Update/Le point

Strategies and tools for the control/elimination of lymphatic filariasis

E.A. Ottesen,[1] B.O.L. Duke,[2] M. Karam,[1] & K. Behbehani[1]

Lymphatic filariasis infects 120 million people in 73 countries worldwide and continues to be a worsening problem, especially in Africa and the Indian subcontinent. Elephantiasis, lymphoedema, and genital pathology afflict 44 million men, women and children; another 76 million have parasites in their blood and hidden internal damage to their lymphatic and renal systems. In the past, tools and strategies for the control of the condition were inadequate, but over the last 10 years dramatic research advances have led to new understanding about the severity and impact of the disease, new diagnostic and monitoring tools, and, most importantly, new treatment tools and control strategies.

The new strategy aims both at transmission control through community-wide (mass) treatment programmes and at disease control through individual patient management. Annual single-dose *co-administration of two drugs (ivermectin + diethylcarbamazine (DEC)* or *albendazole) reduces blood microfilariae by 99% for a full year; even a single dose of one drug (ivermectin or DEC) administered annually can result in 90% reductions; field studies confirm that such reduction of microfilarial loads and prevalence can interrupt transmission. New approaches to disease control, based on preventing bacterial superinfection, can now halt or even reverse the lymphoedema and elephantiasis sequelae of filarial infection. Recognizing these remarkable technical advances, the successes of recent control programmes, and the biological factors favouring elimination of this infection, the Fiftieth World Health Assembly recently called on WHO and its Member States to establish as a priority the global elimination of lymphatic filariasis as a public health problem.*

Global dimension of lymphatic filariasis and prospects for its elimination

Lymphatic filariasis is widespread throughout the tropical and subtropical areas of Asia, Africa, the Western Pacific and some parts of the Americas (*1*), where it is a major cause of acute and chronic morbidity affecting persons of all ages and both sexes. Not only does it lead to great personal suffering from its disabling and disfiguring lesions, but it is also a significant impediment to socioeconomic advancement, both locally and nationally (*2*).

More than 1.1 thousand million people (20% of the world's population) now live in areas where they are at risk of infection with lymphatic filarial parasites (*1*), and a minimum of 120 million people are currently infected (about 107 million with *Wuchereria bancrofti* and 13 million with *Brugia malayi* or *B. timori*). A total of 44 million persons currently suffer from one or more of the overt manifestations of the infection: lymphoedema and elephantiasis of the limbs or genitals, hydrocele, chyluria, pneumonitis, or recurrent infections associated with damaged lymphatics. The remainder of the 120 million infected have "preclinical" hidden damage of their lymphatic and renal systems (*3*); and to this burden of disease must also be added the serious psychosocial consequences that these profoundly disabling lesions often have, including the seldom-mentioned sexual/social dysfunction of men of all ages afflicted with hydroceles or other genital abnormalities and of young women with lymphoedema of the breasts or genitals (*4*).

Although the magnitude of these problems may seem at first to present a dismal control prospect, there is now a great sense of optimism about what

[1] Division of Control of Tropical Diseases, World Health Organization, 1211 Geneva 27, Switzerland. Requests for reprints should be sent to Dr Ottesen at this address.

[2] Consultant, Division of Control of Tropical Diseases, World Health Organization, Geneva, Switzerland.

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can be achieved. In large measure this optimism derives from the recent emergence of practical tools and cost-effective control measures that can be applied on a community-wide basis, while being effectively integrated with other pre-existing national and local public health activities. As a result, an International Task Force for Disease Eradication (*5*) recently identified lymphatic filariasis as one of only six infectious diseases that are currently considered to be "eradicable" or "potentially eradicable";[a] an argument made all the stronger by the earlier successes of filariasis elimination efforts in Japan (*6*), China (Province of Taiwan) (*7*), and many other parts of China (*8*), Republic of Korea (*9*), and the Solomon Islands (*10*), all using control tools much less efficient than those available today. It is the need to have these new control measures widely recognized and put into effect that has prompted us to present this Update article, which details the currently available tools and strategies underlying the newly launched initiative to eliminate lymphatic filariasis globally as a public health problem, in accord with resolution WHA50.29 of the Fiftieth World Health Assembly.[b]

Geographical distribution

Lymphatic filariasis is known to occur in 73 countries/territories (Table 1): 38 in the African Region, 7 in the Region of the Americas, 4 in the Eastern Mediterranean Region, 8 in the South-East Asia Region, and 16 in the Western Pacific Region. The condition has been previously reported from and might still occur in another 40 countries.

Fig. 1 illustrates the distribution of persons infected with lymphatic filariasis, by WHO Region.

Table 1: **Countries/territories with lymphatic filariasis**

African Region	
Angola	Liberia
Benin	Madagascar
Burkina Faso	Malawi
Burundi	Mali
Cameroon	Mauritius
Cape Verde	Mozambique
Central African Republic	Niger
Chad	Nigeria
Comoros	Réunion
Congo	São Tomé and Principé
Côte d'Ivoire	Senegal
Democratic Republic of the Congo	Seychelles
Equatorial Guinea	Sierra Leone
Ethiopia	Togo
Gabon	Uganda
Gambia	United Republic of Tanzania
Ghana	Zambia
Guinea	Zimbabwe
Guinea-Bissau	
Kenya	
Region of the Americas	
Brazil	Haiti
Costa Rica	Suriname
Dominican Republic	Trinidad and Tobago
Guyana	
Eastern Mediterranean Region	
Egypt	Somalia
Oman	Sudan
South-East Asia Region	
Bangladesh	Myanmar
India	Nepal
Indonesia	Sri Lanka
Maldives	Thailand
Western Pacific Region	
American Samoa	Papua New Guinea
China	Philippines
Cook Islands	Republic of Korea
Federated States of Micronesia	Samoa
Fiji	Tonga
French Polynesia[a]	Tuvalu
Kiribati	Vanuatu
Malaysia	Viet Nam

[a] Windward Islands, Leeward Isands, Tuamotu Archipelago, Austral or Tabuai Islands, and Marquesas Islands.

