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BANCROFTIAN FILARIASIS INFECTION, DISEASE, AND SPECIFIC ANTIBODY RESPONSE PATTERNS IN A HIGH AND A LOW ENDEMICITY COMMUNITY IN EAST AFRICA

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Abstract. Bancroftian filariasis infection, disease and specific antibody response patterns in a high and a low endemicity community in East Africa were analyzed and compared to assess the relationship between these parameters and community transmission intensity. Overall prevalences of microfilaremia and circulating filarial antigenemia were 24.9% and 52.2% in the high and 2.7% and 16.5% in the low endemicity community, respectively. A positive history of acute attacks of adenolymphangitis was given by 12.2% and 7.1% of the populations, 4.0% and 0.9% of the adult ($\geq$ 20 years old) individuals presented with limb lymphedema, and 25.3% and 5.3% of the adult males had hydrocele, in the high and the low endemicity community, respectively. Both infection and disease appeared earlier and reached much higher levels in the high than in the low endemicity community. The observed overall and age-specific infection and disease patterns in the two communities were in agreement with the view that these are primarily shaped by transmission intensity. No statistically significant relationships between infection status of fathers and mothers and that of their children were observed in any of the communities for either microfilaremia or for circulating filarial antigenemia. The overall levels (prevalence and geometric mean intensity) of filarial-specific IgG1, IgG2, IgG4, and IgE were significantly higher in the high endemicity community than in the low endemicity community. Surprisingly, the opposite pattern was found for IgG3. Community transmission intensity thus appears to be an important determinant of observed inter-community variation in infection, disease, and host response patterns in Bancroftian filariasis.

INTRODUCTION

Despite a large number of field investigations, the natural history of the development of infection and disease in lymphatic filariasis remains unclear. One consequence of this is that we are still unable to adequately explain the marked heterogeneity in patterns of filariasis infection and disease observed at all population levels, from the individual host to the community. Gaining a better understanding of the natural history (and thus causes of the observed heterogeneity) has become urgent in filariasis given the current global initiative for controlling this parasitic infection of more than 120 million people based on decreasing or even interrupting parasite transmission via the application of mass chemotherapy.[1]

The coastal region of East Africa has long been known to be highly endemic for Bancroftian filariasis.[2–8] As with other endemic foci, a feature of East African filariasis is also the high degree of variability in the burden of infection and disease recorded between endemic communities. Indeed, it has been suggested that the observed between-community variability within this and other endemic regions may be a function of the existence of at least four distinct epidemiologic types of filariasis among endemic communities, namely 1) populations with high microfilaria rates and densities exhibiting many clinical signs, 2) populations with high microfilaria rates and densities with few clinical signs, 3) populations with low microfilaria rates and densities showing many clinical signs, and finally 4) populations with low microfilaria rates and densities showing few clinical signs.[3,9] Traditional explanations for these differences have focused primarily on the roles of the timescale of endemic focus establishment as well as the impact of human migratory patterns, as summarized by Wijers.[3] While plausible, these theories do not provide satisfactory explanations for the differences in the age-relationships of infection and disease observed between communities, especially among those exhibiting comparatively stable and long-term endemicity. They also do not account for more recently suggested sources of the observed heterogeneity, including acquired immunity,[10,11] maternally-derived immune tolerance,[12,13] and adult-worm induced or immune-mediated pathology.[14,15]

Recent work has indicated that one factor that may systematically explain differences in age-patterns of infection and disease between endemic communities in filariasis is parasite transmission intensity. For example, Michael and Bundy used a mathematical modeling approach to demonstrate that variations in community transmission intensity may, via the generation of exposure-driven acquisition of herd immunity, shape the observed age-patterns of infection (microfilaremia) in endemic communities.[11] Similarly, several studies have shown that the prevalence of chronic filarial disease at the community level is correlated with community transmission intensity.[16,17] Other studies have highlighted the effects that exposure or transmission intensity may have on infection variability at the individual host level by affecting maternally-derived neonatal tolerance.[13] These studies clearly indicate the potentially central role that transmission intensity may play in infection, disease, and immune processes in lymphatic filariasis, and suggest that gaining a better understanding of the interrelationships between community transmission levels and these variables at both the community and individual host levels may be critical to understanding the natural history of filariasis.

Here, we report on the first phase of our investigations into the link between transmission intensity and community patterns of Bancroftian filariasis in coastal East Africa. The pat-

terns of infection, disease, and filarial-specific antibody responses were analyzed and compared in two communities with high and low endemicity. Overall community microfilarial prevalences were used as initial criteria for selecting the communities, as indirect indicators of community transmission intensity.[16] Intense longitudinal entomologic surveillance initiated at the time of the survey indeed confirmed that there were considerably more mosquitoes, and that the average individual exposure to infective larvae over the following one year period was more than 10 times higher in the high than in the low endemicity community.

MATERIALS AND METHODS

Study communities. The study was carried out in two communities situated approximately 80 km apart within the same coastal East African *Wuchereria bancrofti* transmission focus, namely Masaika village in the Pangani District (Tanga Region) of Tanzania, and Kingwede village in the Kwale District (Coast Province) of Kenya. Preliminary surveys had indicated that the level of *W. bancrofti* endemicity was higher in Masaika than in Kingwede.

Masaika is located in a hilly fertile area approximately 25 km inland from the Indian Ocean coast. The population is subsistence farmers, growing mainly maize, cassava, rice, and vegetables, and keeping chicken, ducks, and goats as domestic animals. A few cash crops such as oranges, coconuts, and cashew nuts are also produced. Most houses have mud walls and roofing of dried coconut leaves. Domestic water is collected from shallow dugouts in the lower parts of the village and its periphery. Ethnically, the population is very mixed, with more than 20 tribes being represented (the three largest, the Makonde, Bondei, and Zigua, constitute 54% of the population). The majority are Muslims. The whole village population was included in the study.

