

A LONGITUDINAL STUDY OF BANCROFTIAN FILARIASIS IN THE NILE DELTA OF EGYPT: BASELINE DATA AND ONE-YEAR FOLLOW-UP

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Abstract. We initiated a longitudinal study of Bancroftian filariasis to improve understanding of dynamics and risk factors for infection in villages near Cairo, Egypt. Baseline prevalence rates for microfilaremia and filarial antigenemia for 1,853 subjects more than 9 years of age were 7.7% and 11.2%, respectively. Microfilaria counts, antigen levels, and microfilaremia incidence over a 1-year period were all significantly lower in older people. These findings suggest that humans develop partial immunity to *Wuchereria bancrofti* over time. One-year incidence rates for microfilaremia and antigenemia were 1.8% and 3.1%, respectively. Filarial antigenemia, IgG4 antibody to recombinant antigen BmM14, and household infection were all significant risk factors for microfilaremia incidence. Microfilaria counts and parasite antigen levels were significantly reduced by diethylcarbamazine therapy, but many infected subjects refused treatment, and most treated people were still infected one year later. Incident infections approximately balanced infections lost to produce an apparent state of dynamic equilibrium.

Bancroftian filariasis is a major public health problem in the tropics with more than 100 million people infected in 73 countries.¹ Filariasis has been endemic in Egypt for centuries.² Although the infection was considered to be almost eliminated and no longer a public health problem in the 1960s, a recent report documented resurgence of filariasis in the 1980s with an estimated 250,000 people infected and 3.65 million people at risk, mostly in the Nile Delta region.³ Filariasis control in Egypt (as in most of the world) is based on mass diagnosis (examination of thick blood smears for the presence of microfilariae) and selective therapy of infected people with diethylcarbamazine. These efforts are sometimes supplemented by mosquito control measures. While aggressive application of this program has stemmed the resurgence of filariasis to some extent in recent years (Egyptian Ministry of Health, unpublished data), the program is labor-intensive and difficult to sustain; the parasite is down but not out, and it is ready to rise again if control measures are relaxed.

Prior studies by our group have explored the use of newer diagnostic methods for filariasis in Egypt. We have shown that filarial antigen detection is superior to microfilaria detection for identifying infections in populations,⁴ and we have shown that antigen testing of sentinel groups such as school children can be an efficient means of assessing filariasis endemicity in populations.⁵ Assays for IgG4 antibody to recombinant filarial antigens can also be useful tools for measuring exposure to filarial parasites in populations.⁶

Relatively little is known about protective immunity in human filariasis, and there is little direct evidence that such immunity exists. The present study was prompted by the observation that filariasis prevalence rates increase rapidly with age in teenage children in Egypt,⁵ and by results of another study that found that filariasis infection intensity in a village in the Nile Delta tended to decrease with age⁷ (also Weil GJ and others, unpublished data). Relatively few longitudinal studies of filariasis have been conducted, and fewer still have used sensitive diagnostic methods. Therefore, the primary goals of this longitudinal study were to study the dynamics of filariasis in the Nile Delta of Egypt and to test the hypothesis that humans develop immunity to the infection. A secondary objective of the study was to obtain ad-

ditional information on the significance of filarial parasite antigenemia in asymptomatic and amicrofilaremic subjects whom we call antigen-positive endemic normals.⁸

METHODS

Study population. The study was conducted in an area previously studied by our group and known to be endemic for filariasis.⁴ The study villages are located approximately 35 km northeast of Cairo in Shebin El Kanatar District, Qalubya Governorate. The study design called for following a subset of the population that would allow comparison of filariasis incidence rates in children and adults. This was accomplished by selecting all households with a child in the first year class of a preparatory or middle school in Tahoria village that serves children in Tahoria and four nearby villages. All children in this class (mean \pm SD age = 11.9 \pm 0.73 years) were enrolled in a special school-based health screening program. This improved the willingness of families to participate in follow-up health screening activities offered to family members in their homes. Children more than 9 years of age and adults were included in the household study that forms the basis of this report.

Informed consent was obtained from all study subjects (and from parents of minors) for participation in this study. The study was approved by institutional review boards at Ain Shams University in Cairo and at Barnes-Jewish Hospital in St. Louis.

