura J, Greenberg J, Perry R, Weil G, Day K and Alpers M. Comparison of single dose diethylcarbamazine and ivermectin for treatment of bancroftian filariasis in Papua New Guinea. *The American Journal of Tropical Medicine and Hygiene* 1993;**49**:804-811.
43. Gelband H. Diethylcarbamazine salt in the control of lymphatic filariasis. *The American Journal of Tropical Medicine and Hygiene* 1994;**50**:655-662.
44. Jingyuan L, Zi C, Xiaohang H and Zhaoping T. Mass treatment of filariasis using DEC-medicated salt. *Journal of Tropical Medicine and Hygiene* 1992;**95**:132-135.
45. Ottesen EA. Description, mechanisms and control of post-treatment reactions in human filariasis. *Ciba Foundation Symposium* 1987;**127**:265-283.
46. Huijun Z, Piessens WF, Zhenghou T, Wenfang C, Shihai W, Shizhi C, Yangming Y, Laifeng L, Xiaorui C and Genbao G. Efficacy of ivermectin for control of microfilaremia recurring after treatment with diethylcarbamazine. I. Clinical and parasitologic observations. *The American Journal of Tropical Medicine and Hygiene* 1991;**45**:168-174.
47. Weil GJ, Lammie PJ, Richards FO and Eberhard ML. Changes in circulating parasite antigen levels after treatment of bancroftian filariasis with diethylcarbamazine and ivermectin. *The Journal of Infectious Diseases* 1991;**164**:814-816.
48. Dreyer G, Amaral F, Noroes J, Medeiros Z, Addiss D. A new tool to assess the adulticidal efficacy in vivo of antifilarial drugs for bancroftian filariasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* (in press).
49. Ismail MM, Jayasinghe KSA, Premaratne UN, Weil GJ, Abeyewickreme W, Rajaratnam HN, Rezvi Sherif MH, Selvie Perera C. Prolonged clearance of microfilaraemia and antigenaemia in patients with bancroftian filariasis after multiple high doses of ivermectin or DEC (manuscript in preparation).
50. Dreyer G, Noroes J, Amaral F, Adauto N, Medeiros Z, Coutinho A & Addiss D. Direct assessment of the adulticidal efficacy of single-dose ivermectin in bancroftian filariasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* (in press).
51. Olzewski, WL, Jamal S, Dworozynski A, Swoboda E, Pani SP, Monokaran G, Kumaraswami V and Bryla P. Bacteriological studies of skin, tissue fluid and lymph in filarial lymphoedema. *Lymphology* 1994;**27**(Suppl):345-348.
52. Addiss DG, Eberhard ML, Lammie PJ. 'Filarial' adenolymphangitis without filarial infection [letter]. *Lancet* 1994;**343**:597.
53. Ottesen EA. Infection and disease in lymphatic filariasis: An immunological perspective. *Parasitology* 1992, **164**:S71-79.
54. Jamal S. Lymphovenous anastomosis in filarial lymphedema. *Lymphology* 1981;**14**:64-68.
55. Hougard JM, Mbentengam R, Lochouarn L, Escaffre H, Darriet F, Barbazan P, Quillévére D. Campaign against *Culex quinquefasciatus* using *Bacillus sphaericus*: Result of a pilot project in a large urban area of equatorial Africa. *Bulletin of the World Health Organization* 1993;**71**:367-375.
56. Cheong WC and Yap HH. Bioassay of *Bacillus sphaericus* (strain 1953) against mosquitoes of public health importance in Malaysia. *Southeast Asian Journal of Tropical Medicine and Public Health* 1985;**16**:54-58.
57. Maxwell CA, Curtis CF, Haji H, Kisumku S, Thalib AI, Yahya SA. Control of bancroftian filariasis by integrating therapy with vector control using polystyrene beads in wet pit latrines. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1990;**84**:709-714.
58. Rozendaal JA. Impregnated mosquito nets and curtains for self-protection and vector control. *Tropical Diseases Bulletin* 1989;**86**:1-41.
59. Vasuki V, Rajavel AR. Beta-cyfluthrin, a synthetic pyrethroid for mosquito control. *Southeast Asian Journal of Tropical Medicine and Public Health* 1992;**23**:318-323.
60. Abu Hassn A, Narayanan V. Effectiveness of a soap repellent against *Mansonia* mosquitoes in a fresh water swamp forest in Northwestern Malaysia. *Bulletin of the Society for Vector Ecology* 1992;**17**:83-84.

