Lymphatic filariasis: an infection of childhood

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Summary   Lymphatic filariasis (LF), already recognized as a widespread, seriously handicapping disease of adults, was generally thought to occur only sporadically in children. New, highly sensitive diagnostic tests (antigen detection, ultrasound examination) now reveal, however, that LF is first acquired in childhood, often with as many as one-third of children infected before age 5. Initial damage to the lymphatic system by the parasites generally remains subclinical for years or gives rise only to non-specific presentations of adenitis/adenopathy; however, especially after puberty the characteristic clinical features of the adult disease syndromes (lymphoedema, hydrocoele) manifest themselves. Recognizing that LF disease starts its development in childhood has immediate practical implications both for management and prevention of the disease in individual patients and for the broader public health efforts to overcome all childhood illnesses. For the new World Health Organization (WHO)-supported, public-/private-sector collaboration (Global Alliance) to eliminate LF through once-yearly drug treatment, this recognition means that children will be not only the principal beneficiaries of LF elimination but also a population particularly important to target in order for the programme to achieve its twin goals of interrupting transmission and preventing disease.

keywords children, lymphoedema, hydrocoele, treatment, lymphangiectasia, epidemiology, antigenaemia, microfilaraemia, filariasis

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Introduction

Numerous community-based epidemiologic studies and individual case reports attest both to the existence of lymphatic filariasis (LF) infection in children and to the occurrence of clinically evident disease (e.g. lymphoedema/elephantiasis and hydrocoele). From these reports we have recognized that LF can be a disease of children as well as adults, but the true extent and nature of childhood LF has remained very much under-appreciated and incompletely documented.

This under-appreciation can be attributed both to the natural history of the disease itself and to the limitations of previously available diagnostic methods. In the past, most published surveys based their diagnosis of infection on detecting microfilaraemia (MF). It is now clear, however, that this diagnostic approach is not sensitive enough to identify many infections (Weil *et al.* 1997), especially those of low density, as are often found in very young children, and those where adult worms are present but produce no microfilariae. Furthermore, as the subclinical manifesta-

tions of early stage infection are difficult to recognize, and because the more pathognomonic clinical manifestations such as lymphoedema or hydrocoele tend to be associated with long-term infection and thus are relatively infrequent in children, many investigators previously chose to exclude children below the age of 5 in their prevalence surveys, and some even excluded children less than 10 years of age. These factors have led to under-representation of children in epidemiologic studies, underestimates of their infection rate, and to inappropriate paucity of documentation of the importance of LF in children.

Principally, it has been the development of improved diagnostic techniques that has led to our new appreciation of the extent and importance of LF infection and disease in children. The availability of filaria-specific antigen assays providing more sensitive diagnosis, especially in early or low-density infection, and the use of ultrasound and other methods to detect filariasis-specific subclinical pathology have permitted recent studies (Jungmann & Figueredo-Silva 1989; More & Copeman 1990; Amaral *et al.* 1994; Figueredo-Silva *et al.* 1994; Lammie *et al.* 1994; Weil *et al.*

1996, 1997; Nicolas 1997; Faris *et al.* 1998; Dreyer *et al.* 1999a, 2000) to challenge the earlier assumption that LF in children is not a significant public health problem. Indeed, this newly available information now demands a full, critical re-evaluation of the nature and extent of LF in children, in order both to improve our approach to the management of this childhood infection and, equally, to identify the full range of benefits that can be attained by the new programmes underway to eliminate LF as a public health problem globally.

The purpose of this review is to bring together in a comprehensive fashion much of the information already available on LF in children and to focus attention on those critical uncertainties that still need to be resolved.

Materials and methods

Search strategy and sources of information

A Medline-based literature search covering the years 1966–2000 (September) was carried out by exploding the identifier 'filariasis' with the terms 'child', 'children', 'paediatric' and 'adolescent'; retrieved articles were supplemented by bibliographic references from these articles and by World Health Organization (WHO)-published reports and documents. Of all the publications assessed, 83 were selected for inclusion in this review (Table 1, nos. 2–6, 12–86 and 131), because they met the following criteria: they were published either in peer-reviewed journals (nos. 2–6, 12, 13, 15–86, 131 in Table 1) or in official government documents (Table 1, no. 14); they described age-delineated populations endemic for either *Wuchereria bancrofti* or *Brugia malayi* infection which had not been subjected to anti-filarial measures during at least the previous 5 years; and they included a complete description of the relevant diagnostic methods used.

In addition (1) *for the analysis of prevalence or incidence*, studies contained sufficient information to derive standardized age-stratified MF rates; (2) *for comparing MF and antigenaemia prevalence rates*, the same patients were used to determine both parameters; (3) *for analysing gender as a risk factor for infection*, studies provided information on the number or percentage of infected males and females in the respective age groups and in the total population; (4) *for reviewing childhood disease manifestations*, studies contained descriptions of investigator-observed adenopathy, lymphoedema or hydrocoele (graded according to standard scales (Kumar-aswami 2000) and described clinical or subclinical lesions diagnosed as LF; (5) *for analysing congenital predisposition to LF*, studies contained parental and child MF or

antigenaemia status; (6) *for reviewing the immunological aspects of LF infection*, studies contained information on filaria-specific antibody or lymphocyte responses and related them to MF, antigenaemia or clinical status of infection.

From all publications meeting the above criteria, the information presented was accepted as published; there was no independent assessment of quality and no direct contact with authors to try to improve data sets deemed inadequate for inclusion in the review. The goal of the review was to be comprehensive in terms of geographical, parasitological and clinical representation, not necessarily exhaustive in publications cited.

Organization of study findings

For some analyses, studies were grouped according to the endemicity level of microfilaraemia among the adults of a population (low endemicity populations considered for this review as < 10% MF prevalence; intermediate, 10–30%; and high, > 30%).

For other analyses, studies were categorized according to MF detection method used, with high sensitivity assays defined as those evaluating ≥ 100 μl of blood (either venous or capillary) for the presence of microfilariae, and low sensitivity assays evaluating ≤ 60 μl of capillary blood. Where studies used more than one MF detection method to determine infection rates, the method which produced the highest MF rate was selected to represent the study.

Study populations were divided into 5-year age groups (< 5, 5–9, 10–14 and 15–19 years of age) or 10-year age groups (< 10 and 10–19 years of age); adults were defined for this review as ≥ 20 years old. For studies reporting not precisely these age groupings, closest approximations were used.

Antigenaemia detection techniques (ELISA detection with AD12, Og4C3 or PC-Gib13) were considered to be essentially equivalent in sensitivity (Forsyth *et al.* 1985; Weil *et al.* 1987, 1997; More & Copeman 1990; Kumaraswami 2000).