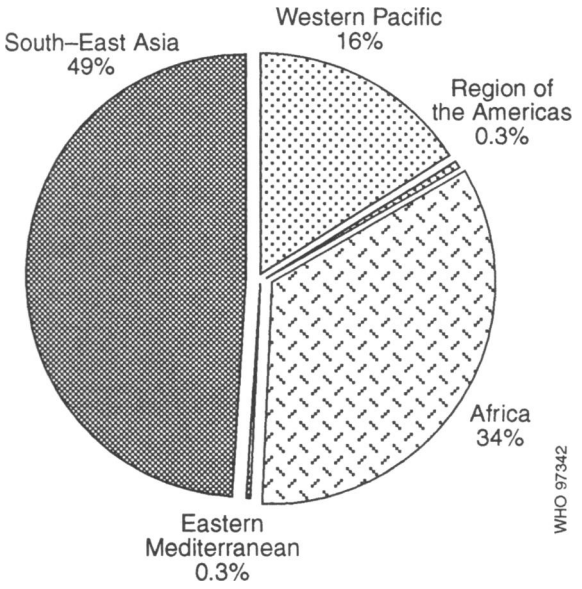
The highest number of infected persons is in the South-East Asia Region, with India alone accounting for 45.5 million. In sub-Saharan Africa the estimate of 41 million cases is less precise, and there is a particular need to determine more accurately the distribution of infection and disease in affected countries. Several countries in Asia have large numbers of cases; and infection and disease are very prevalent in many of the Pacific islands as well.

Brugian filariasis is most highly endemic in India and China (32% and 20%, resp, of the global burden); it is also prevalent in Indonesia, Thailand, Malaysia, Philippines, Viet Nam and Republic of Korea.

[a] The terms eradication (literally "pulling out by the roots") and elimination (literally "thrusting out over the threshold") frequently give rise to much semantic argument when applied in the context of disease control. In any given area subject to control, the reduction in infection loads that follows a reduction in transmission may be expected initially to result in an *elimination of lymphatic filariasis as a public health problem*. This is the first objective. Later, if control measures are continued thoroughly and for a longer time, a second objective may be reached when *all infections with the parasite have been eliminated from the population concerned*. Elimination, of whatever degree, must apply to a given area (which may be a whole country), but there is always a residual risk of reinfection from another endemic area outside. It is only when the infection has been eliminated globally (as was achieved with smallpox) that we can truly use the term eradication. True eradication of lymphatic filariasis from the human population is possible but is a much longer-term goal that would follow from the more immediate practical objective.

[b] *Elimination of lymphatic filariasis as a public health problem*. Document WHA50/1997/REC/1.

Fig. 1. **Distribution, by WHO region, of the 120 million persons currently infected with lymphatic filarial parasites** (*Wuchereria bancrofti, Brugia malayi, B. timori.*)



The burden of lymphatic filarial disease

Lymphatic filariasis has been identified as the second leading cause of permanent and long-term disability (*2*), but the true amount of disability it causes is only beginning to be quantified accurately (*11*, *12*).

However, even now, it is clear that in addition to the direct costs associated with management of the acute and chronic manifestations of disease (which can themselves be appreciable), indirect losses resulting from diminished productivity or incapacitation can be enormous and constitute a severe drain on the economy (both local and national).[c] Furthermore, added to this recognizable economic burden of acute and chronic disease must be the yet unquantified effects of the newly discovered "subclinical" pathology of the renal and lymphatic systems (*3*) which affects essentially all infected individuals.

Finally, defining and quantifying the psychosocial burden of this deforming, mutilating disease of the limbs and genitalia is still an extremely important issue that requires much greater attention than it has received to date. Indeed, it can be confidently predicted that ongoing and future studies will reveal a health burden of lymphatic filariasis that is very much greater than what has previously been recognized.

Control of lymphatic filariasis

Over the past 50 years, since the first introduction of diethylcarbamazine (DEC) in 1947, several endemic countries/territories have expended considerable effort to control or eliminate lymphatic filariasis, generally using the 12-day DEC treatment regimens formerly recommended by WHO (*14*) or modifications to this regimen supplemented in some places by vector control. Among the countries/territories most active in the past with national control programmes have been American Samoa, Brazil, China, Egypt, Fiji, French Polynesia, India, Malaysia, Philippines, Samoa, Sri Lanka, and Thailand.

Some of these antifilariasis campaigns were very successful and others, less so. The recent advances in diagnosis, clinical understanding, control, and treatment of lymphatic filariasis have been so great, however, that the time has come for all countries where the disease is endemic to organize their health services to take full advantage of the new knowledge and techniques in order to eliminate it as a disease of public health importance (*15*). The principal elements of the recommended control strategy and the new tools for effecting it are summarized below.

Principles of the control of lymphatic filariasis

The control of lymphatic filariasis implies both stopping the spread of infection (transmission control) and alleviating the suffering caused by the disease (morbidity control).