61. Panicker KN, Jayasree M, & Krishnamoorthy K. A cost benefit analysis of fish culture strategy towards the control of mansonioides in Shertallai, Kerala state. *Indian Journal of Medical Research* 1992;**95**:157-160
62. Day KP, Spark R, Garner P, Raiko A, Wenger JD, Weiss N, Mitchell GF, Alpers MP and Kazura JW. Serological evaluation of the macrofilaricidal effects of diethylcarbamazine treatment in bancroftian filariasis. *American Society of Tropical Medicine and Hygiene* 1991;**44**:528-535.
63. Chanteau S, Moullia-Pelat JP, Glaziou P, Nguyen NL, Luquiaud P, Plichart C, Martin PMV and Cartel JL. Og4C3 circulating antigen: A marker of infection and adult worm burden in *Wuchereria bancrofti* filariasis. *The Journal of Infectious Diseases* 1994;**170**:247-250.
64. Ramzy RMR, Hafez ON, Gad AM, Faris R, Harb M, Buck AA and Weil GJ. Efficient assessment of filariasis endemicity by screening for filarial antigenaemia in a sentinel population. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994;**88**:41-44.
65. Lizotte MR, Supali T, Partono F, Williams SA. A PCR assay for the detection of *Brugia malayi* in blood. *The American Journal of Tropical Medicine and Hygiene*, 1994 (in press).
66. Chanteau S, Luquiaud P, Failloux A, Williams SA. PCR-based detection of *Wuchereria bancrofti* larvae in pools of mosquitoes. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994 (in press).
67. Plaisier AP, van Oortmarsen GJ, Habbema JDF, Remme J & Alley ES. ONCHOSIM: A model and computer simulation program for the transmission and control of onchocerciasis. *Computer Models and Programs in Biomedicine* 1990;**31**:43-56.
68. Anderson RM, & May RM. *Infectious Diseases of Humans: Dynamics and Control*. Oxford University Press, Oxford, 1991, pp 757.
69. Bundy DAP. *The need for modelling for epidemiology and control of lymphatic filariasis*. Geneva, World Health Organization 1991 (unpublished document FIL/EC/91/WP.26).
70. Grenfell BT & Michael E. Infection and disease in lymphatic filariasis - an epidemiologic approach. *Parasitology* 1992;**104**:S81-91.
71. CDC. Recommendations of the International Task Force for Disease Eradication. *Morbidity and Mortality Weekly Report* 1993;**42**:1-38.



WHO/CTD/TDR

LYMPHATIC FILARIASIS INFECTION & DISEASE: CONTROL STRATEGIES

UNIVERSITI SAINS MALAYSIA, PENANG,
MALAYSIA, 22-24 AUGUST 1994

LIST OF PARTICIPANTS

Dr David Addiss
Division of Parasitic Diseases
Centers for Disease Control and
Prevention (CDC)
Mailstop F-22, Bldg. 102
4770 Buford Highway, N.E.
Atlanta, GA 30341-3724
USA
Fax: 404-488-7761
Tel: 404-488-7770

Dr Norbert Becker
Wissenschaftlicher Direktor
Kommunale Aktionsgemeinschaft zur
Bekämpfung der Schnakenplage e.V.
Ludwigshafen am Rhein (KABS)
Postfach 210780
D-67165 Waldsee
Germany
Fax: 49-062-36-418-622
Tel: 49-062-36-418-60

Dr D.A.P. Bundy
Department of Zoology
University of Oxford
South Parks Road
Oxford OX1 3PS
United Kingdom
Fax: 44-865-281-245
Tel: 44-865-281-246

Dr Jeffrey Chodakewitz
Director
Clinical Research (Infectious Diseases)
Merck Research Laboratories
West Point, PA 19486
USA
Fax: 1-215-834-7555
Tel: 1-215-834-2454