Data and specimen collection. Field teams comprised of a physician, a technician, and one or more local village residents visited houses in the evening. After obtaining informed consent, the teams recorded demographic information on preprinted forms and collected urine and stool specimens for parasitologic examination. Physicians also asked subjects about symptoms and past treatment of filariasis and performed a standardized, directed physical examination as previously described.⁹ All males were examined for the presence of hydrocele by palpation of the scrotum with transillumination reserved for questionable cases. All subjects with obvious or questionable hydrocele were examined by a second physician to confirm the diagnosis. Venous blood samples were collected between 9:00 PM and 1:00 AM for para-

TABLE 1
Baseline filariasis prevalence rates (%) by village*

Village†	(n)	Clinical disease	Microfilaremia	Antigenemia	Antibody
KL	(812)	1.4	10.8	15.0	44.6
KS	(244)	0.8	9.0	8.2	27.9
KT	(116)	0.9	6.0	12.9	34.5
SH	(373)	0.3	2.1	3.8	10.5
TH	(308)	1.6	9.1	12.0	35.1
Total	(1,853)	1.1	7.8	11.2	33.3

* Prevalence rates for microfilaremia, parasite antigenemia, and IgG₄ antibody to BmM14 varied significantly by village ($P < 0.001$ for each variable by chi-square test).

† KL = El Kolsam; KS = Kafr Saad; KT = Kafr Tahoria; SH = Kafr El Shorafa; TH = Tahoria.

sitology and serology studies. Amicrofilaremic subjects with no evidence of clinical filariasis were considered to be endemic normals.

Parasitology results were reported to the local government health center appropriate for each village, and infected subjects were referred to these centers for free treatment of schistosomiasis or intestinal helminths. Patients with microfilaremia, hydrocele, or lymphedema were offered treatment with diethylcarbamazine (DEC) (72 mg/kg orally over a 12-day period) according to Egyptian Ministry of Health policy.

Laboratory tests for filariasis. Microfilariae were detected by membrane filtration (5 μ M; Nuclepore Corp., Pleasanton, CA) of 1 ml of venous blood and microscopic examination of stained filters. Filarial antigen was detected in plasma samples by ELISA as previously described in detail.^{10,11} The filarial antigen test detects adult worm products in human blood, and a positive test result indicates the presence of living adult worms in the host. Prior studies have shown that the test detects antigen in 90–97% of sera from microfilaria carriers and antigen is also detected in a subset of endemic normals who are presumed to have amicrofilaremic infections.⁸ IgG₄ antibodies to recombinant filarial antigen BmM14 were detected by ELISA as previously described.^{6,8} Prior studies have shown that most (90%) subjects with microfilaremia or antigenemia have positive antibody test results; positive antibody test results are also seen in some apparently uninfected endemic normals. Prior studies have shown that the filarial antigen test and the BmM14 antibody test have specificities that approach 100% with nonendemic Egyptian sera.

Data analysis. Database management and statistical analyses were performed with EpiInfo software, version 6.¹²

RESULTS

Baseline data. Data were collected for 1,853 subjects (914 males and 939 females) in 362 households that were scattered in all areas of the 5 study villages. These houses comprised between 12% and 25% of the houses present in these villages. Baseline prevalence rates for several measures of filariasis activity are shown by village in Table 1 and by age in Figure 1. Very little clinical filariasis was observed. There was only one case of lymphedema in the sample population, although several others were present in the study villages. Most hydroceles were small and either not noticed or not considered to be a significant problem by the subjects. No subject reported a history compatible with

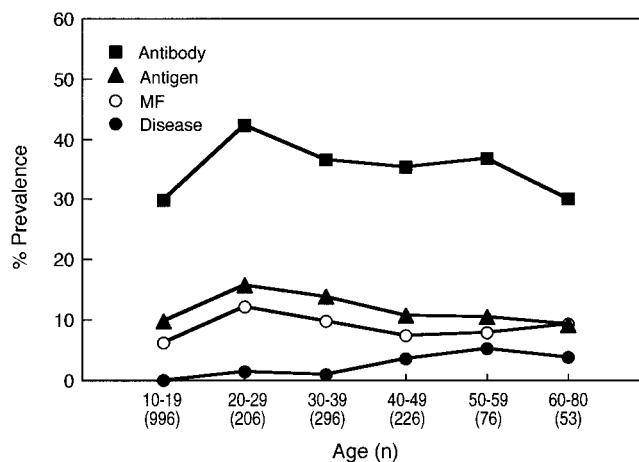


FIGURE 1. Baseline age-specific prevalence rates for clinical filariasis, microfilaremia (MF), filarial antigenemia, and IgG₄ antibody to the recombinant filarial antigen BmM14. Numbers in parentheses indicate the number of subjects studied in each age group.

filarial fever (fever and chills with lymphadenitis and retrograde lymphangitis).

