

## **Sex differentials in susceptibility to lymphatic filariasis and implications for maternal child immunity**

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### SUMMARY

This paper reviews epidemiological data to see if there are sex differentials in prevalence, density and clinical pathology due to lymphatic filariasis. Of 53 studies from Africa, South East Asia, the Indian Subcontinent and The Americas, 43 showed a lower mean prevalence of infection in females than in males. Prevalence is consistently lower in women of reproductive age and this is statistically significant in 16 of 32 studies classified by age and sex. Density of infection is also lower in the reproductive age but may be higher in children and in older women. Clinical disease is also lower in women and pathology has a later age of onset and rise to peak prevalence than in males. The paper assesses the evidence that lower rates of infection and clinical pathology are due to less exposure of females to infective vectors. It seems unlikely that exposure alone could account for these differences which are observed for both bancroftian and brugian filariasis, irrespective of periodicity. Several investigators have suggested that females have increased resistance to infection and this is supported by serological studies showing high antibody positivity to adult worm antigens in females. The review concludes that the association with the reproductive years suggests a pregnancy-associated mechanism. This has important implications for maternal–fetal interactions and maternal filarial infection may influence the development of immunity in children.

### INTRODUCTION

For most tropical diseases the importance of sex differentials in susceptibility to infection has largely remained unexplored. In general males are more susceptible to parasitic infections than females [1, 2], although in some diseases like malaria, susceptibility increases during pregnancy [3,4]. For helminthic infections opinion has been divided on whether sex differentials are related to lower exposure to infective vectors or to immunological factors. This review has the objective of, firstly, analysing the epidemiological data on differences between males and

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females in microfilarial prevalence, mean microfilarial density and lymphatic pathology; and secondly, assessing the relative contribution of exposure and host immunity to the observed patterns of infection. The analysis indicates that there is compelling evidence that in the reproductive age, women experience a lower burden of infection than men. The consistency of this pattern argues against differences in exposure as the main cause and suggests that host immunity – possibly related to pregnancy-associated mechanisms – may act to reduce microfilarial densities. The paper concludes that sex differentials in susceptibility to lymphatic filariasis have important implications for maternal-fetal interactions.

#### PROBLEMS IN ASSESSING EPIDEMIOLOGICAL DATA ON LYMPHATIC FILARIASIS

Filariasis is a complex disease with major distinctions between *Wuchereria* and *Brugia* infections in the natural host range, microfilarial periodicity and vector susceptibility. Signs and symptoms of filariasis differ from one endemic area to another although there is an overlapping of clinical syndromes which makes comparison possible. The quality of epidemiological studies varies and data are often not reported by both age and sex. Prevalence data are reported more often, and are more likely to be grouped by age and sex than microfilarial densities, which are frequently quoted as mean figures. Parameters for clinical disease are often poorly defined and in mass surveys, clinical examinations may be cursory. Entomological and sociological studies may not be available to support explanations for observed sex differences. Finally, DEC (diethylcarbamazine) has been in widespread use for over 30 years and there are few recent studies where its usage does not complicate the interpretation of the epidemiological data. Pre-DEC studies are available but rely on relatively insensitive blood slide assessment. Microfilarial concentration filtration techniques are more sensitive but have been largely used to evaluate control programmes.

#### DIFFERENCES IN PREVALENCE OF INFECTION

##### *Area differences*

##### *Africa*

Table 1 lists prevalence figures for 15 studies conducted in various regions of Africa. In 13 of these prevalence was higher in males than females, comparing the two sexes at all ages. Table 2 compares prevalence in women of reproductive age with men of a similar age range. Many studies classify younger women of childbearing age (15–20 years) in the 10–19 years group and so, for comparability, the most widely used category is 20–39 years. Only 7 of the 15 studied in Table 1 were classified by both age and sex. In all but one (Comores) [16], prevalence was lower in women.

##### *Indian Subcontinent*

The same comparisons are shown for the Indian Subcontinent. Prevalence in women at all ages was lower for 12 of the 14 areas (Table 3), while in the

Table 1. Prevalence (all ages) of microfilaremia of *W. bancrofti* in Africa by sex

Area (reference)	Males		Females	
	Number examined	Prevalence (%)	Number examined	Prevalence (%)
Gambia [5]	283	35	320	38
Gambia and Casamance [6]:				
Coastal village	89	51	70	46
Inland village	119	31	80	14
Swamp	97	40	97	32
Casamance	130	52	124	49
Liberia [7]	864	19	1104	10
Liberian savanna [8]	546	22	709	12
Liberian savanna [9]	338	23	394	21
Nigeria Igwun basin [10]	402	22	326	16
North Cameroun [11]	362	22	264	10
South Tanzania [12]	2167	26	1562	19
Coastal Tanzania [13]	905	23	1098	20
Kenya, two villages [14]	875	23	919	21
Kenya coast [15]	2759	17	1807	13
Comores, Sabah [16]	668	34	758	36