Dr Sun De-Jian
Chief, Department of Epidemiology
Institute of Parasitic Diseases
Chinese Academy of Preventive
Medicine
207 Rui Jin Er Lu
Shanghai 200025
People's Republic of China
Fax: 862-143-76-308
Tel: 862-143-32-670

Dr Gerusa Dreyer
Centro de Pesquisas Aggeu Magalhaes
FIOCRUZ
Universidade Federal de Pernambuco
Ave Moraes Rego s/n
Cidade Universitaria
50730 Recife
Brazil
Fax: 55-81-271-2302/453-2448
Tel: 55-81-271-4000

Professor Adel Gad
Research and Training on Vectors
of Diseases
Ain Shams University
Faculty of Science Building
Abbassia
Cairo
Egypt
Fax: 202-283-9622

Dr Tore Godal
Director
Special Programme for Research and
Training in Tropical Diseases
World Health Organization
CH-1211 Geneva 27
Switzerland
Fax: 41-22-791-4854
Tel: 41-22-791-3802
E-mail: godal@who.ch
@umc@HQVAXI

Professor Yap Han Heng
Vector Control Research Unit
Universiti Sains Malaysia
11800 Pulau Pinang
Malaysia
Fax: 604-657-7200
Tel: 604-654-4776

Dr Pushpa Herath
Malaria Control
Division of Control of Tropical
Diseases
World Health Organization
CH-1211 Geneva 27
Switzerland
Fax: 41-22-791-0746
Tel: 41-22-791-3746
E-mail: herath@who.ch
@umc@HQVAXI

Dr Leda M. Hernandez
Communicable Disease Control Service
Department of Health
San Lazaro Compound
Sta Cruz
Manila
The Philippines
Tel: 632-711-6804/6699

Professor M. Mahroof Ismail
Department of Parasitology
Faculty of Medicine
University of Colombo
Kynsey Road
Colombo 8
Sri Lanka
Fax: 94-1-691-581
Tel: 94-1-695-300

Dr T. Junghanss
Senior Registrar
Medical Department
Swiss Tropical Institute
Socinstrasse 57
CH-4002 Basel
Switzerland
Fax: 41-61-271-8654
Tel: 41-61-284-8111

Dr Mak Joon Wah
Filariasis Research Division
Institute for Medical Research
Jalan Pahang
50588 Kuala Lumpur
Malaysia
Fax: 603-292-0675
Tel: 603-298-6033

Professor J.W. Kazura
Case Western Reserve University
School of Medicine, W137
Division of Geographic Medicine
2109 Adelbert Road
Cleveland, OH 44106-4983
USA
Fax: 1-216-368-4825
Tel: 1-216-368-4818

Professor W.L. Kilama
Director General
National Institute for Medical
Research
P.O. Box 9653
Dar es Salaam
Tanzania
Fax: (255) 51-30660
Tel: (255) 51-30770

Dr A. Bruce Knudsen
Filariasis Control
Division of Control of Tropical
Diseases
World Health Organization
CH-1211 Geneva 27
Switzerland
Fax: 41-22-791-0746
Tel: 41-22-791-3830
E-mail: knudsen@who.ch
@umc@HQVAXI

Dr V. Kumaraswami
Assistant Director
Tuberculosis Research Centre
Spur Tank Road
Chetput
Madras 600 031
India
Fax: 91-44-826-2137
Tel: 91-44-826-5425

Professor W.W. Macdonald
10 Headland Close
West Kirby
Wirral
Merseyside, L48 3JP
United Kingdom
Tel: 44-151-625-7857

Dr Dan Meyrowitsch
Danish Bilharziasis Laboratory (DBL)
Jaegersborg Allé 1 D
2920 Charlottenlund
Denmark
Fax: 45-31-626-121
Tel: 45-31-626-168

Dr Edwin Michael
Department of Zoology
University of Cambridge
Downing Street
Cambridge CB2 3EJ
United Kingdom
Fax: 44-223-336-676
Tel: 44-223-334-430
E-mail: edwin@zoo.cam.ac.uk