Kingwede is located in a flat lowland area close to the Indian Ocean (approximately 3 km from the coast to the village center). A stream passing through the village and a number of deep wells with hand pumps supply the village with domestic water. Most houses are build from coral stone and/or mud, and have dried coconut leaves or iron sheets as roofing material. The population in this village is composed of subsistence farmers, and essentially they grow the same crops and keep the same domestic animals as those in Masaika. However, many males are also employed in jobs outside the village (e.g., in Mombasa) and some are fishermen in the nearby ocean. The major ethnic group is Digo (> 80% of population), and the majority are Muslims. The village had more than 2,000 inhabitants, and therefore only half (the western part with the village center) was included in the study.

Registration of inhabitants. Before fieldwork commenced, permission to conduct the study was obtained from the health and administrative authorities, and meetings were held in the villages to explain the purpose of the study to the inhabitants. Sketch maps of the villages were prepared, houses were numbered, and a house-to-house census was carried out to register the name, age, and sex of inhabitants. A repeat-census was performed three months later to verify information from the first census. During both rounds of census, inquiries were also made about parent/child relationships for individuals less than 20 years old. In addition, a group of elders was requested to independently provide information about parent/child relationships. Only when information from the census agreed with that from the group of elders were relationships accepted and used in the study. The cross sectional clinical and parasitologic surveys took place in July 1998 in Masaika and in August 1998 in Kingwede. Oral informed consent to participate was obtained from adults, and from parents or guardians of individuals less than 15 years old. The study was reviewed and approved by the Medical Research Co-ordinating Committee of the National Institute for Medical Research, Tanzania, the Kenyatta National Hospital Ethical and Research Committee, Kenya, and the Central Scientific-Ethical Committee, Denmark.

Clinical examination. This was carried out by an experienced clinician. It took place in the evening, starting at 8:00 PM. Hydrocele and lymphedema/elephantiasis was graded as previously described,[6] but grades have been omitted in this presentation. Instead, hydroceles ≥ grade II (true hydroceles ≥ 6.0 cm) and lymphedema/elephantiasis ≥ grade I (loss of contour, pitting edema) are included as hydrocele and elephantiasis, respectively. During the clinical examination, individuals were furthermore asked whether they had experienced acute attacks of adenolymphangitis (ADL) during the preceding one-year period, and in what numbers (parents or guardians answered for individuals less than 15 years old). For this purpose, the Ki-Swahili term "Mtoki" was used. It describes a febrile illness associated with lymphadenitis plus/minus a localized painful/tender and warm limb or scrotum.

Examination for microfilariae. Blood sampling took place after the clinical examination, and started at 9:00 PM. From each individual, 100 μl of finger-prick blood was collected into a heparinized capillary tube and transferred to a specimen tube with 1 ml of 3% acetic acid. The exact time of sampling was noted. Specimens were later examined for microfilariae (mf) under microscope by using the counting chamber technique.[18]

Serum preparation. Immediately after finger-prick blood sampling, 5 ml of venous blood was collected in plain vacutainer tubes. Serum was separated by centrifugation after overnight clotting in a refrigerator, and sodium azide was added to a concentration of 15 mM as a preservative. Serum was initially frozen at −20°C in the field, and later stored at −80°C in the main laboratory until use. Before further handling and testing of sera, lipid-coated vira were eliminated by addition of 3 μl/ml of tri-N-butyl phosphate (T-4908; Sigma, St. Louis, MO) and 10 μl/ml of Tween 80 (P-1754; Sigma).[19]

Examination for circulating filarial antigens. Serum specimens were examined for specific circulating filarial antigen (CFA) by using the TropBio enzyme-linked immunosorbent assay (ELISA) kit for serum specimens (catalog no. 03-010-01; TropBio Ltd., Pty., Townsville, Australia). The test was performed according to procedures obtained from the manufacturer and as described previously.[20] Serum specimens with a response ⩾ that of Standard 2 (32 CFA units) were considered positive for CFA, and specimens with a response ⩾ that of Standard 7 were assigned a fixed value of 32,000 CFA units.

Measurement of filarial-specific antibodies. Sera were examined for filarial-specific antibodies (IgG1, IgG2, IgG3, IgG4, and IgE) by an ELISA as previously described.[21,22] A *Brugia pahangi* adult worm homogenate was used as antigen.[21] Optimal dilutions of antigen, serum, and conjugate

TABLE 1
Characteristics of the study populations in Masaika and Kingwede (high and low endemicity community, respectively)*

	Masaika	Kingwede	Statistics
No. of inhabitants ≥ 1 year of age	950	1,013	–
Male : female ratio	1.09	0.81	χ^2 test, $P < 0.001$
Mf prevalence (%)	24.9	2.7	χ^2 test, $P < 0.001$
Mf GMI for mf positive (mf/ml)	458	174	t-test, $P = 0.016$
Mf GMI for all examined (mf/ml)	3.6	0.1	t-test, $P < 0.001$
CFA prevalence (%)	52.2	16.5	χ^2 test, $P < 0.001$
CFA GMI for CFA positive (units)	6,523	673	t-test, $P < 0.001$
CFA GMI for all examined (units)	246	15.6	t-test, $P < 0.001$
Proportion reporting history of ADL (%)	12.2	7.1	χ^2 test, $P = 0.001$
Hydrocele prevalence in males ≥ 20 years old (%)	25.3	5.3	χ^2 test, $P < 0.001$
Lymphedema prevalence in individuals ≥ 20 years old (%)	4.0	0.9	χ^2 test, $P = 0.007$