Table 2. Prevalence (%) of microfilaremia in men and in women of reproductive age in Africa

Age range-years (reference)	Male		Female		P value*
	No.†	Prevalence	No.	Prevalence	
Gambia					
21-40 [5]	70	54.3	118	51.7	< 0.75
Liberia					
20-39 [9]	73	37.0	102	32.3	< 0.75
20-39 [7]	214	31.3	336	14.9	< 0.001
Tanzania					
16-45 [12]	1126	29.0	907	18.5	< 0.001
20-39 [13]	184	39.1	324	26.2	< 0.01
Kenya					
20-39 [14] <sup>a</sup>	68	26.5	87	21.8	< 0.5
20-39 [14] <sup>b</sup>	90	40.0	140	33.6	< 0.5
Comores					
20-39 [16]	117	46.1	171	46.8	—

\*  $\chi^2$  test for significance of difference between males and females.

† Number examined

<sup>a</sup> Mambrui village.

<sup>b</sup> Jaribuni village.

reproductive years, prevalence in women was always lower (Table 4). The study in Ceylon was a large-scale assessment of the anti-filariasis campaign [27].

#### South East Asia

Of 22 investigations in South East Asia, all but 5 showed a lower prevalence in females of all ages (Table 5), while in the reproductive years (Table 6), only one study showed a lower prevalence in men (Tonga) [41].

Table 3. Prevalence (all ages) of microfilaremia on the Indian Subcontinent by sex

Area (reference)	Males		Females	
	Number examined	Prevalence (%)	Number examined	Prevalence (%)
India:				
Madras [17]	4069	16	3333	14
Calcutta [18]	535	16	415	10
Andra Pradesh [19]	5747	20	5553	17
Pondicherry [20]	10675	7	8449	6
Cochin State [21]				
Ernakulam	3901	9	3406	5
Mattancherri	1825	16	1093	12
Bhagalpur town [22]	1008	14	932	11
Bhagalpur rural [23]	820	5	522	5
Assam [24]				
Bokakht*	1122	5	1091	4
Chabua	824	9	915	7
Patna, Bihar [25]	6357	20	3128	16
Formerly East Pakistan [26]:				
Akcha	322	16	280	16
Madarganj	433	17	398	15
Formerly Ceylon [27]†	6838	4	6950	3

\* *B. malayi* the predominant species – in other areas *W. bancrofti* is predominant.

† Study followed widespread control measures.

Table 4. Prevalence (%) of microfilaremia in men and in women of reproductive age in the Indian subcontinent

Age range-years (reference)	Male		Female		P-value*
	No.†	Prevalence	No.	Prevalence	
India:					
21-40 [17]	1461	16.1	1225	13.9	< 0.25
15-44 [18]	308	19.5	171	11.7	< 0.05
15-49 [19]	2919	20.0	2248	15.6	< 0.001
21-40 [20]	4125	7.0	3638	5.8	< 0.05
21-40 [22]	279	7.2	180	5.6	< 0.5
21-40 [23]	289	16.3	202	14.7	< 0.25
21-40 [24] <sup>a</sup>	410	6.8	355	5.9	< 0.75
21-40 [24] <sup>b</sup>	268	13.8	306	8.2	< 0.05
Formerly E. Pakistan:					
20-39 [26] <sup>c</sup>	87	27.6	87	23.0	< 0.5
20-39 [26] <sup>d</sup>	133	21.0	113	13.3	< 0.25
Formerly Ceylon					
15-34 [27]	136145	4.7	146192	4.0	< 0.001

\*  $\chi^2$  test for significance of difference between males and females.

† Number examined.

<sup>a</sup> Bokakhat area.

<sup>b</sup> Chabua area.

<sup>c</sup> Rural.

<sup>d</sup> Semi-urban.