Study exclusion criteria

Studies which met the above criteria but which described populations that had received therapeutic or vector control interventions during the previous 5 years were not included in this review. Publications presenting information as secondary sources and articles reporting 'infection rates' determined only through use of anti-filarial antibody assays were also excluded. Most publications only suggestive of an LF aetiology for the reported clinical sign or symptom were excluded from

Table 1 Studies included: indicating diagnostic methods, numbers of persons in each study and use of information for this review

Study site/date [ref.]	Parasite	Diagnostic method	Population (no. studied)	Children (no. studied)	Prevalence	Gender	Blood volume	Ag/MF	Incidence	Disease manifestation	MF density	CMI	Antibodies	Parent's MF status	Prenatal exposure
No. studies analysed			83	83	39	14	38	6	1	21	9	5	13	8	9
Brazil															
Jungmann & Figueredo-Silva 1989 [2]	Wb	Hst	75	41											
Campello et al. 1993 [12]	Wb	MF, Fil (3 ml)	20*	20						×					×
Amaral et al. 1994 [3]	Wb	US	15	9						×					
Figueredo-Silva et al. 1994 [4]	Wb	MF, Fil (5 ml), Hst	2							×					
Maciel et al. 1996 [13]	Wb	MF, Slide (60 µl)	10 581	4327	×		×								
Dreyer et al. 1999a [5]	Wb	MF, Fil (1–10 ml), US	273	78						×					
China															
Institute against Parasitic Diseases 1998 [14]	Wb	MF, Slide (60 µl)	145 612	68 815	×		×								
Institute against Parasitic Diseases 1998 [14]	Wb	MF, Slide (60 µl)	45 518	24 839	×		×								
Institute against Parasitic Diseases 1998 [14]	Wb	MF, Slide (60 µl)	28 816	15 975	×		×								
Congo, DR															
Peel & Van Oye 1950 [15]	Wb	MF	91*	91											×
Cook Islands															
McCarthy 1959 [16]	Wb	MF, Slide (20 µl)	3816	2083	×	×	×								
Ottesen et al. 1977 [20]	Wb	MF, Fil (1 ml)	39	10								×			
Ottesen et al. 1981 [17]	Wb	MF, Fil (1 ml)	225	88										×	
Ottesen et al. 1982 [18]	Wb	Ab	68	18									×		
Steel et al. 1994 [19]	Wb	MF, Fil (1 ml), Ab	21	21								×	×		
Steel et al. 2001 [21]	Wb	MF, Fil (1 ml), Og4C3	360	176	×	×	×	×			×				
Costa Rica															
Paniagua et al. 1983 [22]	Wb	MF, Fil (1 ml)	2879	1663	×	×	×								
Dominican Republic															
Bloomfield et al. 1978 [23]	Wb	MF, Slide	1	1											
Egypt															
Ramzy et al. 1994 [24]	Wb	MF, Slide (30 µl), AD12	695	695†				×		×					
Faris et al. 1998 [6]	Wb	US	61	12‡											
Weil et al. 1999 [25]	Wb	MF, Fil (1 ml), AD12	1853	719§						×				×	

Table I (*Continued*)

Study site/date [ref.]	Parasite	Diagnostic method	Population (no. studied)	Children (no. studied)	Prevalence	Gender	Blood volume	Ag/MF	Incidence	Disease manifestation	MF density	CMI	Antibodies	Parent's MF status	Prenatal exposure
Fiji															
Burnett & Mataika 1961 [26]	Wb	MF, Slide (20 µl)	1200	640	×		×								
French Polynesia															
Beye et al. 1952 [27]	Wb	MF, Slide (20 µl)	376	175	×		×			×					
Chanteau et al. 1995 [28]	Wb	MF, Fil (1 ml), Ab, Og4C3	1027	128†				×					×		
Gambia															
McGregor et al. 1952 [29]	Wb	MF, Slide (20 µl)	603	328	×	×	×								
Ghana															
Dunyo et al. 1996 [30]	Wb	MF, Cbr (50 µl)	3050	4						×					
Gyapong et al. 1998 [31]	Wb	MF, Slide (20 µl)	1808	703	×		×				×				
Dzodzomenyo et al. 1999 [32]	Wb	MF, Cbr (100 µl)	296	157	×		×			×	×				
Guyana															
Kenny & Hewitt 1949 [33]	Wb	MF, Slide (20 µl)	57	10¶			×			×					
Haiti															
Raccurt et al. 1984 [34]	Wb	MF, Slide (20 µl)	1450	797	×	×	×								
Hitch et al. 1989 [35]	Wb	MF, Slide (20 µl), Ab	121	121									×		
Hitch et al. 1991a [36]	Wb	MF, Slide (20 µl), Ab	129	129									×		
Hitch et al. 1991b [37]	Wb	MF, Slide (20 µl)	176$	176								×			
Lammie et al. 1991 [38]	Wb	MF, Slide (20 µl)	643	325$										×	
Eberhard et al. 1993 [39]	Wb	MF, Fil (1 ml)	77*	77											
Hightower et al. 1993 [40]	Wb	MF, Slide (20 µl)	1034	444$					×					×	×
Lammie et al. 1994 [41]	Wb	MF, Slide (20 µl), Og4C3	419	181	×		×	×			×				
Hitch et al. 1997 [42]	Wb	MF, Fil , Ab	128	64**											
Lammie et al. 1998 [43]	Wb	MF, Slide (20 µl), Og4C3, Ab	39	39								×	×	×	×
India															
Sinha et al. 1959 [44]	Wb	MF, Slide (20 µl)	854	434	×		×								

Table I (*Continued*)

Study site/date [ref.]	Parasite	Diagnostic method	Population (no. studied)	Children (no. studied)	Prevalence	Gender	Blood volume	Ag/MF Incidence	Disease manifestation	MF density	CMI	Antibodies	Parent's MF status	Prenatal exposure
Gubler & Bhattacharya 1974 [45]	Wb	MF, Slide (20 µl)	585	234	×	×	×							
Weil et al. 1983 [46]	Wb	MF, Fil (1 ml), Ab	57††	57**										×
Rao et al. 1984 [47]	Wb	MF, Slide (20 µl)	248	248**	×									×
Rajagopalan et al. 1989 [48]	Wb	MF, Slide (20 µl)	24 946	11 495	×	×	×							
Sanjeevi & Narayanan 1989 [49]	Bm	Ab	29	29**										×
Panicker et al. 1991 [50]	Wb	MF, Slide (20 µl)	3942	1534	×		×							
Tewari et al. 1995 [51]	Wb	MF, Slide (20 µl)	1051	409	×	×	×							
Chandra & Hati 1996 [52]	Wb	MF, Slide (20 µl)	4512	2171	×		×		×					
Das et al. 1997 [53]	Wb	MF, Slide (60 µl)	4201‡‡	2302									×	
Indonesia														
De Rook 1959 [54]	Wb	MF, Slide (15 µl)	1125	614	×		×		×					
Van Dijk 1961 [55]	Wb	MF, Slide (20 µl)	1206	540	×	×	×		×					
Putrali et al. 1975 [56]	Bm	MF, Slide (20 µl)	4950	1994†	×		×							
Sajidiman et al. 1975 [57]	Bm	MF, Fil (1 µl)	287	126	×		×							
Haarbrink et al. 1995 [58]	Bm	Ab	239	22$$								×		
Sartono et al. 1997 [59]	Wb	MF, Fil	60	34¶¶							×			
Japan														
Sasa 1963 [60]	Wb	MF, Slide (30 µl)	32 396	16 017	×		×							
Sasa & Mitsui 1964 [61]	Wb	MF, Slide (30 µl)	21 483	9833	×	×	×							
Marshall & Yasukawa 1966 [62]	Wb	MF, Slide (30 µl)	9003	4587	×	×	×							
Kenya														
Estambale et al. 1994 [63]	Wb	MF, Cbr (100 µl)	1129	582					×					
Wamae et al. 1998 [64]	Wb	MF, Slide, Fil (20 µl, 1 ml), Ab	328	159¶¶								×		
Liberia														
Zielke & Chlebowsky 1979 [65]	Wb	MF, Slide (40 µl)***	3918	1014		×								