Transmission control. If transmission can be reduced and ultimately interrupted, there will first be a reduction in new infections and then complete cessation. Since there is no non-human reservoir of *W. bancrofti*, and only a very minor animal reservoir of *B. malayi* that probably plays little or no role in transmission to humans, this interruption can be achieved in three ways: by reducing and ultimately eliminating the reservoir of microfilariae through

[c] In India, for example, conservative estimates indicate that indirect costs from decreased productivity in individuals with chronic manifestations (*12*) total approximately Rs 40 × 10^9 (US$ 1.1 × 10^9) yearly and that incapacitation from acute inflammatory episodes ("filarial fevers") (*13*) adds another Rs 10 × 10^9 (US$ 290 × 10^6) to this loss. In addition, direct costs from the million hydrocoele operations performed each year (Rs 2 × 10^9) and from local care of elephantiasis or complicating infections (Rs 840 × 10^9) further increase to almost US$ 1.5 × 10^9 the economic costs of this disease every year to this country, where the average labourer earns Rs 35–70 (US$1–2) per day.

treating the human population; by reducing contact between humans (especially microfilaria carriers) and mosquito vectors; and by combining these two approaches. Indeed, the specific strategies chosen for controlling transmission of infection will differ from one endemic area to another, depending on the local parasite–vector situation, the existing health care activities and infrastructure, the availability of funds, and local cultural attitudes.

Disease (morbidity) control. Even when microfilariae have been eliminated, the adult worms, as well as external microbial pathogens, may continue to induce lymphatic pathology and consequent morbidity. It is therefore essential to aim not just for transmission control but also for morbidity control and, as far as possible, prevent further suffering among infected persons even as control of transmission is being established. This morbidity-control effort must continue beyond the immediate period after transmission has been interrupted, since previously established infections (though gradually dying out because of the 4–6-year life span of the parasite), can still be symptomatic because damaged, lymphoedematous limbs remain particularly susceptible to secondary bacterial superinfections.

Essential elements of the strategy to eliminate lymphatic filariasis as a public health problem

Because of the newly available control tools and increased understanding of the damage induced by lymphatic filarial infection, a revised strategy for its control/elimination has been formulated with two essential elements.

- The major focus for control activities should be on *treating the human population* (vector control, when practicable, should be only an adjunct to programmes based on drug treatment).
- "*Mass distribution*" treatment programmes should replace older approaches based on the "selective treatment" of those diagnosed individually to have microfilaraemia.

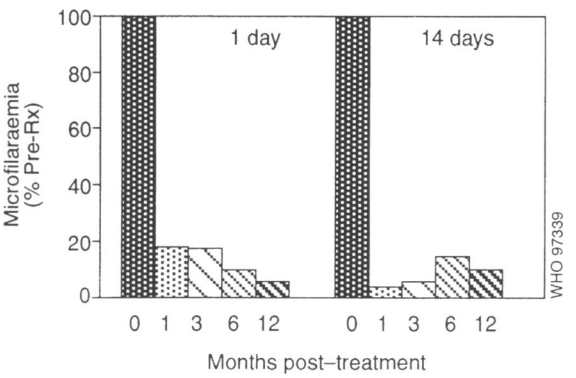
Selecting the drug treatment regimen for control programmes

Three available drugs have now been shown by intensive investigation (*16–21*, *63*, *64*) to be safe and effective microfilaricides for mass treatment to control the transmission of lymphatic filariasis; they include both old (DEC) and new (ivermectin and albendazole) antifilarials. Understanding about how these drugs should be used in control programmes has recently undergone two fundamental shifts. The first came when it was recognized that single-dose treatment (not only with ivermectin, but also with DEC) reduced blood microfilaria levels as effectively and to the same long-lasting degree as the previously recommended 12-day course of DEC (*19*, Fig. 2); the second came from the discovery that concurrent treatment using two drugs (e.g. co-administration of single doses of DEC and ivermectin) is significantly more effective against microfilariae than use of any of the drugs alone.[d] Moreover, the marked microfilaricidal effectiveness of these regimens makes them suitable for annual treatment designed to control transmission immediately and, in the longer term, to prevent morbidity. There is also evidence that the widespread use of such drugs, particularly DEC, is effective in reducing the incidence of clinical lymphoedema (*23*), probably because they sterilize or kill a proportion of the adult worms.

Until recently the macrofilaricidal action of drugs against human lymphatic filarial parasites had been notoriously difficult to assess; it usually depended on long-term studies of the fall-off in blood microfilaria levels (which can be confounded by the occurrence of re-infections) or on the occasional finding of tender, palpable nodules around worms dying along the course of lymphatic vessels. However, investigations in Brazil have recently revolutionized the study of adult lymphatic filarial worms: ultrasound techniques can now be used to visualize adult *W. bancrofti* in the lymphatics and to observe their movements in what is known as the "filarial dance sign" (*24*). Thus, it is now possible to visualize adult worms in the body to determine whether they are motile and alive; and, having located their "nests", to remove them surgically for assessment of drug-induced changes in their somatic tissues or in embryogenesis. Such studies indicate that single