Table 5. Prevalence (all ages) of microfilaremia in South East Asia by sex

Area (reference)	Filtration technique (+/-)	Species	Male		Female	
			Number examined	Prevalence (%)	Number examined	Prevalence (%)
Indonesia :						
Flores [28]	-	<i>B. timori</i>	98	31	103	21
Flores [29]	-	<i>B. timori</i>	104	29	96	19
Sulawesi [30]	-	<i>B. malayi</i>	262	38	223	26
Borneo [31]	+	<i>B. malayi</i>	163	40	126	25
W. Kalimantan [32]	-	<i>B. malayi</i>	192	27	181	24
Celebes [33]	-	<i>B. malayi</i>	1931	29	1727	21
Jakarta [34]	-	<i>W. bancrofti</i>	101	17	95	16
Jakarta [35]	-	<i>W. bancrofti</i>	170	32	186	31
Malaysia :						
Sabah [36]	-	<i>B. malayi</i> (SP)*	3030	10	2434	7
Papua New Guinea :						
Sepik [37]	+	<i>W. bancrofti</i>	41	68	38	68
Cook Islands : [38]	+	<i>W. bancrofti</i> (SP)	165	41	212	27
Tahiti : [39]	-	<i>W. bancrofti</i> (SP)	3390	38	3111	31
French Oceania : [40]	-	<i>W. bancrofti</i> (SP)	1453	35	1127	27
Tonga : [41]	+	<i>W. bancrofti</i> (SP)	150	66	146	71
Samoa : [42]	-	<i>W. bancrofti</i> (SP)	2766	23	2378	15
Philippines :						
Samar [43]	-	<i>W. bancrofti</i>	3565	7	3657	4
Luzon [44]	+	<i>W. bancrofti</i>	124	37	165	17
Japan :						
Katsiyama [45]	-	<i>W. bancrofti</i>	526	6	405	5
Ohno [45]	-	<i>W. bancrofti</i>	463	2	325	2
Korea mainland : [46]	-	<i>B. malayi</i>	278	16	279	10
Vietnam : [47]	-	<i>B. malayi</i> †	5312	3	7249	3
China : [48]	-	<i>W. bancrofti</i>	8224	10	8403	10

\* SP (sub periodic).

† Predominant species.

Table 6. *Prevalence (%) of microfilaremia in men and women of reproductive age in S. East Asia*

Age range-years (reference)	Males		Females		P-value*
	No.†	prevalence	No.	prevalence	
Indonesia :					
20-39 [28]	33	30.3	33	18.2	< 0.25
20-39 [30]	72	58.3	78	30.8	< 0.001
15-50 [31]	103	45.6	70	27.1	< 0.025
21-40 [32]	74	37.8	62	22.6	< 0.10
20-39 [33]	604	39.1	530	23.2	< 0.001
15-50 [35]	103	35.9	116	31.0	< 0.5
Malaysia :					
15-44 [36]	1273	13.5	1097	9.2	< 0.01
Papua New Guinea :					
21-40 [37]	18	77.8	14	57.1	< 0.25
Tahiti :					
20-39 [39]	1068	49.8	1033	35.3	< 0.001
French Oceania :					
21-40 [40]	507	48.3	365	34.8	< 0.001
Tonga :					
21-50 [41]	64	68.0	65	74.0	< 0.75
Samoa :					
20-39 [42]	967	33.6	815	17.7	< 0.001
Philippines :					
20-39 [43]	747	11.1	1000	5.7	< 0.001

\*  $\chi^2$  test for significance of difference between males and females.

† Number examined.

### *The Americas*

In Trinidad, (Table 7), prevalence was lower in females but was the same for both sexes in Brazil.

#### *Prevalence in relation to age*

In most of these studies, prevalence in girls was similar to, or higher, than that in boys, and a number of authors mention that a difference in prevalence is only evident from about age 15 onwards. In the post-reproductive period, prevalence may again be high in women.

### *Males*

The pattern of infection in males is characterized by an increase with age to about 21 years, after which, prevalence plateaus. Fig. 1 shows prevalence figures for males plotted by age from studies in The Gambia [5], French Oceania [40] and Tonga [41]. The shape of the curve is similar in each area, but in Tonga, prevalence was higher because filtration techniques were used which would detect more infections. Piessens [51] has suggested that this plateau effect, which has been observed in bancroftian, malayan and timorian filariasis, reflects that the number of younger, previously amicrofilaremic individuals who develop patent microfilaremia is roughly equal to the number of older subjects who become amicrofilaremic due to a belated development of host resistance. There are some

Table 7. Prevalence (all ages) of microfilaraemia of *W. bancrofti* in The Americas, by sex

Area (reference)	Males		Females	
	Number examined	Prevalence (%)	Number examined	Prevalence (%)
Trinidad [49]	275	19	287	12
Brazil [50]	2116	11	2884	11