Prevalence rates for microfilaremia, antigenemia, and antifilarial antibody varied significantly by village, and these parameters varied in parallel, with antibody rates being higher than antigenemia rates, which were generally higher than microfilaremia rates (Table 1). Prevalence rates for disease, microfilaremia, antigenemia, and antifilarial antibody were significantly lower in children 10–19 years of age than in older subjects. Disease prevalence rates increased with age. In contrast, age prevalence curves for microfilaremia, antifilarial antibody, and antigenemia had convex patterns (Figure 1). No significant gender differences were observed in filarial antigen, microfilaria, or antibody prevalence rates. Positive filarial antigen test results were present in 88.7% of those with microfilaremia and in 5.5% of amicrofilaremic subjects with no clinical evidence of filariasis (endemic normals). IgG₄ antibody to BmM14 was present in 88.9% of subjects with microfilaremia, 77.8% of endemic normals with positive antigen test results, and 26.1% of antigen-negative endemic normals.

Intensity of infection. The mean \pm SD number of microfilariae/ml in microfilaria carriers was 168 ± 252 (median = 48.5). The mean \pm SD filarial antigen level for positive sera was 31.4 ± 34 ng/ml (median = 18). When microfilaria counts and filarial antigen levels for infected subjects were plotted against age, infection intensities appeared to be lower in older people, but the relationship was nonlinear. Antigen levels were significantly lower in people more than 40 years of age than in younger subjects, and microfilaria counts were significantly lower in people more than 30 years of age (Table 2). Variances for microfilaria counts and antigen levels were higher in younger subjects. Neither measure of infection intensity differed significantly by gender.

One year follow-up data. A total of 1,423 subjects were restudied one year after the baseline examination, and this number represents 76.8% of those studied in year 1. These subjects did not differ significantly from subjects lost to follow-up with regard to age, sex, or infection status. No new cases of clinical filariasis were identified at the one-year time

TABLE 2
Effect of age on filariasis infection intensity

	Mean	SD	P*
Microfilaremia (MF/ml)			
Age <31† years	207	284	0.02
Age >30 years	95	153	
Antigenemia (ng/ml)			
Age <41 years	33.4	35.5	0.038
Age >40 years	20.1	28.9	

* Nonparametric Mann-Whitney two-sample test.
† The same trend was observed when an age >40 years was used to separate older and younger subjects (183 versus 98 MF/ml, respectively), but this difference was not statistically significant (P = 0.13).

point. Incidence rates for microfilaremia and filarial antigenemia were 1.8% and 3.6%, respectively. Data on risk factors for incidence of microfilaremia are shown in Table 3. A positive filarial antigen test result was the strongest risk factor for incidence of microfilaremia with a relative risk of 26.1. IgG4 antibody to BmM14 was a significant risk factor for incidence independent of filarial antigenemia as were household infection (microfilaremia or antigenemia), residence in Kafr Tahoria village, and age. The incidence of microfilaremia was significantly higher in subjects less than 31 years of age than in older subjects. Incidence of filarial antigenemia was significantly increased in subjects with a positive antibody test result at baseline and in residents of village Kafr Tahoria. Males and females had statistically equivalent incidence rates for microfilaremia and filarial antigenemia.

Parental infection as a risk factor for infection in children. Filarial infection in either parent was a significant risk factor for infection in children 10–16 years of age (Table 4); this relationship was equally strong for paternal and maternal infections and true whether infections were defined as microfilaremia or filarial antigenemia.