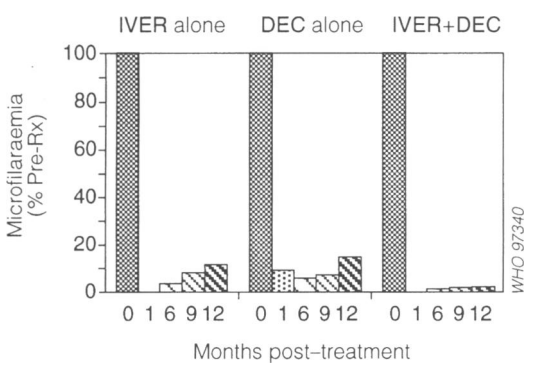
[d] Ivermectin is currently approved and registered in Australia, France and the USA for treating onchocerciasis and strongyloidiasis, and is registered for the treatment of *onchocerciasis* in the 35 countries where this disease is endemic. It is donated for use against onchocerciasis by its manufacturer, Merck and Co., Inc., and is now being received by 15–20 million patients annually (*22*). Ivermectin has not yet been registered specifically for lymphatic filariasis, but extensive clinical trials have indicated that it is effective, safe and well-tolerated (*16*). It is clear that both the two-drug regimens (ivermectin + DEC or ivermectin + albendazole) are superior to any of the drugs used alone for long-term reduction of microfilarial density and prevalence (see Fig. 3; ref. *19*, *63*, *64*). When ivermectin becomes generally available, these two-drug regimens will almost certainly become the "annual-dose" treatments of choice for the control/elimination of lymphatic filariasis.

Fig. 2. **Comparative efficacy (determined by reductions in blood microfilaraemia expressed as a percentage of pre-treatment values) between a single dose of DEC (6 mg/kg) and the same dose of DEC repeated daily for 14 days.** Bars indicate geometric mean values at different months post-treatment for 40–74 patients with bancroftian filariasis studied at four sites with these treatment regimens. Statistically significant differences between the two treatment regimens were seen only at months 1 and 3 post-treatment ($P < 0.05$) (plotted using data complied for meta-analysis by Wu-chun Cao et al., ref. *19*).



doses of 6 mg/kg DEC will kill up to 50% of adult *W. bancrofti*, but that further or higher doses given soon afterwards produce no additional macrofilaricidal action (*24*). Nothing is yet known of the factors that make some adult worms susceptible or how or when "nonsensitive" worms may later become susceptible. Evidence is accumulating, however, that the killing of adult worms by DEC, even though it transiently increases blockage of the lymphatics, is beneficial in the long-run, since there is increased flow of lymph through newly formed collateral channels and through the partially recanalized existing lymphatics.

Fig. 3. **Improved efficacy of two-drug treatment (single doses of ivermectin + DEC administered concomitantly) compared to single doses of either drug alone.** Bars represent values (see legend, Fig. 2) derived from 19 patients with bancroftian filariasis in each study group. Two-drug treatment was statistically better than either drug alone at 6, 9 and 12 months post-treatment and was significantly better also than DEC alone at month 1 (plotted using data in Moulia-Pelat et al., ref. *18*).



For many endemic countries the choice of drug regimen to be used is open, *but in those parts of sub-Saharan Africa where infections with* Onchocerca volvulus *or* Loa loa *are co-endemic with those of* W. bancrofti, *the use of DEC must be avoided*, since it can induce severe and dangerous adverse reactions by rapidly killing the microfilariae of these other two African filariids (*25*).

Thus, for use throughout the world, *except in the loiasis or onchocerciasis zones* of sub-Saharan Africa, either of the following two approaches is recommended:

- Once-yearly "single-dose" treatment (for 4–6 years) with either:
  - — a two-drug regimen (optimal): *ivermectin* (200 µg/kg body weight) co-administered with either *DEC* (6 mg/kg) or *albendazole* (400 mg);[d] or
  - — a one-drug regimen: *DEC* (6 mg/kg) alone.[e]
- DEC-fortified salt (0.2–0.4% w/w) substituted for regular table/cooking salt for 6–12 months.[f]

For the endemic zones of sub-Saharan Africa where onchocerciasis or loiasis may coexist with bancroftian filariasis (and where it is therefore unsafe to use DEC), the recommended treatment is the following:

- Once yearly, single-dose administration (for 4–6 years) of either:

[e] This regimen is as effective in reducing microfilaraemia one full year after treatment as the older "standard" 12-day course of DEC (see Fig. 2; ref. *19*), but has fewer adverse effects, is better accepted by the treated populations, and reduces both drug and delivery costs (*24*). Adverse reactions, though greater than those seen with DEC-fortified salt, are transient, well-tolerated, and generally less than those following the 12-day course of DEC.

[f] The use of DEC-fortified salt for cooking and seasoning needs over a period of at least 6–12 months is an extremely effective means of markedly reducing or even eliminating lymphatic filariasis from treated populations (*23, 26–29*). It is well-tolerated, can be safely used during pregnancy, and can be iodized. However, its use does raise the cost of the salt consumed, and it is important that there be some mechanism for control of the salt supply to the population.

— *a two-drug regimen* (optimal): *ivermectin* (200 μg/kg) + *albendazole* (400 mg)[g]; or
— *a one-drug regimen*: *ivermectin* (400 μg/kg) alone.[h]

Selecting the population to be treated

Mass drug distribution programmes should now be the approach to treatment in those communities where lymphatic filariasis is endemic. All members of the population who are eligible[i] should be treated, thereby eliminating the need to assess (laboriously and with recognized inaccuracy) the presence of infection in each individual. In control programmes, mass distribution should entirely replace the now outmoded "selective treatment" strategy, which was based on individual detection and treatment of infected persons.