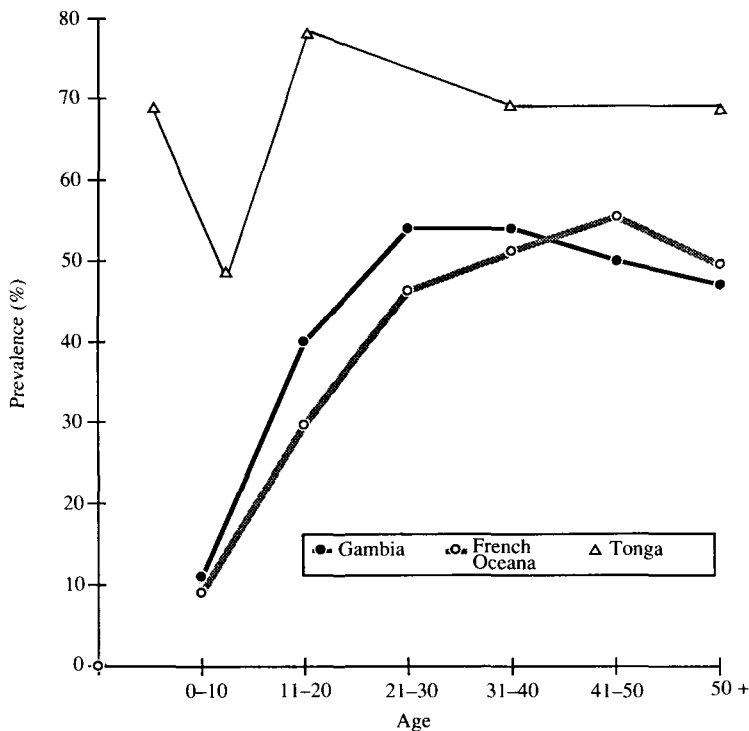


Fig. 1. Prevalence (%) of microfilaraemia in males by age in Gambia, French Oceania and Tonga. [5, 40, 41]

communities in which there is no stabilization with age, and prevalence rates continue to rise. Most notable in this regard is Papua New Guinea [37] where 100% prevalence in males older than 40 years has been reported. Since hyper-reactive malarious splenomegaly is also endemic in this region of Papua New Guinea, this may alter the host immune response to filariasis.

### Females

Among females, prevalence rates often do not show the same pattern as in males: in French Oceania [40] they continue to rise; in Liberia [7] they plateau at a later age than in males and in Papua New Guinea, rise to a plateau of 82% prevalence in women over 40 years. As noted, much of the variation relates to the reproductive years. If women are less exposed, or have lighter infections, the question arises whether lower prevalence partly relates to the insensitivity of

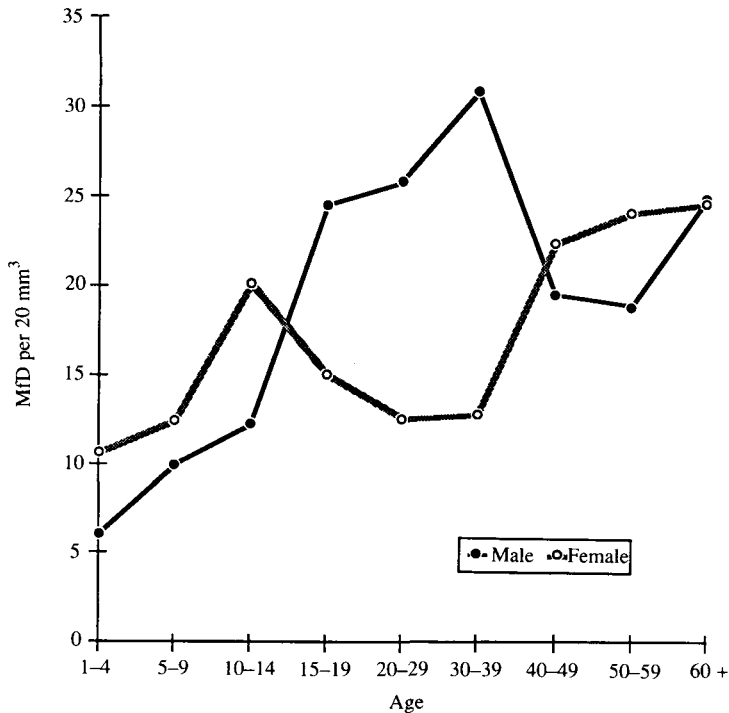


Fig. 2. Geometric mean microfilarial densities by age and sex in Sada, Comores (from Bruhnes, 1975) [16]. Periodic *W. bancrofti*, sample size 1426.

blood slide techniques to detect low density parasitemias. This would seem to be the case in the Tongan study where 68% and 74% respectively of men and women aged 21–50 were positive by filtration (Table 6) but only 33% of males and 26% of females by blood slide. There is evidence from a small number of investigations using both sensitive and insensitive methods that microfilarial densities decrease in women of reproductive age. This suggests that the main difference between the sexes is that women of reproductive age have lighter infections and difficulties in detecting these by blood slide is reflected in their lower prevalence figures.