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Table I (*Continued*)

Study site/date [ref.]	Parasite	Diagnostic method	Population (no. studied)	Children (no. studied)	Prevalence	Gender	Blood volume	Ag/MF	Incidence	Disease manifestation	MF density	CMI	Antibodies	Parent's MF status	Prenatal exposure
Chlebowsky & Zielke 1980 [66]	Wb	MF, Slide, Fil (20 µl, 1 ml)	850	345	×		×			×					
Malaysia Hassan 1959 [67]	Bm	MF, Slide (20 µl)	3529	1793	×		×								
Myanmar Hairston & Meillon 1968 [68]	Wb	MF, Slide 60 µl	11 440	5037	×		×								
Papua New Guinea Kazura et al. 1984 [69]	Wb	MF, Fil (4 ml), Cbr (20 µl)	79	28	×		×				×				
Day et al. 1991a [70]	Wb	MF, Fil (2 ml)	132	42†††	×										
Day et al. 1991b [71]	Wb	Ab	30	10				×					×		
Turner et al. 1993 [72]	Wb	MF, Fil (1 ml), Og4C3	674	×‡‡‡				×							
Mahanty et al. 1994 [73]	Wb	Ab	59	42											
Kazura et al. 1997 [74]	Wb	MF, Fil (1 ml)	1666	659	×		×			×	×		×		
Alexander et al. 1998 [75]	Wb	MF, Fil (1 ml)	2000	288						×				×	
Sri Lanka Cooray 1960 [131]	Wb	Hst	48¶	11¶						×					
Dissananyake et al. 1980 [76]	Wb	Ab	340	340**	×		×								×
Suriname Blumberg et al. 1951 [77]	Wb	MF, Slide (30 µl)	1716	922	×		×								
Tanzania McMahon et al. 1981 [78]	Wb	MF, Cbr (100 µl)	2003	1011	×		×			×	×				
Magnussen et al. 1995 [79]	Wb	MF, Cbr (100 µl), Og4C3, Ab	7¶	2¶		×				×	×		×		
Meyrowitsch et al. 1995 [80]	Wb	MF, Cbr (100 µl)	3086	2¶	×					×	×				
Simonsen et al. 1995 [81]	Wb	MF, Cbr (50 µl)	842	264†	×		×								
Simonsen et al. 1996 [82]	Wb	MF, Cbr (50 µl), Og4C3, Ab	924	106	×		×	×			×		×		

Table 1 (*Continued*)

Study site/date [ref.]	Parasite	Diagnostic method	Population (no. studied)	Children (no. studied)	Prevalence	Gender	Blood volume	Ag/MF	Incidence	Disease manifestation	MF density	CMI	Antibodies	Parent's MF status	Prenatal exposure
Simonsen & Meyrowitsch 1998 [83]	Wb	MF, Cbr (100 µl), Og4C3, Ab	22†	22								×	×		×
Tonga															
Desowitz & Hitchcock 1974 [84]	Wb	MF, Slide (60 µl), Fil (1 ml)	296	127	×		×								
Trinidad															
Chadee et al. 1995 [85]	Wb	MF, Slide, Fil (60 µl, 1 ml)	592	274	×	×	×								
Venezuela															
Briceno Rossi & Hewitt 1949 [86]	Wb	MF, Slide	16	2¶						×					

MF, microfilaraemia; Ag, antigenaemia; CMI, cell mediated immunity; Ab, antibodies; Hst, histology; Fil, Filtration or Knotts technique; US, ultrasound examination; Slide, blood film examination for microfilaria; Cbr, chamber concentration technique; Og4C3 [More & Copeman 1990] or AD12 [Weil et al. 1987], antigen assays; IH, immediate hypersensitivity assay.
* Placental examinations.
† <15—16-year-olds.
‡ Only asymptomatic children included.
$ No. estimated based on maternal association only.
¶ Clinical cases only.
** Cord blood examinations.
†† MF+ and MF− mothers.
‡‡ Estimated from 946 families with 2302 children.
$$ Frequency in 10–19-year-olds estimated from figures in text.
¶¶ Estimated from figures in reference.
*** MF+ mothers examined.
††† Ages 5–14 only.
‡‡‡ Age stratification provided in PNG Health Plan, 1991.

Quick reference finder

For technical reasons the references had to be listed in two parts: in the References (R) section, as is customary, and in an Appendix (A). For quick finding of complete references, please see Table below.