The question of what level of endemicity should trigger mass treatment in affected communities is one for which there is as yet no empirical answer. While some workers have advocated cessation of control efforts when microfilarial prevalence falls below 1% of the population (as determined by diagnostic (microscopic) techniques less sensitive than those now available), three important facts should also be considered. First, it is clear that premature cessation of certain control programmes in the past was largely responsible for programme failure and subsequent resurgence of filariasis. Second, the drug regimens most likely to be employed in control programmes, i.e. those including ivermectin and/or albendazole, have very much broader public health benefits than those limited to filariasis alone (Table 2), so their community-wide distribution can be readily justified. Third, recently developed predicitive models (see below) indicate that only one or two rounds of community-wide treatment may be enough to interrupt transmission in areas where the prevalence of infection is very low, with larger number of treatment rounds being required for high-prevalence areas. Thus, for both practical and public health purposes, efforts should be made to treat all of those communities where lymphatic filariasis is endemic.

Effectiveness of the tools for lymphatic filariasis control/ elimination programmes

New drug-treatment regimens: effectiveness in community-wide treatment programmes

While experience with community-wide control programmes using single-dose treatments involving ivermectin or the various two-drug regimens is still limited (see below), experience using single-dose DEC is extensive. Indeed, single-dose ("spaced dose") DEC given at weekly, monthly, 6-monthly or yearly intervals has been enthusiastically advanced for many years, especially in the Pacific Islands and Indonesia (*31–34*). While more frequent single-dose DEC regimens (usually weekly or monthly) 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 (*34*). For bancroftian filariasis the greatest experience with control programmes using repeated single-dose yearly DEC has been in Tahiti (n = 50000 (*33*)) and Fiji (n = 7600 (*34*)), where four or five yearly administrations of single-dose DEC resulted in decreases in microfilarial density of 78% and 97%, respectively, and decreases in microfilarial prevalence of 57% and 86%, respectively, when measured 1 year after the last treatment. Similarly, in Kerala, India (n = 22700, (*35*)), a control programme for *B. malayi* that used just two annual administrations of single-dose DEC resulted in a decrease in microfilarial density of 81% and in microfilarial prevalence of 75%. 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 are approximately the same as those for *individuals* treated with single doses of DEC and followed sequentially for 12 months or more (*19*).

[g] This annual regimen has significantly greater efficacy than ivermectin alone (ref. *63*), essentially clearing completely all microfilariae for more than one year. It is just as effective as the ivermectin + DEC regimen (Fig. 3) and has the added advantage of being probably the most effective combination of drugs available for treating gastrointestinal worms (*30*).

[h] This single-annual-dose regimen of ivermectin is equivalent to the single-dose DEC regimen in its microfilarial efficacy and its tolerability (see Fig. 3, ref. *16*, *19*), and it can be safely used in areas where onchocerciasis and loiasis may be co-endemic with lymphatic filariasis. When used alone, a dose of 400 μg/kg is significantly better in effecting microfilarial clearance than 200μg/kg (*16*), which is sufficient when the drug is used in combination with either albendazole or DEC.

[i] Eligibility means those individuals for whom the drugs are not specifically contraindicated. In all community-wide distribution programmes such contraindications are acute illness, very old age, or infirmity. For pregnant women, none of the three drugs recommended for treatment (i.e. DEC, ivermectin, albendazole) when given as single doses (or for DEC when incorporated into fortified salt) has been reported to affect the outcome of pregnancy; and none of these drugs is proscribed by the manufacturers for single-dose use in pregnant women participating in community-wide treatment programmes. Even for children as young as 2 years of age all three drugs are considered safe.

Table 2: **Broad antiparasitic effectiveness of "single-dose" drugs used to control lymphatic filariasis**

Infection	Ivermectin effectiveness[a]	Infection	Albendazole effectiveness[a]
Ascaris	4+	Ascaris	4+
Strongyloides	4+	Strongyloides	2+
Enterobius	3+	Enterobius	3+
Trichuris	1+/3+	Trichuris	2+/3+
Hookworm	1+	Hookworm	4+
Larva migrans (cutaneous)	4+	Larva migrans (cutaneous)	3+
Onchocerciasis	4+	Cysticercosis	—[b]
Lice	3+	Hydatids	—[b]
Scabies	4+	*Giardia*/trichomonads	—[b]
		Micro-/Cryptosporidia	—[b]

[a] Effectiveness qualitatively expressed on a 1+ to 4+ (most effective) scale.
[b] Requires more than a single dose of albendazole

Experience with the two-drug, single-dose yearly regimen (ivermectin + DEC) is much more limited, having thus far been studied at the community level only in Papua New Guinea. There, the coverage of the communities was about 75% of the total population (excluding pregnant women and children under 5 years of age); the reduction in microfilaraemia density was >90% one year after treatment with the combined regimen; and the prevalence decreased progressively after two annual treatments, achieving an 85% reduction in treated communities even when pre-treatment microfilaraemia rates were extremely high (30–80%). Transmission indices were similarly reduced (*36*). Additional studies using this regimen are currently under way in India, Samoa, and Fiji.