* Mf = microfilaria; GMI = geometric mean intensity; CFA = circulating filarial antigen; ADL = adenolymphangitis.

were determined by titration. Prior to measurement of IgE, sera were absorbed with a protein A-agarose bead suspension (Ken-En-Tec A/S, Copenhagen, Denmark) at a ratio of 50: 140 to remove IgG4-blocking antibodies.[23]

Data analysis. The Mf intensities were adjusted for sampling time by multiplying the counts with a time-specific factor, as previously described.[24] Geometric mean intensities (GMIs) of microfilaremia, antigenemia, and filarial-specific antibody levels were calculated as antilog[(Σ log x + 1)/n] – 1, with x being the number of mf/ml, number of CFA units, and ELISA optical density values, respectively, and n the number of individuals included. IgG4:IgE ratios were first calculated for individual sera, and IgG4:IgE ratio GMIs were thereafter calculated as described earlier. Prevalences were compared by chi-square tests, and GMIs were compared by t-tests or one-way analysis of variance (as appropriate) on the log-transformed values. The odds of being mf or CFA positive for each chronic disease category was calculated from 2 × 2 tables using the standard formula: odds ratio = $(a \times d)/(b \times c)$, with a, b, c, and d being the numbers of individuals infected and with disease, not infected but with disease, infected but without disease, and not infected and without disease, respectively. The relationship between infection status (mf or CFA) of parents and that of their children was analyzed by logistic regression, with age group of children (1–4, 5–9, 10–14, and 15–19 years) as the confounding variable. P values < 0.05 were considered statistically significant.

RESULTS

Characteristics of the examined populations. Masaika had 950 inhabitants one year of age and older (Table 1), and 47% of them were less than 20 years old. The part of Kingwede selected for the study had 1,013 inhabitants one year of age and older (Table 1), and 57% of these were less than 20 years old. The male to female ratio was significantly lower in Kingwede than in Masaika mainly because many young adult males (especially in the 20–29-year-old age group) had left Kingwede in search of employment elsewhere. Masaika had 285 inhabited houses (average = 3.3 individuals per house, range = 1–14), and the selected part of Kingwede had 180 (average = 5.6 individuals per house, range = 1–22).

Microfilaremia. In Masaika and Kingwede, 848 (89.2%) and 825 (81.4%) individuals, respectively, had their blood examined for mf. The overall prevalence of microfilaremia was significantly higher in Masaika (24.9%) than in Kingwede (2.7%) (Table 1). The age-stratified prevalence in the two communities is shown in Tables 2 and 3 and Figure 1. In both communities, microfilaremia was rare in young children. Thus, the two youngest mf-positive individuals were three and five years old in Masaika and 14 and 15 years old in Kingwede. The prevalence increased with age in both communities, and among adults ≥ 20 years old the mf prevalences were 35.2% in Masaika and 5.9% in Kingwede. In both communities the mf prevalence was higher among males than among females. This was particularly pronounced for those ≥ 20 years old (Masaika: 45.2% versus 25.5%; $P < 0.001$, by chi-square test; Kingwede: 10.1% versus 3.4%; $P = 0.015$, by chi-square test).

The mf intensities among mf-positive individuals ranged from 10 to 19,160 mf/ml in Masaika and from 10 to 2,520 mf/ml in Kingwede. The overall mf GMI was significantly higher in Masaika than in Kingwede, both when calculated for all examined individuals (3.6 versus 0.1 mf/ml) and for mf-positive individuals only (458 versus 174 mf/ml, respectively) (Table 1). In Masaika, the first of these indices increased with age to reach a maximum in the 50–59-year-old age group (Figure 2A), whereas there was no clear relationship to age when the mf GMI was expressed for mf-positive individuals only (Figure 2B). Too few mf-positive individuals were present in Kingwede for analysis of the effect of age on mf GMIs.

Antigenemia. Circulating filarial antigenemia was determined in 837 (88.1%) and 770 (76.0%) individuals from Masaika and Kingwede, respectively. The overall CFA prevalence was significantly higher in Masaika (52.2%) than in Kingwede (16.5%) (Table 1). The youngest CFA-positive individuals in Masaika and Kingwede were two and one years old, respectively. The prevalence of CFA positivity generally increased from the younger to the older age groups (Tables 2 and 3 and Figure 1). The CFA prevalence in adults (≥ 20 years old) was slightly, but not significantly, higher among males than among females in Masaika (68.8% versus 62.1%), whereas it was significantly higher among males than among females in Kingwede (38.8% versus 20.9%; $P = 0.02$, by chi-square test).

The majority of those who were mf positive were also CFA positive (97.6% for Masaika and 95.5% for Kingwede), but many were CFA positive without being mf positive. The proportion of CFA-positive individuals who were negative for mf was significantly higher in Kingwede than in Masaika (83.3% versus 52.8%; $P < 0.001$, by chi-square test), and it decreased

TABLE 2

Population size and *Wuchereria bancrofti* microfilaremia and antigenemia in relation to age group in the high endemicity community (Masaika)*

		Microfilaremia				Antigenemia			
Age group (years)	Total population	Number examined	Number mf positive (%)	GMI among all, mf/ml	GMI among mf positives, mf/ml	Number examined	Number CFA positive (%)	GMI among all, units	GMI among CFA positives, units
1–4	99	84	1 (1.2)	–	–	73	6 (8.2)	9	1,651
5–9	111	103	8 (7.8)	0.7	923	102	30 (29.4)	48	4,715
10–14	139	129	23 (17.8)	1.9	356	129	60 (46.5)	105	2,553
15–19	95	80	20 (25.0)	4.0	649	80	45 (56.3)	397	8,691
20–29	162	142	47 (33.1)	6.2	388	143	86 (60.1)	477	8,055
30–39	138	122	34 (27.9)	4.8	566	123	77 (62.6)	544	7,356
40–49	83	77	29 (37.7)	6.8	235	76	54 (71.1)	788	5,399
50–59	45	41	19 (46.3)	21.0	790	41	32 (78.0)	2,235	10,757
≥ 60	78	70	30 (42.9)	14.1	564	70	47 (67.1)	1,041	11,885
Total	950	848	211 (24.9)	3.6	458	837	437 (52.2)	246	6,523