#### DIFFERENCES IN MICROFILARIAL DENSITIES BY AGE

Figs. 2–5 show a reduction in microfilarial densities in women of reproductive years in the Comores [16] and Papua New Guinea [37] (periodic bancroftian filariasis), in Sabah [36] (sub-periodic *B. malayi*) and French Oceania [40] (sub-periodic bancroftian filariasis). In Sabah (Fig. 4) the range of microfilarial counts is also shown, and these are not as wide in females of reproductive years as in males of the same age. The reduction in densities in the Comores is particularly interesting because, contrary to other studies, prevalence at all ages, and in the reproductive years, was higher in females (Tables 1 and 2). In Papua New Guinea, filtration techniques were used so densities should not be under-represented in women. Three studies [33, 52, 53] used probit analysis to plot median microfilarial densities (MFD-50) by sex and age. These are shown in Table 8 and the same trend



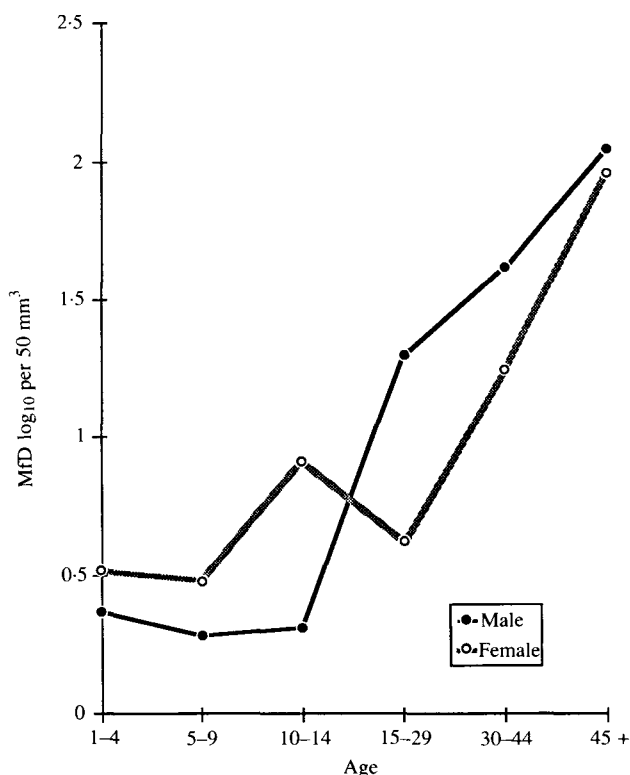


Fig. 3. Mean  $\log_{10}$  (microfilarial count + 1) by age and sex in Papua New Guinea (from Knight et al; 1979) [58]. Periodic Bancroftian filariasis, sample size 233.

to lower microfilarial densities in women aged 20–39 years is evident. Other studies show a similar pattern to the above (Andra Pradesh [19], Ceylon [27], Mattancheri in Cochin [21]), in which microfilarial densities in both sexes are similar for the youngest and oldest age groups, but differ in the middle years.

#### Summary

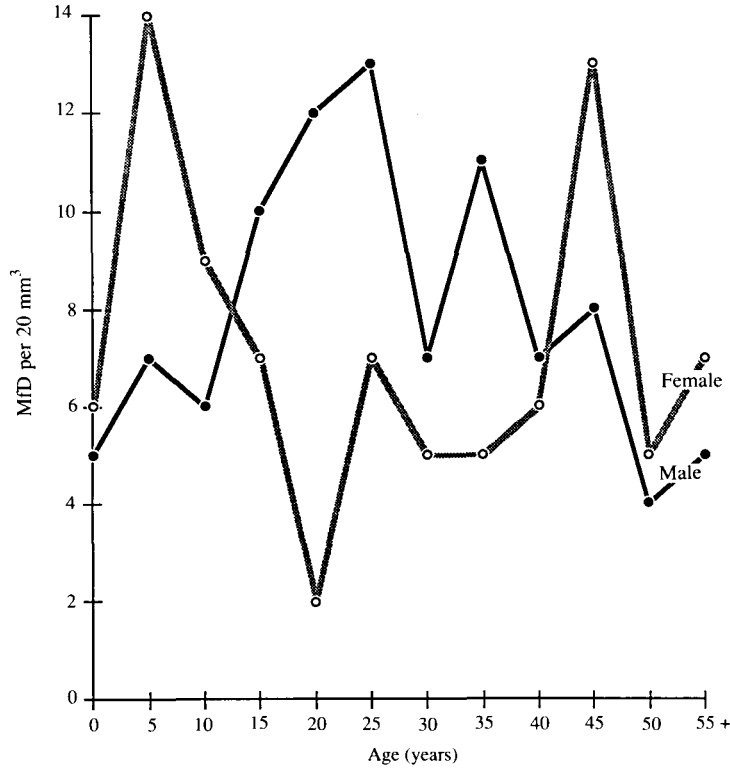
These epidemiological studies suggest that density of infection is lower in women of reproductive age under widely different conditions of exposure. Difficulties in detecting low density infections may in some cases explain the lower prevalence of infection which is observed virtually everywhere.