No.	R/A	Reference	No.	R/A	Reference
2	R	Jungmann & Figueredo-Silva 1989	46	R	Weil et al. 1983
3	R	Amaral et al. 1994	47	R	Rao et al. 1984
4	R	Figueredo-Silva et al. 1994	48	A	Rajagopalan et al. 1989
5	R	Dreyer et al. 1999a	49	R	Sanjeevi & Narayanan 1989
6	R	Faris et al. 1998	50	A	Panicker et al. 1991
12	A	Campello et al. 1993	51	A	Tewari et al. 1995
13	A	Maciel et al. 1996	52	R	Chandra & Hati 1996
14	A	Institute Against Parasitic Diseases 1998	53	A	Das et al. 1997
15	A	Peel & Van Oye 1950	54	A	De Rook 1959
16	A	McCarthy 1959	55	A	Van Dijk 1961
17	R	Ottesen et al. 1981	56	A	Putrali et al. 1975
18	A	Ottesen et al. 1982	57	A	Sajidiman et al. 1975
19	R	Steel et al. 1994	58	A	Haarbrink et al. 1995
20	A	Ottesen et al. 1977	59	R	Sartono et al. 1997
21	R	Steel et al. 2001	60	A	Sasa 1963
22	A	Paniagua et al. 1983	61	A	Sasa & Mitsui 1964
23	R	Bloomfield et al. 1978	62	A	Marshall & Yasukawa 1966
24	R	Ramzy et al. 1994	63	A	Estambale et al. 1994
25	R	Weil et al. 1999	64	A	Wamae et al. 1998
26	A	Burnett & Mataika 1961	65	A	Zielke & Chlebowsky 1979
27	A	Beye et al. 1952	66	A	Chlebowsky & Zielke 1980
28	R	Chanteau et al. 1995	67	A	Hassan 1959
29	A	Mc Gregor et al. 1952	68	A	Hairston & Meillon 1968
30	A	Dunyo et al. 1996	69	A	Kazura et al. 1984
31	A	Gyapong et al. 1998	70	A	Day et al. 1991a
32	A	Dzodzomenyo et al. 1999	71	R	Day et al. 1991b
33	A	Kenny & Hewitt 1949	72	A	Turner et al. 1993
34	A	Raccurt et al. 1984	73	A	Mahanty et al. 1994
35	A	Hitch et al. 1989	74	A	Kazura et al. 1997
36	A	Hitch et al. 1991a	75	A	Alexander et al. 1998
37	R	Hitch et al. 1991b	76	R	Dissanayake et al. 1980
38	R	Lammie et al. 1991	77	A	Blumberg et al. 1951
39	R	Eberhard et al. 1993	78	A	McMahon et al. 1981
40	R	Hightower et al. 1993	79	R	Magnussen et al. 1995
41	R	Lammie et al. 1994	80	A	Meyrowitsch et al. 1995
42	R	Hitch et al. 1997	81	A	Simonsen et al. 1995
43	R	Lammie et al. 1998	82	R	Simonsen et al. 1996
44	A	Sinha et al. 1959	83	A	Simonsen & Meyrowitsch 1998
45	A	Gubler & Bhattacharya 1974	84	A	Desowitz & Hitchcock 1974
			85	A	Chadee et al. 1995
			86	A	Briceno Rossi & Hewitt 1949
			131	R	Cooray 1960

(a)

Adult prevalence
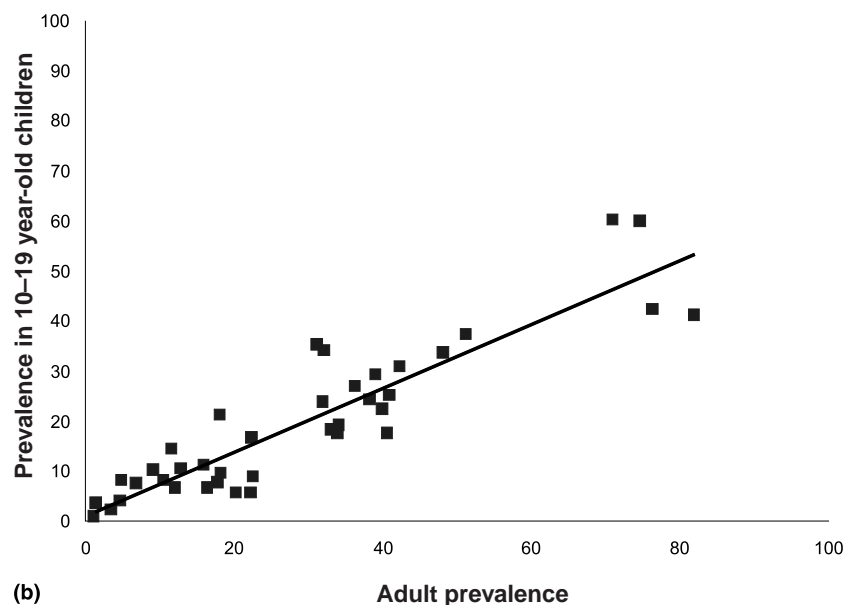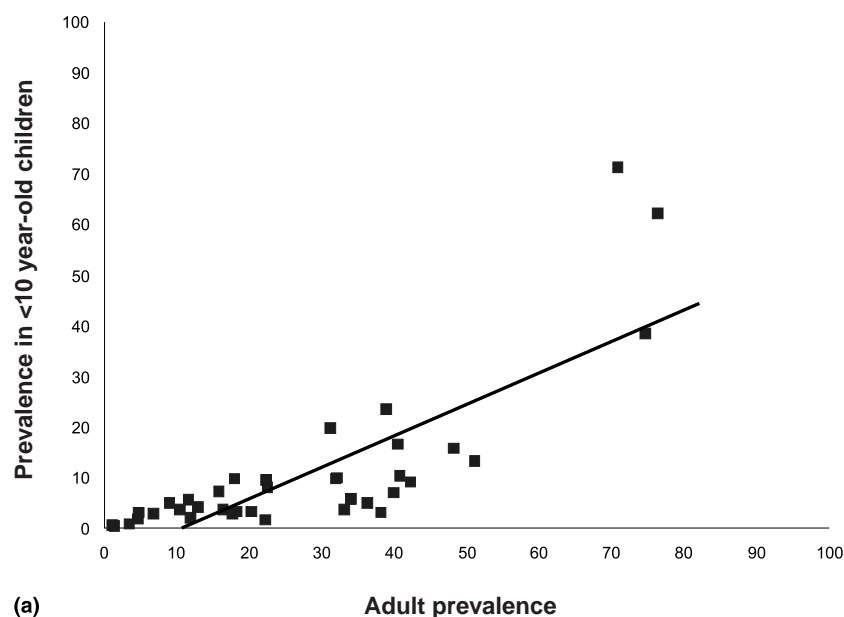

(b)

Adult prevalence

Figure 1 Correlation of childhood LF prevalence with adult LF prevalence (both determined by MF rates) for two age groups [<10-year old (a) and 10–19-year olds (b)]. Closed boxes (■) represent the childhood (*y*-axis) and adult (*x*-axis) prevalence rates from the reviewed studies (some 'overlapping points' cannot be visualized in the figure); the correlation coefficient was 0.80 for the <10-year age group ($n = 38$ studies) and 0.91 for the 10–19-year age group ($n = 39$ studies). The line is the least-squares fit for the data points, across all studies, with the strength of the correlations (R^2) being 0.63 and 0.82 and the corresponding regression equations being $Y = 0.62x - 6.65$ and $Y = 0.64x + 0.90$ for the <10 and 10–19-year olds, respectively (in Table 1, nos. 13, 14, 16, 21, 22, 26, 27, 29, 31, 32, 34, 41, 44, 45, 48, 50–52, 54–57, 60–62, 66–70, 74, 77, 78, 81, 82, 84, 85).

analysis but some are referenced as 'other clinical presentations'.

Statistical analysis

Linear regression analysis, chi-square, Spearman regression, Pearson correlation, Wilcoxon rank sum, Cochran-Armitage, Student's *t* and Fisher's exact-*t* tests were used to analyse findings as appropriate.