* mf = microfilaria; GMI = geometric mean intensity (only given if > 3 mf-positive individuals in group); CFA = circulating filarial antigen.

with age in both communities (Figure 3). As a result, the CFA prevalence was 2.1 and 6.1 times higher than the mf prevalence in Masaika and Kingwede, respectively, and this difference was more pronounced among young individuals (2.8 versus 17.3 times in the 1–19-year-old age group) than among adults (1.9 versus 4.3 times in the ≥ 20-year-old age group).

The overall CFA GMI was significantly higher in Masaika than in Kingwede (Table 1), both when calculated for all examined individuals (246 versus 15.6 units) and for CFA-positive individuals only (6,523 versus 673 units). In Masaika, both of these indices increased with age, but whereas the first reached a maximum in the 50–59-year-old age group (Figure 2C), the second continued to increase up to the oldest age group (Figure 2D). No clear relationship of CFA GMI to age was observed in Kingwede, either when calculated for all individuals or for CFA-positive individuals only.

Chronic filarial disease. The age prevalence patterns of chronic filarial disease in the two communities are shown in Tables 4 and 5. Hydrocele was the most common chronic manifestation. The youngest males with hydrocele in Masaika and Kingwede were 20 and 31 years old, respectively. Among adult males (≥ 20 years old) the prevalence of hydrocele was significantly higher in Masaika (25.3%) than in Kingwede (5.3%) (Table 1).

In both communities, elephantiasis was a less common manifestation and was confined to the legs. The youngest individuals with leg elephantiasis were 11 and 30 years old, respectively, in Masaika and Kingwede. Among individuals ≥ 20 years old, the prevalence of leg elephantiasis was significantly higher in Masaika (overall = 4.0%, 2.8% for males and 5.1% for females) than in Kingwede (overall = 0.9%, one male and two females) (Table 1).

The relationship between chronic manifestations and infection status was analyzed by odds ratios among individuals ≥ 20 years old for both mf and CFA (Figure 4). In Masaika, individuals with hydrocele had the same odds of being mf positive and negative, and of being CFA positive and negative. Individuals with elephantiasis in this community had the same odds of being mf positive or negative, but lower odds of being CFA positive. When hydrocele and elephantiasis patients were combined to a chronic disease group, this group had the same odds of being mf positive or negative, and of being CFA positive or negative. In Kingwede, this analysis was only possible by combining hydrocele and elephantiasis patients into a group with chronic disease. This chronic disease group had higher odds of being mf positive than mf negative, but equal odds of being CFA positive or negative.

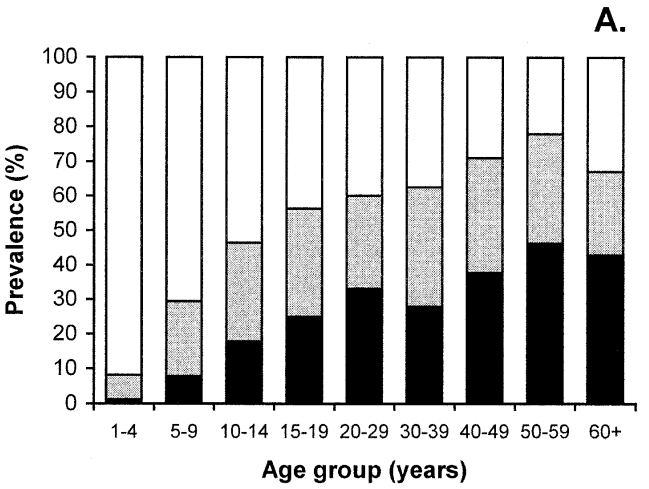
History of ADL attacks. Significantly more individuals reported having experienced one or more ADL attack during the one-year period preceding the survey in Masaika (12.2%) than in Kingwede (7.1%) (Table 1). In both communities, the prevalence of reported ADL attacks was higher among individuals ≥ 20 years old than in younger individuals (Tables 4 and 5), but this difference was only significant for Masaika (15.1% versus 8.8% in Masaika; $P = 0.005$, by chi-square test; 7.6% versus 6.4% in Kingwede). Among those reporting at-

TABLE 3

Population size and *Wuchereria bancrofti* microfilaremia and antigenemia in relation to age group in the low endemicity community (Kingwede)*

		Microfilaremia				Antigenemia			
Age group (years)	Total population	Number examined	Number mf positive (%)	GMI among all, mf/ml	GMI among mf positives, mf/ml	Number examined	Number CFA positive (%)	GMI among all, units	GMI among CFA positives, units
1–4	163	141	0 (0.0)	–	–	108	4 (3.7)	8	403
5–9	154	139	0 (0.0)	–	–	129	9 (7.0)	9	218
10–14	157	145	1 (0.7)	–	–	139	19 (13.7)	13	595
15–19	102	78	2 (2.6)	–	–	77	15 (19.5)	18	706
20–29	179	125	6 (4.8)	0.3	137	122	29 (23.8)	24	800
30–39	104	86	8 (9.3)	0.6	172	86	21 (24.4)	24	873
40–49	58	37	1 (2.7)	–	–	35	8 (22.9)	20	477
50–59	52	41	1 (2.4)	–	–	40	8 (20.0)	18	750
≥ 60	44	33	3 (9.1)	–	–	34	14 (41.2)	56	978
Total	1,013	825	22 (2.7)	0.1	174	770	127 (16.5)	16	673

* mf = microfilaria; GMI = geometric mean intensity (only given if > 3 mf-positive individuals in group); CFA = circulating filarial antigen.