### FACTORS AFFECTING DENSITY OF INFECTION IN WOMEN

#### *Area specific factors*

##### *South East Asia*

Although exposure must be an important factor influencing the epidemiology of lymphatic filariasis, a number of investigators consider that immunity to infection is enhanced in women. This divergence of opinion is seen clearly in discussion of the data from American Samoa, where sub-periodic *W. bancrofti* is endemic. Murray [42] was in no doubt that women had better immunity than men. He



Range												
Male	1-8	1-208	1-303	1-72	1-185	1-84	1-157	1-195	1-42	1-92	1-21	1-121
Female	1-33	1-172	1-89	1-62	1-75	1-80	1-29	1-36	1-52	1-49	1-131	3-29

Fig. 4. Median and range of microfilarial counts (*B. malayi*, sub-periodic) in Sabah, by age and sex (from Barclay, 1969). [36]

states that clothing was of no significance because males and females dressed alike. Lower rates in women were not due to differences in occupational exposure because mosquitoes caught in the centre of the village had a much higher infection rate than those collected at the edge or further away. He considered that transmission took place in the village and women were more exposed than men. A completely contrary view was taken by McCarthy and Fitzgerald [54] who stated that, while women were covered from neck to knee, men frequently worked bare from the waist up. They considered that transmission took place in the bush tracks and plantations which were frequented most by males, but no entomological data was presented. In the Cooke Islands where *W. bancrofti* is also sub-periodic, transmission was said to take place in and around the villages [55].

#### Indian Subcontinent

A similar disagreement in interpretation of sex differences was apparent in studies from East Pakistan where bancroftian filariasis is transmitted by *Culex*

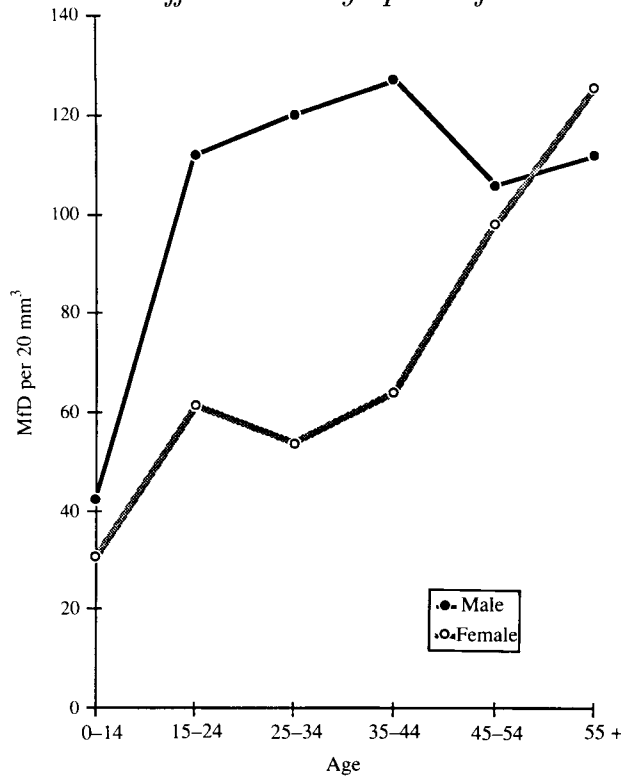


Fig. 5. Mean microfilarial densities by age and sex in French Oceania (from Rosen, 1954) [40]. Non-periodic *W. bancrofti*, sample size 2580.

Table 8. Median microfilarial density (MfD-50) of *B. malayi* in Indonesia and of *W. bancrofti* in two areas of Haiti

Age	Indonesia - Celebes		Haiti - Limbe City		Haiti - Leogane Suburbs	
	Male	Female	Male	Female	Male	Female
0-9	3.7 (55)	3.5 (55)	8.3 (192)	13.6 (185)	18.7 (27)	11.8 (27)
10-19	5.9 (107)	4.7 (92)	12.7 (160)	15.2 (260)	10.7 (27)	13.5 (31)
20-29	8.2 (101)	4.1 (64)	10.2 (158)	4.5 (222)	28.8 (23)	10.8 (33)
30-39	9.1 (87)	4.3 (3.7)				
≥ 40	5.0 (42)*	5.8 (28)*	12.4 (86)†	22.1 (94)†	13.8 (21)	27.0 (32)

Number examined in parenthesis.

\* 40-49 years.

† 40-59 years.

*pipiens fatigans*. Barry and colleagues [56] found no difference in the microfilarial rate in the first 19 years, but a divergence thereafter. They explained this by the cloistering of females at home and more open clothing on males. Yet another study in the same area, and at approximately the same time, noted that in the rural areas (and the sample of Barry and colleagues included 190 rural villages), men, women and children all worked in the fields [26].