Effect of DEC therapy. Only 39% of those offered DEC took the treatment. Asymptomatic subjects were reluctant to take a 12-day course of medication that sometimes causes significant side effects. Changes in microfilaria counts and filarial antigen levels in treated and untreated subjects are shown in Table 5. Microfilaria counts and antigen levels were both significantly decreased after treatment. Treatment with DEC was significantly associated with clearance of microfilaremia, although a majority of treated subjects were

TABLE 4
Parental infection as a risk factor for filarial infection in children 10–16 years of age

	Total children	Child +*	% Child +	P†
Microfilaremia				
Father +	47	6	12.8	0.03
Father –	498	23	4.6	
Mother +	67	7	10.4	0.04
Mother –	652	29	4.4	
Either parent +	94	12	12.8	0.01
Both parents –	391	20	5.1	
Filarial antigenemia				
Father +	57	10	17.5	0.04
Father –	488	40	8.2	
Mother +	107	20	18.7	<0.01
Mother –	607	40	6.6	
Either parent +	119	30	25.2	<0.01
Both parents –	353	23	6.5	

* + Indicates a positive test result for microfilaremia or antigenemia, as indicated in the table.
† P values calculated by chi-square test.

microfilaremic one year after therapy. This treatment was not associated with increased clearance of filarial antigenemia over the rate of clearance observed in untreated subjects. The high rates of clearance of microfilaremia and antigenemia in untreated subjects were unexpected and striking. We went back to interview most of these people, and none had been treated with DEC; repeat blood testing confirmed clearance of infections.

Natural history of filarial antigenemia in amicrofilaremic subjects. One-year follow-up examinations were performed for 67 antigen-positive endemic normal subjects. These people had not been treated with DEC. No subject developed clinical filariasis during the period studied. Isolated filarial antigenemia persisted in a majority (58%) of subjects, but significant numbers of people developed microfilaremia (21%) or cleared antigenemia (21%). Incidence of microfilaremia was more common in antigen-positive subjects less than 31 years of age (12 of 48 versus 2 of 19), but this difference was not statistically significant.

Dynamic equilibrium. Figure 2 shows an accounting of filarial infections gained and lost over one year in the study population. Infections cleared (spontaneously or after treatment with DEC) were offset by incident infections; filariasis

TABLE 3
One year incidence of microfilaremia by age, antigen, antibody, or household infection status

	n	Microfilaremia	%	Relative risk*	P†
Age (years)					
10–30	899	21	2.3	0.3 (0.1–1.04)	0.04
>30	412	3	0.7		
Filaria antigenemia					
Present	67	14	20.9	26.1 (12–56)	<0.001
Absent	1,244	10	0.8		
IgG ₄ antibody to BmM14					
Present	380	18	4.7	7.8 (2.9–18.4)	<0.001
Absent	931	6	0.6		
Household infection‡					
Present	466	12	2.6	5.2 (1.7–15.9)	<0.001
Absent	801	4	0.5		

* 95% confidence limits are shown in parentheses.
† Significance of difference by chi-square test.
‡ Limited to microfilaremia for this analysis.

TABLE 5
Clearance of *Wuchereria bancrofti* infections in one year with and without diethylcarbamazine (DEC) therapy*

	No DEC†	DEC†	P‡
MF clearance 1 year	26% (16.5–38.6)	45% (32.6–63.3)	0.02
Median decrease MF count	13%	99%	<0.001
Antigen clearance	20% (12.3–26.9)	18% (8.4–33.4)	NS
Median decrease Ag level	27%	43%	0.02

* MF = microfilaremia.

† 95% confidence limits are shown in parentheses.

‡ Significance by chi-square test. NS = not significant.

prevalence rates were fairly constant over one year despite attempted selective treatment of microfilaria carriers with DEC.

DISCUSSION

This study has provided important new information on the dynamics of filarial infection in Egypt. The villages studied had low to moderate prevalence rates for filarial infection and relatively little clinical filariasis. Baseline prevalence rates for microfilaremia, filarial antigenemia, and antifilarial antibody varied in parallel among the 5 villages and confirmed the relative low sensitivity of microfilaria detection for infections, even when membrane filtration is used. Microfilaria detection with thick smears would have grossly underestimated the prevalence of filariasis in this area.⁴ Prevalence rates of IgG4 antibodies to the recombinant filarial antigen BmM14 were higher than rates for microfilaremia or antigenemia. Prior studies have shown that this test is quite specific for exposure or infection by filarial parasites,^{6,13} and *Wuchereria bancrofti* is the only filarial parasite of humans known to be endemic in Egypt.

The villages with the highest and lowest filariasis prevalence rates in our study are separated by only 5 km. This type of focality is a regular feature of filariasis in Egypt.^{2,3,14} Recent studies by our group suggest that environmental and socioeconomic factors may explain much of this variability (Farid H and others, unpublished data).