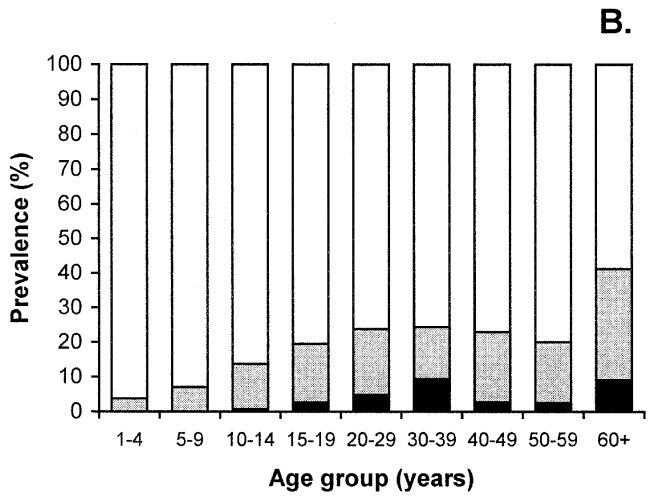


FIGURE 1. Age-specific prevalence of individuals who were microfilaria (mf) and circulating filarial antigen (CFA) positive **(black part of bar),** mf negative and CFA positive **(gray part of bar),** and mf and CFA negative **(white part of bar)** in Masaika **(A)** and Kingwede **(B).**

tacks, the mean numbers were 2.0 (range = 1–5) in Masaika and 2.7 (range = 1–12) in Kingwede.

There was no statistically significant difference in prevalence of reported history of ADL attacks between mf-positive and mf-negative individuals (12.7% versus 16.5% in Masaika; 15.8% versus 7.0% in Kingwede) or between CFA-positive and CFA-negative individuals (13.4% versus 17.8% in Masaika; 7.5% versus 6.8% in Kingwede; $P > 0.05$, by chi-square test for all tests) in either community. In Masaika, the prevalence of individuals reporting ADL was much higher among individuals with elephantiasis than in those without it (72.2 versus 12.7%; $P < 0.001$, by chi-square test), whereas no difference was seen in relation to hydrocele status (16.4 versus 18.8%). In Kingwede, there were too few individuals with hydrocele or elephantiasis for statistical analysis of their ADL status.

Relationships between mf and CFA status in parents and their children. Among mf- and CFA-examined individuals < 20 years old, the mothers and fathers were identified and

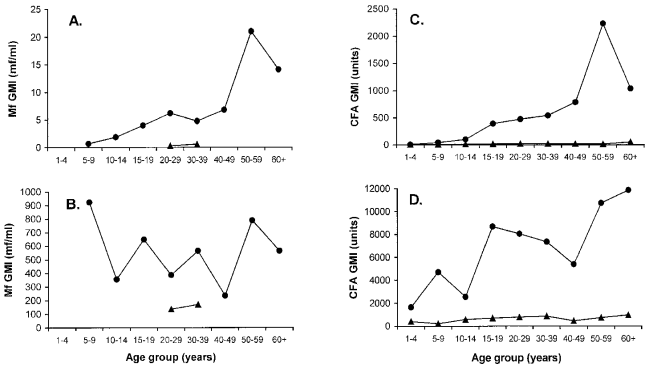


FIGURE 2. Age-specific microfilaria (mf) geometric mean intensity (GMI) among all examined individuals **(A)** and among mf positive individuals only **(B),** and age-specific circulating filarial antigen (CFA) GMI among all examined individuals **(C)** and among CFA-positive individuals only **(D)** in Masaika (●) and Kingwede (▲). Mf intensities are only shown if the group has more than three mf-positive individuals.

examined for mf and CFA for 286 (74.7%) and 183 (47.8%), respectively, in Masaika and in 312 (68.9%) and 149 (32.9%), respectively, in Kingwede. The relationship between mf and CFA status of the children and that of their mothers and fathers is shown in Table 6. Generally, prevalences of mf and CFA positivity were higher in children of both mothers and fathers who were mf and/or CFA positive, than in mothers and fathers who were mf and/or CFA negative. However, logistic regression analysis showed no statistically significant relationships between infection status of fathers and mothers and that of their children, either for mf or CFA ($P > 0.05$, for all tests).

Overall filarial-specific antibody responses. In Masaika and Kingwede, 828 (87.2%) and 766 (75.6%) individuals, respectively, were examined for filarial-specific IgG1, IgG2, IgG3, IgG4, and IgE antibodies. The overall prevalences of positivity and geometric mean intensities (calculated for all examined individuals) in the two communities are shown in Figure 5. For IgG1, IgG2, IgG4, and IgE, both parameters were

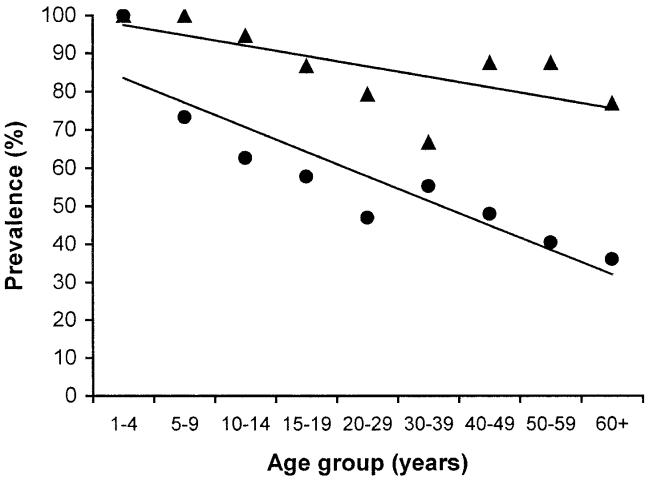


FIGURE 3. Age-specific prevalence of microfilaria-negative individuals among those being positive for circulating filarial antigen in Masaika (●) and Kingwede (▲). This is based on individuals examined for both indices. Linear regression lines are shown.