Results

Studies used for assessment

Table 1 lists 83 studies meeting the criteria for inclusion in this review (the numbers below refer to individual studies listed in this table). All were published between 1949 and 2000, 80 in peer-reviewed scientific journals and three (Institute Against Parasitic Diseases 1998) in official government scientific meeting reports. Seventy-eight
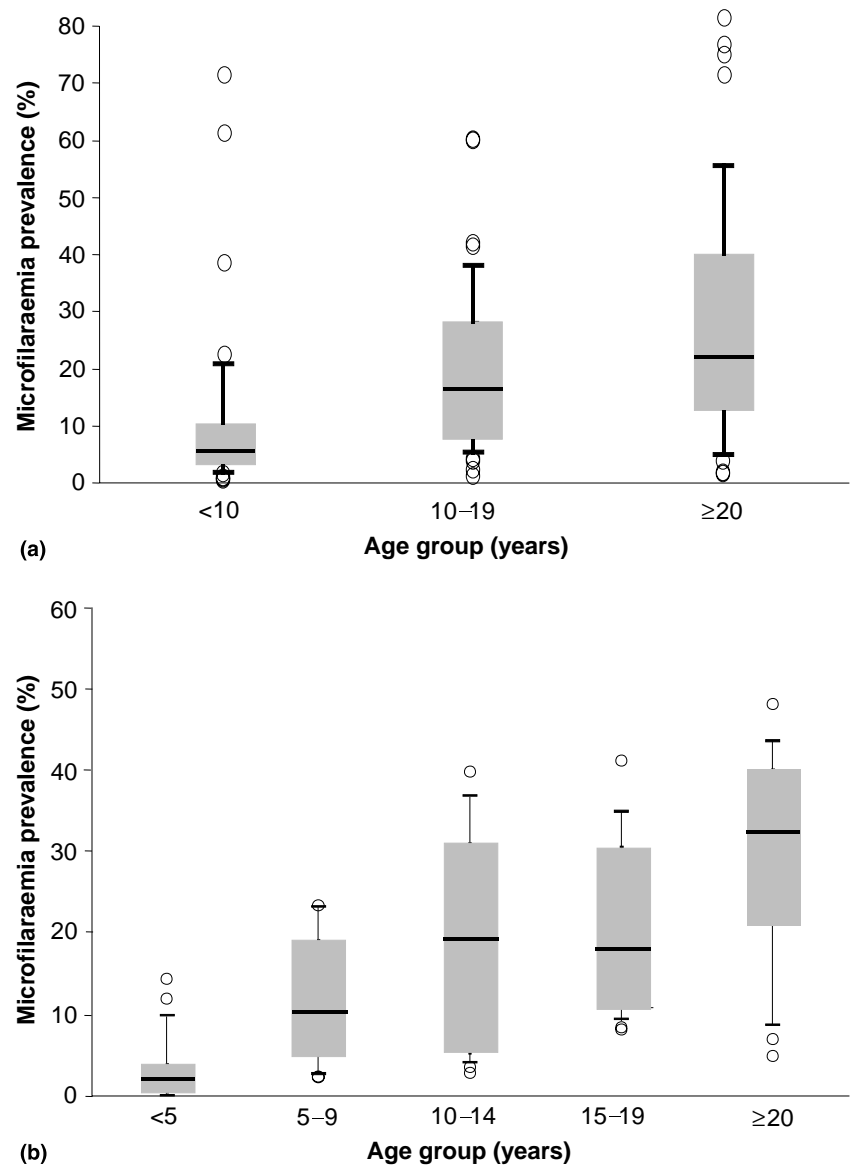
Figure 2 Microfilaraemia prevalence in children: (a) by 10-year age groups (in Table 1, nos. 13, 14, 16, 21, 22, 26, 27, 29, 31, 32, 34, 41, 44, 45, 48, 50–52, 54–57, 60–62, 66–70, 74, 77, 78, 81, 82, 84, 85); (b) by 5-year age groups (in Table 1, nos. 13, 16, 21, 26, 27, 41, 45, 48, 54, 57, 60, 66–68, 72, 78, 82, 84, 85). Each box is composed of three horizontal lines representing the 25th, 50th (median), and 75th percentiles of the prevalence rates. Vertical lines denote the 10th and 90th percentiles, and circles indicate prevalence values lying outside these percentiles (some 'overlapping' points cannot be visualized in the figure).

studies described *W. bancrofti* endemic populations and five, *B. malayi*.

Thirty-nine studies provided information useful for analysing childhood MF prevalence rates. Of these, nine reported on low endemicity populations [13, 14 (two studies), 22, 48, 50, 52, 60, 68], 21 on intermediate endemicity populations (14, 16, 21, 26, 31, 32, 34, 41, 44, 45, 51, 54–56, 61, 62, 67, 77, 78, 82, 85), and nine on high endemicity populations (27, 29, 57, 66, 69, 70, 74, 81, 84). Ten-year age stratifications were possible in 39 of the study populations [13, 14 (two studies), 16, 21, 22, 26, 27, 29, 31, 32, 34, 41, 44, 45, 48, 50–57, 60–62, 66–70, 74, 77,

78, 81, 82, 84, 85], and 5-year stratifications in 19 populations (5, 16, 21, 26, 27, 41, 45, 48, 54, 57, 60, 66–68, 72, 78, 82, 84, 85). As delineated in Table 1, varying numbers of studies were used, as appropriate, to analyse each of the different infection, diagnostic and disease parameters evaluated.

Epidemiology of LF in children

Earlier studies determined the prevalence of LF in children by MF rates. Perhaps not surprisingly, MF prevalence in children from different populations was found to be

Table 2 Blood volume used in diagnostic assay as a factor affecting MF prevalence estimates

	Age group (years)	
	<10	10–19
High-volume techniques [21, 22, 32, 57, 66, 69, 74, 78, 84]		
Adult *vs*. child correlation ($\rho_{x,y}$)	0.86 ($R^2 = 0.73$; $P < 0.003$)	0.92 ($R^2 = 0.84$; $P < 0.001$)
Childhood rate as a percentage of adult rate	51.9	71.3
Low-volume techniques [13, 14, 16, 26, 27, 29, 31, 34, 41, 44, 45, 48, 50–52, 54–56, 60–62, 66–68, 77, 81, 82, 84, 85]		
Adult *vs*. child correlation ($\rho_{x,y}$)	0.6 ($R^2 = 0.36$; $P < 0.001$)	0.87 ($R^2 = 0.76$; $P < 0.001$)
Childhood rate as a percentage of adult rate	26.0	63.7