*Africa*

Jordan [57] stated that in many parts of Africa, the night-biting *Anopheles gambiae* and *funestus* were the main vectors and it was unlikely that one sex would be more exposed than the other. Ripert and colleagues [11] confirmed that in North Cameroun *A. gambiae* females were caught mostly in homes at the beginning of the rainy season. Fadzean [6] insisted, nonetheless, that Gambian men were more exposed as they sat outside in the evening, while women were protected by the smoke from the fires as they cooked. In the Comores, Brunhes [16] agreed that transmission took place in the huts at night, but said that men were more nocturnally mobile, visiting their polygamous wives in neighbouring villages. On the Kenyan coast, socio-economic differences between Arabs and Bantu farmers were reflected in their infection rates [14]. However, in both socio-economic groups, microfilarial densities were lower in women of reproductive age

*Serological parameters to estimate exposure*

Grove and colleagues [44] considered that immunological parameters may provide the best index of exposure to infection with *W. bancrofti*. In The Philippines they found prevalence, microfilarial densities and antibodies to *B. malayi* adult worm antigen to be lower in females at all ages except less than 10 years. Their study suggests that, in this area, exposure was less in all females older than 10 years. On the contrary, in Papua New Guinea, although prevalence was lower in females aged 15–44 years than in males, antibody seropositivity rates to adult antigens were higher in women (15–29 years: 86.7% *v.* 71.4%; 30–44 years: 85.2% *v.* 63.6%) [58]. The authors considered that higher levels of filaria antibodies indicated a different type of immune response. Similar findings were presented in a study in Haiti [52] and it was suggested that female hormones might influence the expression of parasitemia in bancroftian filariasis.

*Summary*

From the evidence presented, it would seem that exposure alone cannot account for the consistently lower prevalence and density of infection in women from so many different areas and cultural conditions, exposed to both *W. bancrofti* and *B. malayi* infections. Although more serological studies are needed, there is much to support the hypothesis that immunological factors, which may be hormonal and pregnancy-mediated, could explain the lower burden of infection in women of reproductive years.

## DIFFERENCES IN CLINICAL MANIFESTATIONS

At a community level, there seems to be a relationship between a high prevalence of infection and lymphatic disease. At the same time, patients with elephantiasis are likely to be amicrofilaremic and a correlation between severity of lymphatic lesions and host response, either cellular or humoral, to parasite antigens, has been described [59, 69]. If host responses are enhanced during the reproductive years, clinical disease might be expected to increase. However, there

Table 9. Prevalence of clinical manifestations of filariasis in El Kashish village, Egypt by sex and age

Age range (years)	Males		Females	
	No. examined	%	No. examined	%
0-9	17	6	30	13
10-19	38	24	15	20
20-29	14	79	13	15
30-39	13	69	12	42
40-49	6	83	8	50
50+	14	86	11	36
Total	102	46	89	25

seems little evidence that this occurs, and overall, clinical manifestations are lower in females than males.

#### *Clinical disease associated with W. bancrofti infections*

Table 9 shows the age and sex distribution of clinical manifestations of filariasis in a village in Egypt [61]. Pathology was lower in women from age 20 onwards and whereas peak prevalence of clinical disease was reached in women over 60 years, it occurred earlier in men (50-59 years). As in most areas where *W. bancrofti* is endemic, difference in clinical disease was due largely to the frequency of hydrocele in men. Although female genitalia were not examined, it is unlikely that many cases would have been observed since external genital involvement, for unknown reasons, is rare. Nonetheless, examination of females by male field-workers is culturally unacceptable in some areas (eg Pakistan) [26], and makes comparison between the sexes difficult. It is considered that more cases of hydrocele are detected in men than lymphodema in women [62] but hydroceles may form more easily than limb lymphodema because of the smaller increase in lymphatic pressure involved. When elephantiasis rates are reported to be higher in women, the differences are often not statistically significant because of the small number of patients.

In Igwun, Nigeria, 49 females (68.1%) and 61 males (55.5%) showed signs of lymphatic filariasis, but the authors state that their sample was not random [10]. Another unusual feature of this study was that all clinical signs were associated with microfilaremia. In the Sepik region of Papua New Guinea, 32% of males and 26% of females had a history of acute lymphangitis, but 37% (16) females suffered from obstructive disease compared to 25% (14) men [37]. Peak prevalence occurred at age > 40 years in 10 of 11 women and at age 31-40 in 6 of 7 men. In the Cooke Islands, filarial fevers were significantly more frequent in males (45% v. 21.3%;  $P < 0.024$ ) [38].

#### *Clinical disease associated with B. malayi infections*

In *B. malayi* areas, the predominant lesion is elephantiasis, especially of the legs and below the knee. Lower elephantiasis rates have been observed for sub-periodic *B. malayi* in women in Malaysia [36, 63]. For periodic *B. malayi*, in West Kalimantan, Indonesia, 25 males (13%) but only 5 females suffered from

elephantiasis [32]. Similar results were seen in S. Sulawesi and the disease appeared at an earlier age in males [30]. In West Flores, elephantiasis rates were similar but total filarial disease was higher in males (62% *v.* 48%) [29].