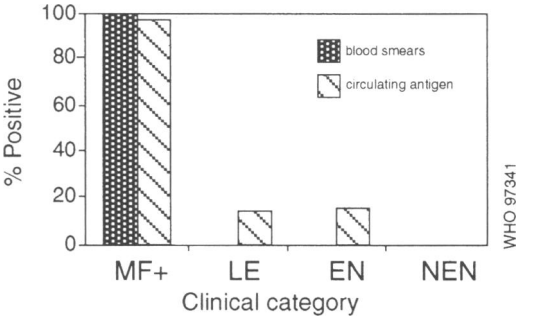
Diagnostic tools: effectiveness for surveillance and monitoring

Before applying any new strategies and methods of control in large-scale campaigns, reliable, practical techniques are needed to assess accurately and rapidly the distribution of infection, its level of endemicity, and the amount of associated disease. Furthermore, it is necessary to be able to monitor the changes in these parameters in order to evaluate the outcome of the control measures.

New diagnostic tools. In the past, surveys for lymphatic filariasis depended on the examination of blood films, which, in most areas, had to be collected around midnight because of the nocturnal periodicity of microfilariae in the blood. Alternative methods based on detection of antibodies by immunodiagnostic tests did not prove satisfactory, since they failed both to distinguish between active and past infections and had problems with specificity owing to their cross-reactivity with common gastrointestinal parasites (*3*, *37*).

Two new effective diagnostic techniques for control programmes are, however, now available. The first detects circulating *W. bancrofti* protein antigens using specific monoclonal antibodies (*38*, *39*); circulating antigens can be detected in essentially all microfilaraemic subjects and in a proportion of amicrofilaraemic persons with previously hidden (i.e. "cryptic") infections (Fig. 4; ref. *38*, *40*). The test can

Fig. 4. **Diagnosis of bancroftian filariasis by parasitological detection of microfilariae in the blood (examination of two 20-µl blood smears) or by serological detection of circulating antigen.** Percent positivity is recorded for each group of study individuals: MF+ = microfilaraemic individuals (n = 57), with or without associated manifestations of filarial disease; LE = patients (n = 64) with lymphoedema or hydrocoeles but no detectable microfilaraemia: EN = "endemic normal" individuals (n = 70) residing in the endemic area but having no clinical indication of filarial infection; NEN = "nonendemic normal" individuals (n = 35) from North America with no exposure to human filarial infection (plotted using data in Weil et al., ref. *38*).



be performed with blood taken at any time of day (*40*), and antigen levels fall to zero after the adult worms have all been killed (*41*). The assay has now been commercialized, field-proven, and is available in enzyme-linked immunosorbent assay (ELISA) or card-test formats at preferential pricing for endemic-country control programmes (*40*, *42*). Unfortunately no comparable assay exists for *Brugia* infections.

The second new diagnostic tool, which has outstanding sensitivity and specificity, detects parasite DNA, either in the human (*43*) or mosquito (*44*) host, using the polymerase chain reaction (PCR). Assays have now been developed, both for *W. bancrofti* and *B. malayi*, that are capable of detecting a single microfilaria in 1 ml of blood or a single infective larva (L3) in a sample of 100 mosquitos. Using these tests, a technician can screen 1000 blood samples or 3600 mosquitos per day. These PCR assays are highly specific and sensitive; detect only current infections; provide "same-day" results; and samples can be preserved at ambient temperature for months before they are examined. Their main drawback is the need for special training and equipment in a central laboratory with good quality control.

Rapid epidemiological assessment. Because lymphatic filariasis is a disease that is geographically widespread but often focal in distribution, simple rapid methods for mapping epidemiologically the prevalence of infection are essential before appropriate control operations can be initiated. Rapid diagnostic techniques for identifying communities with filarial infection are now being developed to replace the older slow, tiresome, night-blood-screening campaigns. Among the new methods being evaluated are the following: estimation of disease or microfilaria-carrier rates from reviews of existing health reports and hospital or clinic records; clinical examination of adult males for hydrocoeles, with extrapolation to gauge the overall prevalence of infection (*45*); examination of mosquito vectors for infection, using traditional entomological methods (or DNA-based tests, if feasible); and evaluation of antigenaemia rates in day-time fingerprick blood specimens from children or other "sentinel" cohorts in the population. Though further experience is needed with the practical application of these "community-diagnostic" tools, their availability promises to change dramatically how filariasis control/elimination programmes are initiated and managed.

Disease control techniques: effectiveness in reducing morbidity

Elephantiasis, lymphoedema and acute adenolymphangitis. Until recently it was not appreciated how much could be done for individuals who were suffering from the chronic clinical manifestations of lymphatic filarial disease. In most instances, a sense of hopelessness inhibited any active intervention; more aggressive approaches depended on surgery, but the sheer number of sufferers meant that only relatively few could benefit.

Now, however, evidence from both careful clinical observations and immunohistological and bacteriological studies of tissue from lymphoedematous limbs, scrota, and breasts indicates that bacterial and fungal superinfections play an extremely important role in triggering the great majority of adenolymphangitis episodes in tissues whose lymphatic function had been compromised initially by damage from filarial infection (*46–48*). Furthermore, the recurrent episodes themselves do additional damage to the lymphatic vessels and progressively exacerbate the lymphoedema and elephantiasis of the affected parts.

Simple hygiene measures, supplemented with antibiotics, can (and do) have a profound effect in preventing debilitating and damaging episodes of adenolymphangitis (*46*, *49*) and also promote repair and recovery of a considerable amount of the overt tissue damage caused by repeated filarial and bacterial infections. Effective hygiene measures are as follows:

- regular twice-daily washing of the affected parts with soap and water;
- raising the affected limb at night;
- regularly exercising the limb to promote lymph flow;
- keeping the nails clean;
- wearing shoes; and
- using local antiseptic or antibiotic creams (or, in severe cases, systemic antibiotics) to treat small wounds or abrasions.