MF, microfilaraemia; high volume techniques use ≥ 100 µl of blood; low volume techniques use ≤ 60 µl; R^2, strength of linear correlation in regression analysis; reference [14] comprises two separate studies; references [66 and 84] provided data for analysing both the high-volume and low-volume techniques.
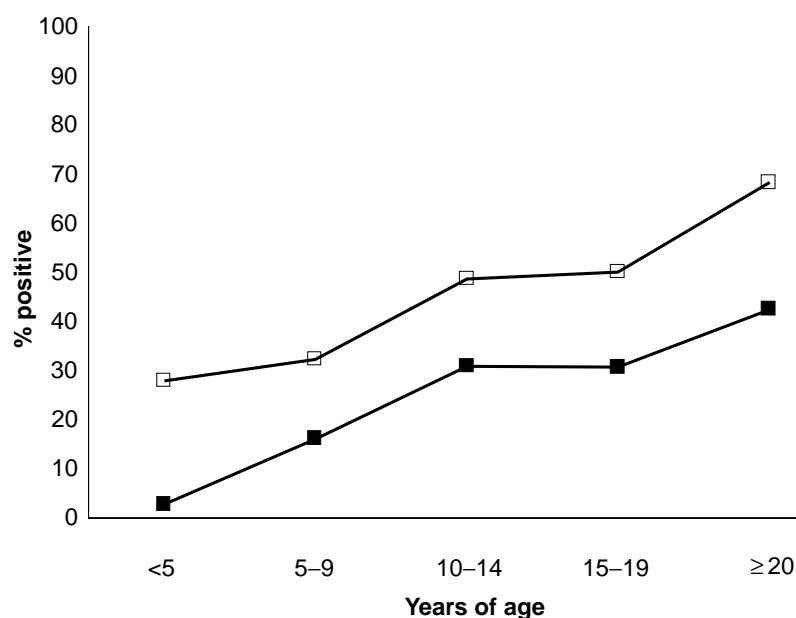
Figure 3 Differences in LF prevalence estimates based on antigenaemia (Ag) and MF detection assays from one published study (Simonsen *et al*. 1996). Open boxes (□) depict prevalence results from the antigen assay, while closed boxes (■) represent results from the MF assay (cf. Table 3).

significantly related to the level of endemicity seen in their respective adult populations. This correlation held for both the < 10-year olds (Figure 1a; $R^2 = 0.63$; $P < 0.001$) and the 10–19-year-olds (Figure 1b; $R^2 = 0.82$; $P < 0.001$); findings were similar when the 5-year age groups were analysed (data not shown). Indeed, if childhood prevalence rates are expressed as a percentage of the adult rates, rather constant relationships were found for each of the two age groups [averaging 30% for < 10-year olds (95% confidence interval 24–36%) and 69% for 10–19-year olds (95% confidence interval 60–80%)], and they were independent of both population endemicity level and the specific MF detection technique used (data not shown).

It is because of this link between adult and child MF prevalence rates that the different levels of endemicity found in different populations probably account for the wide variation seen in the earlier descriptive reports of MF prevalence in children (Figure 2). Such prevalence ranged between 0.3 and 71% in the 39 studies reporting on children stratified by 10-year age groupings, with the older children having significantly ($P < 0.001$) higher rates than the younger ones. Similarly, in the 19 studies grouped by 5-year intervals (10 with 'complete' data sets and nine missing data from one of the age groups), prevalence was also seen to increase progressively from the younger to the older age groups, but again with an appreciable variation

Table 3 LF infections detected and missed by microfilaraemia (MF) and antigenaemia (Ag) assays

Study site [ref.]	Age group (years)	No. of persons in study	No. MF+	No. MF−	MF prevalence	No. Ag+	Ag prevalence	No. cryptic infections*	Cryptic infections in age group (%)	LF infections missed by MF assay (%)†
Cook Islands [21]	<5	44	6	38	13.6	16	36.4	10	22.3	62.5
	5–9	55	11	44	20.0	18	32.7	7	12.7	38.9
	10–14	49	10	39	20.4	19	38.8	9	18.4	47.3
	15–19	28	5	23	17.9	10	35.7	5	17.9	50.0
	≥20	184	78	106	42.3	117	63.5	39	21.2	33.3
	All ages	360	110	250	30.6	180	50.0	70	19.4	38.8
Egypt [24]‡	11–15	695	75	620	10.8	111	16.0	36	5.2	32.4
Haiti [41]‡	≤5	49	7	42	14.3	12	24.5	5	10.2	41.7
	6–10	74	17	57	23.0	35	47.3	18	24.3	51.4
	11–15	58	23	35	39.7	32	55.2	9	15.5	28.1
	16–20	56	17	39	30.4	26	46.4	9	16.1	34.6
	≥20	182	57	125	31.3	101	55.5	44	24.2	43.6
	All ages	419	121	298	28.9	206	49.2	85	20.2	41.3
Tanzania [82]‡	<5	36	1	35	2.8	10	27.8	9	25.0	90.0
	5–9	31	5	26	16.1	10	32.3	5	16.1	50.0
	10–14	39	12	27	30.8	19	48.7	7	17.9	36.8
	15–19	36	11	25	30.6	18	50.0	7	19.4	38.9
	≥20	151	64	87	42.4	103	68.2	39	25.8	37.9
	All ages	293	93	200	31.7	160	54.6	67	22.8	41.9

* Cryptic infection: MF− but Ag+; none of these studies includes the recently described individuals with 'cryptic' infections who are MF− and Ag− but have adult worms visualized by ultrasound [Dreyer et al. 1996].

† Calculated as 100 × (no. cryptic infections)/(no. cryptic infections + no. MF+).