Professor David H. Molyneux
Director
Tropical Health Sciences
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool L3 5QA
United Kingdom
Fax: 44-51-707-0155
Tel: 44-51-708-9393

Dr J.-P. Moullia-Pelat
Head, Clinical and Epidemiological
Research Department
Institut Territorial de Recherches
Médicales Louis Malardé
B.P. 30
Papeete, Tahiti
French Polynesia
Fax: 689-431-590
Tel: 689-416-464

Professor V. Navaratnam
Director
Drug Research Centre
Universiti Sains Malaysia
11800 USM, Pulau Pinang
Malaysia
Fax: 604-657-7957
Tel: 604-657-7888

Dr Eric A. Ottesen
Filariasis Control
Division of Control of Tropical
Diseases
World Health Organization
CH-1211 Geneva 27
Switzerland
Tel: 41-22-791-3225
Fax: 41-22-791-0746
E-mail: ottesen@who.ch
@umc@HQVAX1

Dr S.P. Pani
Deputy Director
Vector Control Research Centre
Medical Complex
Indira Nagar
Pondicherry 605 006
India
Fax: 91-413-334-22
Tel: 91-413-373-96

Dr K.N. Panicker
Deputy Director
Vector Control Research Centre
Medical Complex
Indira Nagar
Pondicherry 605 006
India
Fax: 91-413-334-22
Tel: 91-413-234-373-96

Dr B.P. Patnaik
National Malaria Eradication
Programme
22 Sham Nath Marg
P.O. Box 8616
New Delhi 110054
India
Fax: 91-11-301-7924
Tel: 91-11-301-251-7745

Mrs Fiona Perréard
Special Programme for Research and
Training in Tropical Diseases
World Health Organization
CH-1211 Geneva 27
Switzerland
Fax: 41-22-791-4854
Tel: 41-22-791-3283

Dr C.P. Ramachandran
Chief
Filariasis Control
Division of Control of Tropical
Diseases
World Health Organization
CH-1211 Geneva 27
Switzerland
Fax: 41-22-791-4854
Tel: 41-22-791-3877
E-mail: ramachandran@who.ch
@umc@HQVAX1

Datin Dr (Mrs) S. Selvaraju
Deputy Director
Vector-Borne Disease Control
Programme
Ministry of Health
Kuala Lumpur 50590
Malaysia
Fax: 603-293-1590
Tel: 603-298-9222

Dr H.S. Sidhu
School of Biological Sciences
Universiti Sains Malaysia
11800 Pulau Pinang
Malaysia
Fax: 604-657-7200
Tel: 604-654-4776

Dr Paul E. Simonsen
Danish Bilharziasis Laboratory
(DBL)
Jaegersborg Allé 1 D
2920 Charlottenlund
Denmark
Fax: 45-31-626-121
Tel: 45-31-626-168

Dr S. Suvannadabba
Director of Filariasis Division
Department of Communicable Disease
Control
Ministry of Public Health
Devaves Palace
275 Samsen Road
Bangkok 10200
Thailand
Fax: 668-466-0140

Dr Paul Turner
Anton Breinl Centre for
Tropical Health & Medicine
James Cook University
of North Queensland
Townsville
Queensland 4811
Australia
Fax: 61-77-71-5032
Tel: 61-77-21-2281

Professor Walter H. Wernsdorfer
Cranachstrasse 8
Vienna
Austria 1130
Fax/Tel: 43-1-804-0764

Dr G. Wernsdorfer
Cranachstrasse 8
Vienna
Austria 1130
Fax/Tel: 43-1-804-0764

Dr Widarso
Chief
Sub-Directorate of Filarial Control
Programme
Directorate of Vector Borne Diseases
Control
Ministry of Health
Jl. H.R. Rasuna Said Kav. X 5
N° 4: 04 s/d 09
Jakarta
Indonesia
Fax: 62-21-420-7807

Dr Steven A. Williams
Department of Biological Sciences
Clark Science Center
Smith College
Northampton, MA 01063
USA
Fax: 1-413-585-3786
Tel: 1-413-585-3826