One major goal of our study was to attempt to determine whether humans develop protective immunity to filarial parasites. Although there is little direct evidence in the literature on this point, convex infection prevalence/age curves (seen also in this study) are often cited to support the notion that humans develop at least partial immunity to new infections after years of exposure to the parasite.¹⁵ Further evidence in favor of immunity in humans comes from a study by Day and others, who found that parasite antigen levels in a highly endemic area in Papua New Guinea increased significantly in people less than 21 years of age over an interval of 18 months but were stable in older adults.¹⁶ This finding suggested that children were more susceptible to new infections than adults. The present study provides further support for the hypothesis that humans develop immunity to filariasis after years of exposure to the parasite. In addition to convex infection prevalence/age curves, we found that filariasis infection intensities (microfilaria counts and antigen levels) tended to decrease with subject age; this confirmed results obtained in a prior study of a single Egyptian village⁷ (also Weil GJ and others, unpublished data). The new finding that filariasis incidence was higher in children than in adults from the same households is consistent with results reported by Vanamail and others, who found that filariasis incidence rates (based on detection of microfilariae in thick blood smears) in southern India decreased with age.¹⁷ Alternate explanations for these data would be that older people experience fewer mosquito bites (with decreased exposure to infective larvae) than children or that other factors such as the location of bites or skin thickness account for the apparent protective effect of age. Data from a study performed in one of our study villages make the first explanation seem unlikely; while children experienced significantly more mosquito bites than adults in the same houses,⁷ the difference (22% excess bites in children) seems to be too small to fully explain observed differences in age-specific microfilaria incidence or infection intensity.

This study has provided new information on the issue of parental infection as a risk factor for infection in children. Prior studies have shown that maternal helminth infections can induce fetal immune responses¹⁸ and that prenatal sensitization to parasite antigens may have long term effects on immune responses to helminth antigens.¹⁹ Lammie and others found that children of microfilaremic mothers in Haiti had higher infection prevalence rates than offspring of uninfected mothers. They attributed this apparent increased susceptibility to prenatal conditioning of the immune system, since paternal infection was not associated with infection in children.²⁰ However, relatively few fathers were tested in that study.



BASELINE	EVENTS	1 YEAR LATER
a. MF Positive 112/1423 7.9%	MF Clearance 38 (33%) — MF Incidence 24 (1.8%) 	MF Positive 97/1423 6.8%
b. Antigen Positive 165/1395 11.8%	Antigen Clearance 32 (19%) — Antigen Incidence 44 (3.6%) 	Antigen Positive 177/1395 12.7%

FIGURE 2. An accounting of filarial infections lost and gained over the course of one year in the sampled population as assessed by microfilaremia (MF) (a) or filarial antigenemia (b). Note that microfilaria carriers in the sample population were offered diethylcarbamazine therapy (only 39% of these accepted treatment), but the surrounding population was not surveyed for infection or treated during this time.

The present study had a larger sample size than most prior studies of this issue. As in prior studies, we have no information on the infection status of mothers during gestation, but we assume that many of the women who were infected at the time of our study were also infected during their pregnancies. Our results are similar to those recently reported by Alexander and others²¹ and by Das and others²² in that infection in either parent was associated with a significantly increased risk of infection in children, and there was no special risk associated with maternal infection. Unlike Alexander and others, we found that the risk associated with parental infection was independent of village of residence, but this does not exclude the possibility that the association was caused by environmental factors affecting exposure to infection that are shared between parents and children residing in the same houses. Indeed, our results suggest strongly that genetic and/or local environmental factors are important determinants of filariasis clustering in families; by age 10 years, these factors appear to be more important risk factors for infection in children than the infection status of the mother during gestation.