‡ Estimates from reported prevalence rates; if not specifically stated, all MF+ individuals are assumed to be Ag+.
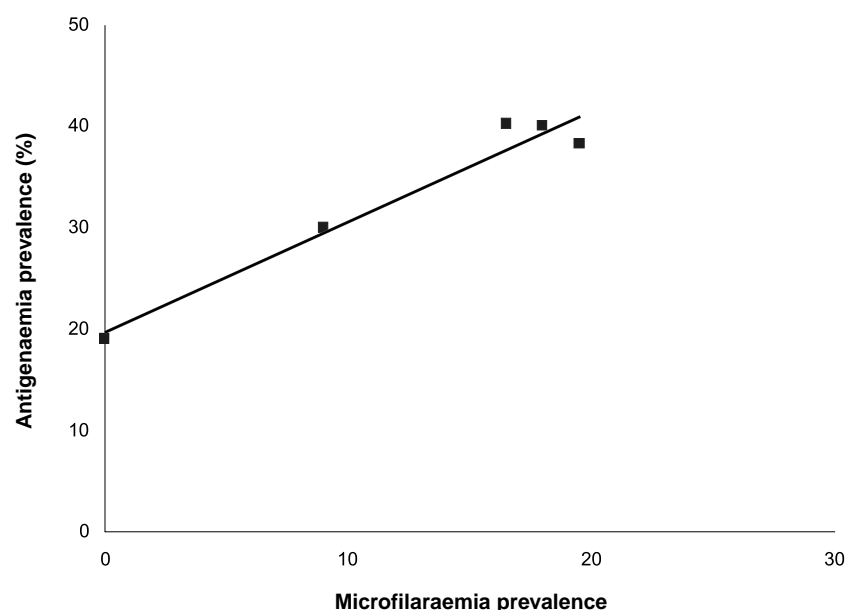
Figure 4 Correlation between antigenaemia (Ag) and MF prevalence rates in <10-year olds. Closed boxes (■) represent the Ag and MF values determined in the five studies analysed (Turner *et al.* 1993; Lammie *et al.* 1994; Chanteau *et al.* 1995; Simonsen *et al.* 1996; Steel *et al.* 2001). The correlation coefficient for the Ag and MF prevalence pairs for all studies was 0.98 ($R^2 = 0.95$; $Y = 1.10x + 19.6$).
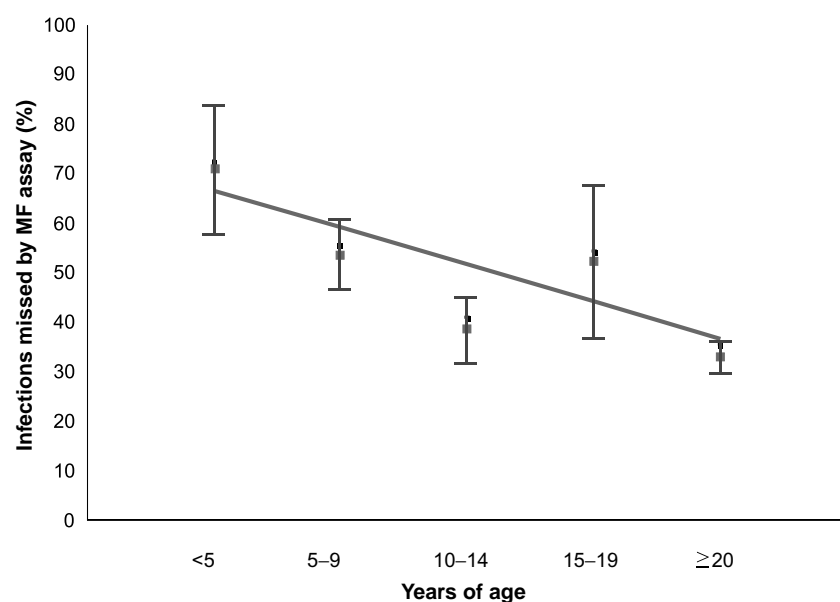

Figure 5 Percentage of LF infections missed if microfilaraemia detection was used as the diagnostic, instead of antigenaemia detection (see text). Closed boxes (■) represent the geometric means of values from five studies (Lammie *et al.* 1994; Ramzy *et al.* 1994; Simonsen *et al.* 1996; Steel *et al.* 2001). Bars represent ±1 SEM. Strength of correlation: $R^2 = 0.68$; regression equation: $Y = -7.49x + 74.0$.

in all age groups that is likely principally to be due to the different endemicity levels in the populations (Figure 2).

Thirty-eight studies were examined to ascertain what influence different MF detection *methods* might have on estimates of LF prevalence in children. Nine studies described the use of high blood volume assays (i.e. ≥ 100 µl) and 31, the use of low blood volume assays (i.e. ≤ 60 µl – usually 20 µl blood smears). As seen in Table 2, when high blood volume techniques were used, the correlations

between the MF rates of adults and those of both the younger and older children were strong and statistically significant. Low blood volume techniques also produced a strong correlation between adult rates and those for the 10–19-year olds, but the correlation with the rates for the younger children, although still significant, was weaker. Furthermore, in the younger children (< 10-year old group) high-volume techniques could detect a prevalence of MF that was just over half that found in adults, but the
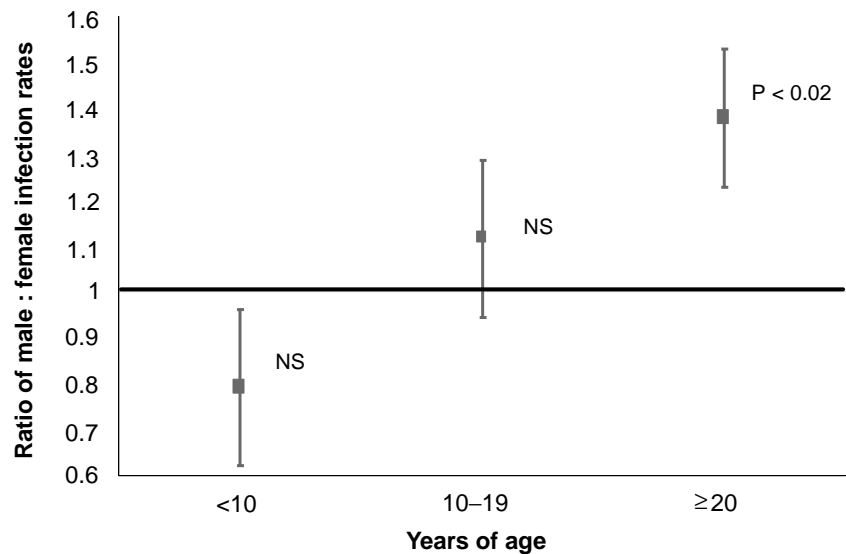
Figure 6 Male–female ratio of MF prevalence by age group. Mean ratios (±SEM) are plotted for two childhood age groups and for adults. Only the adults show a significant gender imbalance (male predominance; $P < 0.02$). NS: not statistically significant.

low-volume techniques detected an MF prevalence in these children only about one-fourth of that found in adults.

Determination of LF in children by antigen detection is much more effective than by microfilaria detection, as illustrated in Figure 3 and Table 3. The greater effectiveness of antigenaemia detection is seen for all ages, but it is proportionately more pronounced in < 5-year old children (ranging from 42 to 90% in the three studies with this age group described in Table 3). The tight correlation between prevalence detection by antigenaemia and MF in the < 10-year old age group is shown in Figure 4 (correlation coefficient = 0.98; $R^2 = 0.96$; $P < 0.004$), which also demonstrates that this under-diagnosis of infection by MF assays is independent of population endemicity level. Finally, as indicated in Table 3, at least one-third of all infections are 'missed' using only MF detection to diagnose infections, and as Figure 5 shows, the proportion of infections missed by MF assays is significantly greater ($P < 0.001$) in the younger age groups than in older children or adults.

In the single study (Lammie et al. 1998) detailing the incidence of LF in very young children, a cohort of 39 children was examined for antigenaemia and MF first at age 2 (antigenaemia = 6%; MF = 0%) and then 2 years later at age 4. Living in an area with an overall MF prevalence of approximately 30%, these children were found to have a 2-year incidence between ages 2 and 4 years of only 2% for MF but 20% for antigenaemia. This emphasizes not only how early in life young children acquire LF infection, but also how much more sensitive diagnosis of infection is using the antigen assay. Other studies (cross-sectional in design) confirm both this early

age positivity and a progressive increase of antigen positivity with age (Lammie et al. 1994; Ramzy et al. 1994; Simonsen et al. 1996; Steel et al. 2001) Furthermore, a similar longitudinal study found that among microfilaria-negative children, antigen positivity is the best predictor for the development of MF during the subsequent year (Weil et al. 1999).