Such measures help both to prevent the development of lymphatic disease in infected persons who are still asymptomatic and to halt its progression in those with a slight degree of lymphatic damage who remain "in balance" until the affected part comes under pressure-stress, e.g. from prolonged physical work or standing. Even patients with advanced lymphoedema or elephantiasis can be helped by these simple methods, since lymphoscintigraphy studies have shown the presence of extensive collateral lymphatic channels which, if kept free from secondary infection, can serve to re-establish lymph flow (*50*).

Studies are now in progress to determine optimal regimens for managing clinically afflicted

patients, relying mainly on diligent attention to local hygiene of the affected parts. However, to put such measures into effect in the usually poverty-stricken areas where lymphatic filariasis flourishes requires good community health education followed by the establishment of community self-help groups to stimulate and maintain personal commitment to the hygiene activities needed for this "morbidity control". The most successful strategy has been to work initially with the most severely affected persons and later to include all those who are infected or at risk of infection, thus involving the entire community in a self-help campaign of morbidity prophylaxis. This new strategy can be applied worldwide, since wherever lymphatic filariasis occurs the hitherto despondent sufferers soon become enthusiastic to rid themselves of the disease, prevent its further development or recurrence, and spare their children a similar fate. Thus, morbidity control measures for lymphatic fiariasis complement and help to ensure the success of concurrent mass treatment campaigns designed primarily to control transmission.

Asymptomatic microfilaraemia. A second new approach to morbidity control arises from the recognition that patients with asymptomatic microfilaraemia very much need to be treated. Although such patients are certainly infected and harbour adult worms, their asymptomatic state probably results both from a down regulation of their immune inflammatory response to the parasites (*3*) and a partial compensating capacity of their lymphatic systems, since such individuals have appreciable hidden damage that was not previously recognized. Lymphoscintigraphy reveals that they have abnormally dilated lymphatics and abnormal lymph flow (*50*); also, they frequently show some degree of haematuria and/or proteinuria, reflecting low-grade renal damage *which is reversible by antifilarial treatment* (*51*). Such persons should clearly receive treatment (if possible including DEC with its partial adult-worm killing effect (*23*, *52*)), and their responses should be monitored just as closely as those of individuals with the more commonly recognized overt manifestations of filarial disease.

Other clinical syndromes resulting from lymphatic filariasis. For management of the other clinical syndromes associated with lymphatic filariasis, such as tropical pulmonary eosinophilia, chyluria, etc., there has been little recent research and no new advances in treatment recommendations beyond the use of DEC and/or surgery as applicable (*53*).

Vector control: effectiveness of different options

Vector control has traditionally played an important role in the control of lymphatic filariasis. Measures designed to reduce vector biting densities and/or human–vector contact still provide useful supplements to the effects of treating the human population to reduce transmission, but they should not be relied upon exclusively in filariasis control campaigns.

Several current techniques appear capable of reducing transmission of filarial parasites, but most still require both validation of their impact in large-scale control programmes and assessment of their cost-effectiveness. Among the most promising are the following: biocides, especially *Bacillus sphaericus* (a self-reproducing, toxin-producing bacterium) for the control of *Culex quinquefasciatus* mosquitos (*54*); polystyrene beads to limit the breeding of vectors, especially in enclosed urban breeding sites, such as latrines and cesspits (*55*); insecticide-impregnated bednets and curtains, such as those used for malaria control (*56*); and indoor spraying of insecticides that are long-lasting and residually active (*57*).

For the long-term successful application of all these methods of vector control, community participation is essential.

Mathematical/computer-based models: effectiveness in prediction and evaluation

Mathematical models, which constitute powerful tools for the analysis, prediction and evaluation of control strategies, have recently been developed for lymphatic filariasis (*58*, *59*). These take into account the complex inter-relationships between the parasite and its human and vector hosts, all of which will be affected by long-term control measures. Such models have proved to be of great value in guiding and assessing onchocerciasis control efforts (*60*), and are now ready for application to the problems of transmission, intervention, and control of lymphatic filariasis.

Establishing programmes for the control/elimination of lymphatic filariasis

Control programmes

The specific details of each national control programme differ from country to country, but the important first steps in establishing such programmes for filariasis control/elimination are common to all:

assess the magnitude of the problem (using the newest, most cost-effective diagnostic and mapping tools available); design a filariasis control strategy that will best fit into other health care activities; and develop a national control strategy and specific plan of action.

In countries where control programmes are already operational, but using the older tools and strategies, those responsible for the programmes should take account of the recent advances in control methods (including the important elements of community participation) and introduce them where possible into the executing, monitoring, evaluation and management activities of the existing campaigns. For most endemic countries, however, control programmes for lymphatic filariasis will be starting *de novo*, and hence will have the opportunity to take full advantage of the new tools and methods from the start.

Integration of the filariasis control/elimination activities with ongoing public health activities can be particularly important for the success of all programmes. For example, in areas where onchocerciasis is co-endemic with lymphatic filariasis and where yearly distribution of ivermectin is being used in control programmes (e.g., in the Onchocerciasis Control Programme in West Africa and the new African Programme for Onchocerciasis Control), careful consideration should be given to how control of these two filarial infections can be integrated. Similarly, where school-based (or other) intestinal parasite control programmes are under way using intermittent albendazole treatment, filariasis control can also be very cost-effectively integrated with such acitivities.