TABLE 4
Clinical manifestations related to *Wuchereria bancrofti* infection in the high endemicity community (Masaika)*

Age group (years)	Elephantiasis		Hydrocele†		History of ADL	
	Number examined	Number positive (%)	Number examined	Number positive (%)	Number questioned	Number of positive responses (%)
1–4	87	0 (0.0)	40	0 (0.0)	87	0 (0.0)
5–9	104	0 (0.0)	68	0 (0.0)	104	10 (10.0)
10–14	127	1 (0.8)	72	0 (0.0)	127	13 (10.2)
15–19	80	0 (0.0)	38	0 (0.0)	79	12 (15.2)
20–29	141	1 (0.7)	67	10 (14.9)	140	19 (13.6)
30–39	124	7 (5.6)	59	10 (16.9)	123	26 (21.1)
40–49	75	4 (5.3)	33	8 (24.2)	75	11 (14.7)
50–59	41	1 (2.4)	22	8 (36.4)	41	5 (12.2)
≥ 60	71	5 (7.0)	36	19 (52.8)	71	7 (9.9)
Total	850	19 (2.2)	435	55 (12.6)	847	103 (12.2)

* ADL = adenolymphangitis.
† ≥ stage II (males only).

significantly higher in Masaika than in Kingwede ($P < 0.001$, by chi-square test and *t*-test for all tests). Surprisingly, the opposite pattern was found for IgG3, in which both prevalence and intensity were significantly higher in Kingwede than in Masaika ($P < 0.001$, by chi-square test and *t*-test for both tests). The overall geometric mean IgG4: IgE ratio was significantly higher for Masaika than for Kingwede (2.35 and 0.48, respectively; $P < 0.001$, by *t*-test).

DISCUSSION

The overall patterns of Bancroftian filariasis infection and disease in the two study communities resembled those reported earlier from this[3–8] and other endemic regions in Africa.[25,26] Thus, infection (microfilaremia and antigenemia) and chronic disease (hydrocele and elephantiasis) was rare in young individuals, but appeared with increasing prevalence and intensity in older individuals. However, marked differences were observed between the communities, both in age of appearance and in overall levels of infection and chronic disease. Coastal East Africa is populated by a large number of relatively small and closely related Bantu tribes, and the tribal composition in the study communities differed to some extent. The tribes in question, however, are by no means isolated from each other, their cultural differences are minor, intermarriage frequently occurs, and it appears unlikely that genetic or behavioral differences would affect their exposure or susceptibility to Bancroftian filariasis, and hence, the epidemiologic patterns reported here.

Infection was diagnosed by detection of mf in night blood and by analyzing serum for *W. bancrofti*-specific CFA.[20] As seen in other endemic communities,[27–29] overall and age-specific prevalences of CFA were considerably higher than those of mf, implying that many more individuals were actually infected than those in whom mf were detected. This was more pronounced in the low than in the high endemicity community, and it was more pronounced in children than in adults (especially in the low endemicity community). Different levels of transmission in the two communities may be responsible for this effect. Thus, the sensitivity of a diagnostic test for mf detection is dependent on the intensity of infection, and therefore will generally be higher in a high than in a low endemicity community. Low transmission intensity is furthermore likely to give a higher probability for non-fecund single sex infections and infections with male and female worms in different localities of the human body than high transmission intensity. These results also mean that the predictive value of the CFA test compared to the mf detection test will be higher in a low than in a high transmission area. The magnitude by which surveys based on mf detection underestimate the actual prevalence of infection, and its apparent dependence on endemicity level and age, have important practical implications when considering the selection of target populations for filariasis control. In particular, this study indicates that children

TABLE 5
Clinical manifestations related to *Wuchereria bancrofti* infection in the low endemicity community (Kingwede)*

Age group (years)	Elephantiasis		Hydrocele†		History of ADL	
	Number examined	Number positive (%)	Number examined	Number positive (%)	Number questioned	Number of positive responses (%)
1–4	150	0 (0.0)	74	0 (0.0)	150	2 (1.3)
5–9	144	0 (0.0)	67	0 (0.0)	144	4 (2.8)
10–14	145	0 (0.0)	70	0 (0.0)	145	18 (12.4)
15–19	81	0 (0.0)	33	0 (0.0)	81	11 (13.6)
20–29	137	0 (0.0)	46	0 (0.0)	137	14 (10.2)
30–39	91	2 (2.2)	37	1 (2.7)	91	5 (5.5)
40–49	38	0 (0.0)	17	2 (11.8)	38	2 (5.3)
50–59	43	0 (0.0)	15	1 (6.6)	43	5 (11.6)
≥ 60	34	1 (2.9)	17	3 (17.6)	34	0 (0.0)
Total	863	3 (0.3)	376	7 (1.9)	863	61 (7.1)

* ADL = adenolymphangitis.
† ≥ stage II (males only).