Prior studies in Egypt have shown that a significant proportion of asymptomatic and amicrofilaremic people who reside in endemic areas have positive test results for filarial antigenemia,⁴ and this observation has been confirmed in many other endemic areas. Prior studies have also provided strong evidence that positive filarial antigen test results in endemic normal individuals are not artifacts and that they are true indicators of cryptic or amicrofilaremic infections.⁸ The current study has provided new information on the natural history of infections in this group of subjects. First, none of the subjects developed clinical filariasis over one year of observation (albeit in an area with little clinical filariasis). The second finding was that 21% of the subjects with isolated filarial antigenemia were microfilaremic one year later. This result, along with the observation that subjects with isolated parasite antigenemia often have subclinical pathology detectable by ultrasound,²³ supports the idea that antigen-positive endemic normal subjects should be treated for filariasis, both for their own benefit and to decrease the future prevalence of microfilaremia in their communities. However, the need for such therapy cannot be considered urgent; most subjects with isolated parasite antigenemia remained antigen-positive and amicrofilaremic one year later. It is possible that these subjects have stable, postpatent infections with immunity to microfilariae.²⁴ Twenty-one percent of the untreated subjects with isolated filarial antigenemia were antigen-negative one year after the initial survey, and many subjects with microfilaremia also spontaneously cleared their infections. Clearance of microfilaremia and antigenemia in untreated subjects is likely to be immune-mediated. Additional research is clearly needed to attempt to define immune targets and mechanisms of immunity in these interesting, self-cured subjects.

Although filarial antigenemia was the strongest risk factor identified for incidence of microfilaremia within one year, antibody to BmM14 and residence in an infected household were also highly significant risk factors. It is not surprising that IgG4 antifilarial antibodies were linked to incidence, since such antibodies could be induced by early infections or heavy exposure to the parasite. The household infection

risk factor is interesting but also not difficult to explain. Filariasis is not directly transmitted from person to person; like many parasitic diseases, it is essentially an environmental disease that happens to be caused by a living organism. Filariasis is believed to be mainly transmitted in or near houses in Egypt;¹⁴ if one person in a house is infected, other household members should also be exposed and at increased risk.

Infection incidence also varied significantly among villages. The village with the highest incidence rate (Kafr Tahoria) was studied by our group in 1990–1991.⁴ Microfilaremia prevalence in subjects more than 10 years of age was 28% at that time, but this decreased after widespread distribution of DEC by our group and by local health officials about 4 years prior to the present study. We believe that the high rate of filariasis incidence observed in Kafr Tahoria represents resurgence of infection in a village where treatment stopped short of elimination of the parasite and where environmental conditions still favor transmission.

The high rates of spontaneous clearance of infections observed in this study have not been reported before, but they should not have been surprising in view of the relatively low infection prevalence in this area with ongoing transmission; new infections must be balanced by lost infections if a steady state is to be maintained. Data shown in Figure 2 illustrate a dynamic equilibrium state in which a low incidence of infection in the large, uninfected population was approximately balanced by a relatively high rate of loss of infection in the smaller, infected population. It remains to be seen whether these interesting results can be confirmed in other endemic areas.

The time-honored approach of mass diagnosis with selective DEC therapy of microfilaria carriers has not been particularly effective for control of filariasis in many endemic areas.^{1,25} The present study illustrates why this might be the case. First, many infections are missed when thick blood smears are used for diagnosis. Selective treatment of microfilaria carriers does not treat the antigen-positive endemic normal group, and this group appears to be at high risk for incidence of microfilaremia. Second, many people with infections identified by mass screening are not treated because they are lost to follow-up or because they refuse therapy. Diethylcarbamazine often causes side effects in asymptomatic microfilaria carriers, and it is difficult to ensure compliance with the standard 12-day regimen that has been recommended as first-line therapy for many years. The third problem with this approach is that a single course of DEC does not cure most cases of Bancroftian filariasis.²⁶ Parasite antigen and microfilaria levels decreased significantly after treatment with DEC in the present study, but the antigen clearance rate (which may indicate cure) was no higher in treated than in untreated subjects.

In conclusion, this study has highlighted weaknesses of the old strategy of mass diagnosis and selective therapy for filariasis control, and our results support the new approach that is currently being promoted by the World Health Organization.²⁵ One version of the new approach begins with a program of selective diagnosis by screening sentinel populations to establish the presence of filariasis in a community. This is followed by annual mass therapy of endemic populations, preferably with newer single-dose combination regimens that are more effective for suppression of micro-

filaremia than DEC monotherapy.²⁷ Unlike selective therapy, mass therapy has the potential to rapidly alter equilibrium set points to increase microfilaria clearance rates and thereby reduce transmission and incidence. The source of infection should be reduced with each cycle of mass therapy if high levels of coverage are achieved. This new plan is sound; the challenge now will be to implement programs tailored to local conditions in each endemic country and to muster the political will and resources to sustain the programs until the goal of elimination of filariasis as a public health problem is achieved.²⁵

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