Managing the programmes

It is particularly important for the efficient management of filariasis control/elimination programmes to take advantage of the following new techniques for simplifying and streamlining activities:

— rapid epidemiological assessment methods;

— simple drug regimens for control of transmission;

— diagnostic tests for antigenaemia or parasite DNA for survey and monitoring needs;

— mathematical models;

— modern vector control methods to supplement chemotherapy-based transmission control;

— morbidity control tools using health education and community participation; and

— integration of control activities, particularly annual mass treatment, with other aspects of the health care system using similar intervention strategies.

An elaborate management structure should not be necessary for lymphatic filariasis control programmes, provided that there is good integration with other components of the health care system (including primary health care). Furthermore, specific programme costs for medications will probably be minimal, because all the preparations recommended are, or are expected to be, available very inexpensively.[j]

Cost implications

The cost of new lymphatic filariasis control/elimination programmes is of particular importance because the disease itself has often not been accorded a high priority by health planners. However, this attitude is likely to change now that its public health and socioeconomic importance are becoming more apparent and that new, more effective and cheaper methods of epidemiological assessment, of mass treatment to control transmission, and of controlling morbidity have all become available. Furthermore, as has recently been the case with onchocerciasis (*22*), once it is recognized that lymphatic filariasis is an infection that can now be controlled and eventually eliminated, resources are likely to be allocated because the benefits of this investment can be calculated directly and are sizeable.[k]

Countries that already have control programmes should be able to reallocate their resources to more effective and cost-effective approaches and thus be able to expand them to provide greater, and ultimately countrywide, coverage. For countries where no control programme has yet started, the costs of lymphatic filariasis control can now be more easily justified, especially when the control is inte-

[j] Diethylcarbamazine (DEC) costs approximately US$ 0.02 per treatment; for albendazole the cost is US$ 0.05–0.11 (depending on the manufacturer); ivermectin (Mectizan ®) is currently donated free by its manufacturer (Merck & Co., Inc.) for control of onchocerciasis and to countries collaborating with WHO to test the feasibility of eliminating lymphatic filariasis by yearly treatment with ivermectin, alone or in combination with DEC or albendazole.

[k] For example, in footnote *c* the annual costs of lymphatic filariasis in India were conservatively estimated at US$ 1.5×10^9. In contrast is the relatively small cost of community-wide annual treatment programmes for filariasis, with a single annual dose of DEC being administered for 4–5 consecutive years. Total programme costs for implementing this revised strategy (which already began on a limited scale in 1996) averaged Rs 1 per person. If this programme could be extended to include all 420 million endemic-area residents in India, the total annual investment (for the 4–5 years required for elimination) would be approximately RS 420 million (US$ 12 million), <1% of the economic (to say nothing of the social) burden of lymphatic filariasis to the country. Elsewhere, in similar "stand-alone" filariasis control programmes based on a once-yearly mass treatment strategy, total programme costs have averaged US$ 0.05–0.08 per person per year.

grated with other ongoing health-care activities and when it includes treatment with ivermectin or albendazole, which have additional beneficial actions on gastrointestinal parasites and, for ivermectin, on ectoparasites also (including scabies and lice; see ref. *61*, *62*).

Throughout the world, lymphatic filariasis should now be recognized as a disease whose elimination as a public health problem could be accomplished very cost-effectively. The erstwhile despondency among sufferers of this disease should soon be replaced by increasing popular enthusiasm and demand for treatment with the newly available tools and strategies.

Résumé

Stratégies et instruments permettant de combattre/d'éliminer la filariose lymphatique

La filariose lymphatique affecte 120 millions de personnes dans 73 pays du monde entier et le problème continue de s'aggraver, tout particulièrement en Afrique et dans le sous-continent indien. L'éléphantiasis, les lymphœdèmes et les pathologies génitales touchent 44 millions d'hommes, de femmes et d'enfants; 76 millions d'autres ont des parasites dans le sang, sources de lésions internes inapparentes des systèmes lymphatiques et rénaux. Dans le passé, les instruments et stratégies utilisés dans la lutte contre cette affection étaient inadéquats, mais, au cours des dix dernières années, la recherche a fait des progrès considérables qui ont permis de mieux comprendre la gravité et l'impact de la maladie, et ont débouché sur de nouveaux instruments de diagnostic et de suivi et, ce qui est plus important, de nouveaux outils de traitement et stratégies de lutte.

La nouvelle stratégie vise à combattre la transmission à l'aide de programmes de traitement de masse, à l'échelle de la communauté, et à lutter contre la maladie grâce à la prise en charge individuelle des malades. L'administration associée en *une seule dose* de deux médicaments (ivermectine + diéthylcarbamazine (DEC) *ou* albendazole) réduit les microfilaires dans le sang de 99% pendant une année entière; même avec une seule dose de médicament (ivermectine ou DEC) administrée annuellement on parvient à des réductions de 90%; les études de terrain confirment qu'une telle réduction des quantités de microfilaires et de la prévalence peut interrompre la transmission. De nouvelles approches de la lutte contre la maladie, basées sur la prévention de la surinfection bactérienne, permettent maintenant d'enrayer ou même d'annuler les séquelles — lymphoedèmes et éléphantiasis — de l'infection filarienne. Prenant en considération les progrès techniques remarquables qui ont été accomplis, le succès des programmes de lutte récents et les facteurs biologiques favorisant l'élimination de cette infection, la Cinquantième Assemblée mondiale de la Santé a récemment demandé à l'OMS et à ses Etats Membres de classer en priorité l'élimination de la filariose lymphatique au niveau mondial en tant que problème de santé publique.

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