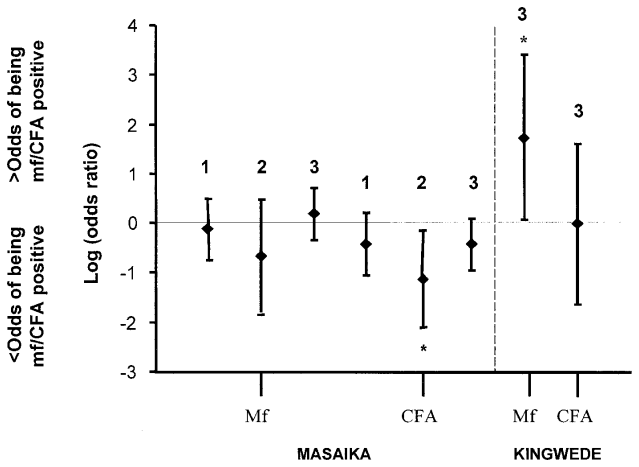


FIGURE 4. Odds ratios (with 95% confidence intervals) of being microfilaria (mf) or circulating filarial antigen (CFA) positive among individuals ≥ 20 years old with or without chronic disease in Masaika and Kingwede. 1 = hydrocele patients; 2 = elephantiasis patients; 3 = chronic disease patients (hydrocele or elephantiasis combined). * = statistically significant.

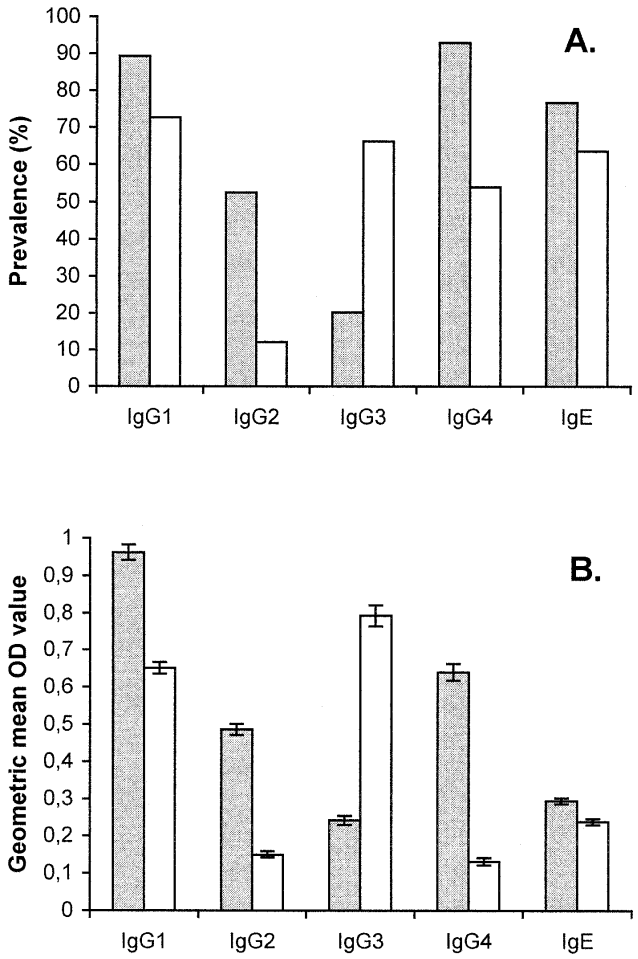


FIGURE 5. Overall prevalence **(A)** and geometric mean intensity **(B)** of filarial-specific IgG1, IgG2, IgG3, IgG4, and IgE in Masaika **(gray bars)** and Kingwede **(white bars).** Vertical lines indicate standard errors.

and low endemicity communities are likely to have much higher prevalence of infection than has hitherto been reflected by the tests for mf.

In both communities, the earliest cases of CFA positivity were seen in the youngest age group of children. In contrast, the earliest cases of mf positivity appeared at a much younger age in the high (three years) than in the low (14 years) endemicity community. From the age of first appearance, prevalences of both CFA and mf positivity increased gradually with age, but reached much higher levels in the high than in the low endemicity community. However, it is noteworthy that the age-prevalence curve appeared more non-linear in the high than in the low endemicity community. Predictions from mathematical models suggest that this pattern could reflect the impact of varying transmission intensities on immunity development.[11] Alternatively, the slight decrease in rate of acquisition of new infections observed in the older age groups, especially in Masaika, may be reflective of decreased exposure to infection in these age groups.

The mean of mf intensities among all examined individuals in the high endemicity community increased with age, as observed previously.[17] This is probably contributable to new infections arising from the continued transmission, which reduce the number of amicrofilaremic individuals thereby increasing mean mf intensity. In contrast, mean mf intensity among those infected remained fairly uniform, or perhaps even decreased slightly with age. A similar lack of a positive relationship between age and mf intensity among microfilaremic individuals has been observed in other endemic populations,[6,7,26] and may be due to some mf or adult worm intensity regulation mechanism, probably immune-mediated,

TABLE 6

Relationship between the *Wuchereria bancrofti* microfilaria (mf) and circulating filarial antigen (CFA) status in parents and their children less than 20 years old

	Masaika			Kingwede		
	Number of children examined	Number of children mf positive (%)	Number of children CFA positive (%)	Number of children examined	Number of children mf positive (%)	Number of children CFA positive (%)
Mf+ mothers	70	11 (15.7)	26 (37.1)	11	1 (9.1)	3 (27.3)
Mf– mothers	216	24 (11.0)	74 (34.3)	301	0 (0.0)	21 (7.0)
Mf+ fathers	95	15 (15.8)	45 (47.4)	16	1 (6.3)	3 (18.8)
Mf– fathers	88	5 (5.7)	23 (26.1)	133	1 (0.8)	15 (11.3)
CFA+ mothers	189	27 (14.3)	73 (38.6)	51	1 (2.0)	3 (5.9)
CFA– mothers	97	8 (8.2)	27 (27.8)	261	0 (0.0)	21 (8.0)
CFA+ fathers	138	17 (12.3)	54 (39.1)	55	1 (1.8)	8 (14.5)
CFA– fathers	45	3 (6.7)	14 (31.1)	94	1 (1.1)	10 (10.6)

within the host. The numbers of microfilaremic individuals in the low endemicity community were too low to allow for a similar analysis. In contrast to the findings for microfilaremia, mean CFA intensities continued to increase with age among the CFA-positive individuals in the high endemicity community. The CFA has been considered to be an expression of adult worm burden.[20] If true, this implies that the adult worm burden among those infected continue to increase with age. The earlier proposed host infection regulation mechanism in Masaika must therefore primarily be directed against mf.