#### *Summary*

Clinical disease is generally lower in females and age of onset, as well as peak prevalence, is likely to occur at an older age. This may be the result of lower prevalence and density of infection in the reproductive years, which delays the onset of clinical pathology.

#### IMPLICATIONS FOR MATERNAL-FETAL INTERACTIONS

##### *Increased resistance a gender or a pregnancy-associated mechanism?*

Lower microfilarial loads in the reproductive years suggests a pregnancy-enhanced immunity. Experimental data in jirds have shown non-pregnant females to be less susceptible to infection than male animals [64]. Yet in a later study, older female jirds (retired breeders) were found to be more susceptible than young female jirds [65]. It was suggested that resistance to *B. pahangi* infections derived from the absence of testicular lymphatics as a preferential anatomical site for the development of adult filariae. It was found that significant microfilaremias occurred only in animals harbouring considerable worm burdens in the testes. The reason for increased susceptibility in old age was, however, not clear since a study by Wesley [66] had found that resistance was androgen dependent, and resistance in females attributed to the lack of androgen rather than the presence of estrogen. Declining estrogen levels in old female jirds would be unlikely to increase susceptibility.

The data reviewed above, while substantiating the experimental evidence of increased resistance in females, favour the interpretation that hormonal changes during pregnancy may depress parasitemia. This would explain the higher parasitemias seen in post-reproductive jirds, and does not conflict with the conclusion that androgen increases susceptibility in males.

##### *Effects of maternal microfilaremia on development of childhood immunity*

A mechanism which reduces the burden of infection in the child-bearing years would be beneficial if either:

- (a) morbidity from filarial infection increased during pregnancy or
- (b) host immunity of the mother during pregnancy influenced the development of immunity in her offspring.

Table 10 summarizes some results of animal experimental and clinical studies of prenatal exposure to filarial antigens, and one experimental study of filarial infection during pregnancy and lactation [67–75]. Experimental data suggest that immune response in the offspring is mediated by the presence of infection in the mother, and that filarial infection is more severe during pregnancy and lactation in animals recently infected. Acute infections in human filariasis would be rare in women living for many years in endemic areas, although acute infection may occur in migrants, whose immune response is known to differ from residents of endemic areas [76]. Two studies [41, 77] indicate that some children have higher

Table 10. Summary of experimental and clinical studies on maternal–fetal interactions

Author (Model/Sample)	Results
	Experimental studies
Chatterjee et al. [67] (cotton rats)	Infection in pregnancy and lactation associated with higher microfilarial densities, extended patency period, higher recovery rate of adult worms
Schrater et al. [68]. (gerbils)	Gender associated (female) resistance to infection eliminated when mother was microfilaremic during pregnancy.
Haque and Capron [69] (rats)	Transplacental transfer of <i>Dipetalonema</i> microfilariae resulting in impaired spleen cell response to T cell mitogens and filarial antigens. Progeny developed heavy microfilarial loads.
Klei et al. [70] (jirds)	Progeny of microfilaremic mothers developed microfilaremia and had smaller lymphatic inflammatory lesions.
	Clinical studies
Dutta et al. [71] (hospital)	Filaria-specific maternal antibodies crossed placenta and persisted to six months
Dissanayke et al. [72] Weil et al. [73] Argarwal et al. [74] (hospital)	Antifilarial antibodies of isotypes which do not cross placenta (IgM and IgE) found in cord sera.
Rao et al. [75] (hospital)	Microfilariae occasionally observed in cord blood.

than average microfilarial densities but it is not known whether this is due to host factors or exposure. Ottesen and colleagues [78] found that significant clustering of patients with filariasis was most compatible with genetic transmission of disease susceptibility. The alternative hypothesis, that susceptibility was environmentally determined, was also compatible, but estimated to be 1.9 times less likely than the genetic hypothesis. Familial predisposition was not associated with HLA antigen specificities. Maternal infection, resulting in a predisposition to infection in offspring, as indicated by the experimental data [70], would be another possibility.

#### CONCLUSIONS

The observation that microfilarial densities are lower in women of reproductive age may be important for a clearer understanding of the epidemiology of filarial infection and disease, particularly as it relates to pregnancy and to the development of immunity and predisposition to infection in children born to women living in endemic areas. The mechanisms which result in greater resistance to infection are not understood, but hormonal factors associated with pregnancy may restrict the fertility of adult worms or render the host more refractory to reinfection by the parasite. It would seem important to address the question of

how increased resistance can be achieved, seemingly without an increase in lymphatic pathology. One of the major problems facing vaccine development in filariasis is how to stimulate an immune response which alters the balance between host and parasite without producing deleterious responses in terms of pathology. An investigation of immune changes in pregnancy may give some insight into this subtle interaction.

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