In lymphatic filariasis, chronic disease is thought to result from mechanical damage to the lymphatics by adult worms or their products, immunologic responses to parasite antigen, and/or secondary opportunistic bacterial and/or fungal superinfection of the damaged lymphatic vessels.[14] The relative contributions of these components are not well known, but in theory they might all contribute to the earlier appearance and higher prevalence of hydrocele and elephantiasis observed in the high than in the low endemicity community. Thus, higher levels of transmission may result in higher worm burdens and more intense stimulation of potential harmful host responses, both of which could lead to increased vulnerability to secondary infections. Positive associations between community transmission intensity, microfilarial level, and burden of chronic disease have also been observed in earlier studies.[17,26,30]

The association between chronic disease (hydrocele and elephantiasis) and infection status in adults was also analyzed in this study for both mf and CFA to assess the relationship of this association with community transmission intensity. It has often been assumed, especially in immunologic analyses, that individuals with chronic disease are mostly infection negative. However, this was not confirmed in the present study. Thus, there was no negative relationship between infection and disease status for either hydrocele in Masaika or for combined chronic disease in any of the communities. Although the prevalence of both mf and CFA in Masaika was lower in those with elephantiasis than in those without this, this difference was only significant for CFA. The study is therefore in agreement with a recent meta-analysis that showed no evidence for a general negative association between microfilaremia and chronic disease in lymphatic filariasis.[31]

The history of experience of acute attacks of ADL during the preceding one-year period was investigated through interviews carried out during the clinical examination. The number of cases recorded may to some extent be an overestimate, since other conditions could be mistaken for ADL attacks by the villagers when trying to recall past disease experience. This is probably especially so in the low endemicity community, where the population has less experience with ADL attacks. The overall frequency and age patterns observed conformed well to those of other studies carried out through continued surveillance in communities with similar levels of endemicity.[32–34] Surprisingly, no association was observed between reported history of ADL attacks and mf or CFA status in Masaika or Kingwede. The proportion of individuals reporting ADL attacks in the high endemicity community was significantly higher in those with elephantiasis than in those without, as reported elsewhere,[32–35] whereas no such association was observed between ADL attacks and hydrocele.

A number of previous studies have indicated that maternal but not paternal microfilaremia correlates significantly with increased probability of microfilaremia in their children.[6,12,36] Based on these observations, it has been suggested that intrauterine exposure to filarial antigen increases the risk of infection in the offspring. A model-based comparative study has also indicated that this relationship may vary with the level of endemicity, with neo-natal tolerance being more pronounced in a high than in a low endemicity community.[13] Other studies have indicated that children of both mf-positive mothers and fathers are more likely to be mf positive than children of mf-negative parents.[37,38] Based on these studies, it appears that parental and not only maternal infection is the more important risk for infection in the offspring, probably due to increased household exposure. The present study analyzed the relationship between infection status of parents and that of their children not only for mf, but also for the first time for CFA. As in previous studies, no information on the infection status of mothers during gestation, or of the infection status of the parents in early childhood, was available. However, since the mf status in most individuals living in endemic areas appears to remain constant for many years,[39] it was considered reasonable to use the parents present infection status for the analyses. In both communities, children of infected parents generally had higher mf and CFA prevalences than those of non-infected parents, and this was not related to the mothers only. Although these differences were not statistically significant, they weigh more towards the notion that household exposure may be the important risk factor in determining infection status in children rather than maternal infection.

Specific antibody responses differed considerably between the two communities. Thus, overall prevalences and mean intensities of IgG1, IgG2, IgG4, and IgE were significantly higher in Masaika than in Kingwede, whereas the opposite was seen for IgG3. Endemicity level and intensity of transmission therefore appear to be important factors determining the pattern of antifilarial immune responses in the endemic community, which should be taken into account when examining and comparing immunologic response patterns in different populations. IgG4 has been claimed to be a marker of infection in lymphatic filariasis,[40,41] and both prevalence and intensity of this isotype was higher in Masaika than in Kingwede. However, in both communities its prevalence of positivity was much higher than that of both mf and CFA, as also observed by others.[29,38] Therefore, being IgG4 positive does not necessarily denote active infection but may be related to intensity of exposure to infective larvae.[42] The higher IgG3 prevalence and intensity in the low endemicity community was surprising, and this observation is not in agreement with earlier suggestions that IgG3 is associated with pathology in lymphatic filariasis.[43] The relative level of specific IgG4 to IgE has been suggested in both schistosomiasis[44] and lymphatic filariasis[41] to be related with protective immunity, whereby resistance and permissiveness would be associated with low and high IgG4:IgE ratios, respectively. If this were correct, it would appear that the population in Kingwede is more resistant to infection compared to that of Masaika. The patterns of specific antibodies in relation to infection, disease, age, and gender in the two communities will be analyzed in more detail in subsequent papers.

Overall, these results indicate that differences in community transmission intensity may underlie many of the observed differences in infection, disease, and host response patterns in

the two study communities. Transmission intensity thus appears to be an important determinant of inter-community variation in these patterns in Bancroftian filariasis.

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