An earlier comprehensive review of gender as a risk factor for LF prevalence in adult populations found a significant predominance of infection among males (Brabin 1990). Figure 6 shows the results from the analysis of 14 studies assessing gender as a potential risk factor for LF infection among children (in Table 1, nos. 16, 21, 22, 29, 34, 45, 48, 51, 55, 61, 62, 65, 78, 85) Among the adults in the 14 studies, the previously described male predominance was confirmed as statistically significant ($P < 0.02$). But for children no significant gender difference in MF prevalence was observed (< 10-year olds, $P = 0.08$; 10–19-year olds, $P = 0.33$). Furthermore, the level of LF endemicity in populations did not influence these gender relationships in either adults or children (data not shown).

The influence of parental LF infection status on childhood infection (defined by microfilaraemia or antigenaemia) was examined in eight studies (in Table 1, nos. 17, 25, 38, 40, 43, 53, 75, 83), two of which (Lammie et al. 1991; Hightower et al. 1993) described overlapping but not identical populations (Table 4). Although there was an appreciable lapse of time in most of these studies between the birth of the child and assessment of the MF or antigenaemia status in the children and the parents, still maternal MF was seen as a relative risk factor for childhood MF, ranging from 1.56 to 2.85 (statistically

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Table 4 Parental filarial infection status as a risk factor for childhood filarial infection

Study site [ref.]	Child status*	Maternal status†	No. children MF+	No. children MF−	RR‡	CI 95%§	χ2¶ P-value	Paternal status*	No. children MF+	No. children MF−	R.R.	CI 95%	χ2 P-value
Microfilaraemia (MF)													
Haiti [40]	0–19	+	38	97	2.49	1.65–3.75	<0.001						
		−	35	274									
Haiti [38]	0–15	+	32	67	2.44	1.57–3.78	<0.001	+	14	42	1.43	0.75–2.73	n.s.
		−	30	196				−	15	71			
India [53]	0–20	+	20	116	2.85	1.82–4.46	<0.001	+	15	138	1.79	1.07–3.00	<0.05
		−	100	1838				−	105	1816			
Tanzania [83]	10–20	+	1	7	1.75	0.13–24.33	n.s.**						
		−	1	13									
Egypt [25]††	10–16	+	7	60	2.35	1.07–5.16	n.s.**	+	6	41	2.76	1.18–6.45	<0.05**
		−	29	623				−	23	475			
Papua New Guinea [75]	4–10	+	79	103	1.56	1.05–2.31	<0.05	+	66	78	2.02	1.25–3.26	<0.001
		−	22	57				−	15	51			
Aggregated study groups		+	177	450	4.19	3.50–5.01	<0.001	+	101	299	4.11	3.27–5.15	<0.001
		−	217	3001				−	158	2413			
Antigenaemia (Ag)													
Egypt [25]††	10–16	+	20	87	2.84	1.73–4.66	<0.001	+	10	47	2.14	1.13–4.04	<0.05
		−	40	567				−	40	448			
Haiti [43]‡‡	0–3	+	24	75	2.52	1.02–6.22	<0.05						
		−	5	47									
Aggregated study groups		+	44	162	3.3	2.13–4.60	<0.001						
		−	45	614									

* Age (years, range) of children when assessments for microfilaraemia or antigenaemia were made.
† MF-positive/negative or Ag-positive/negative (determined at same time child was studied, and in Haiti [43] where maternal assessments were made 16 years before the children were studied, and in Haiti [43] where maternal assessments were made at the time that the children were born).
‡ Relative risk of a child being positive if the parent is positive.
§ Confidence interval.
¶ Chi-square statistical test; n.s.: not significant (P > 0.05).
** Fisher's test (two-tailed).
†† AD12 circulating antigen assay [Weil et al. 1987].
‡‡ Og4C3 circulating antigen assay [More & Copeman 1990].

significant in four of six studies). The paternal relative risk ranged from 1.43 to 2.76, being statistically significant in three of four studies. The aggregated data yielded a relative risk for a child's being microfilaraemic when the mother was microfilaraemic of 4.19 ($P < 0.001$); for the father it was 4.11 ($P < 0.001$).

Two studies also provided similar information but were based on filarial antigenaemia, not MF status (Table 4). The relative risk of a child being antigen-positive if a parent was antigen-positive was at least twice that of a child with antigen-negative parents, the association with maternal status being more highly significant ($P < 0.001$) than that with paternal status ($P < 0.05$).

The potential for congenital LF infection was reviewed in three studies reporting the identification of microfilariae in placental tissues and in four reporting the presence of microfilariae in cord blood (Table 5). All microfilariae-positive placentas and cord blood specimens were derived from mothers who were microfilaraemic. Three of the seven infants with microfilaria-positive cord blood specimens were found to be amicrofilaraemic upon subsequent examination before 8 months of age (Rao *et al.* 1984; Eberhard *et al.* 1993) two were lost to follow-up (Rao *et al.* 1984), two did not have their follow-up reported (Bloomfield *et al.* 1978; Hitch *et al.* 1997).

Immunological evaluation of umbilical cord blood (foetal-origin) for antibodies and antigens revealed the presence of filaria-specific IgM and IgE (antibody classes that should not cross the placental barrier) in one-third to one-half of samples associated with MF+ mothers

(Dissanayake *et al.* 1980; Weil *et al.* 1983; Sanjeevi & Narayanan 1989; Hitch *et al.* 1997), and filaria-specific antigen (Og4C3) was detected in six of 29 cord blood samples (Hitch *et al.* 1997). With regard to *in vitro* cord blood mononuclear cell (CBMC) proliferative responses to filarial antigens, nine of 61 samples examined had positive responses, but these were independent of maternal MF status and were not statistically different from responses in non-endemic (negative) controls (Hitch *et al.* 1997).

Such findings suggest that exposure to, or rarely even passive acquisition of, microfilariae during the prenatal or perinatal period does occur, but actual prenatal infection with adult worms is unlikely. They also suggest that prenatal sensitization to filarial antigens, or to maternal anti-filarial (idiotypic) antibodies, occurs much more commonly.

Clinical manifestations and pathology of LF in children

Table 6, listing 133 childhood cases of hydrocoele and 57 cases of lymphoedema or elephantiasis attributed to LF (in Table 1, nos. 5, 24, 27, 30, 32, 33, 52, 54, 55, 63, 66, 74, 78, 80, 86), shows clearly that the same chronic pathology seen in adults with LF is also found in children, although it is unusual in children < 10 years of age. Furthermore, the fact that the stage of morbidity most frequently reported was Grade II (Kumaraswami 2000) or higher suggests that the earlier stages of this chronic progressive disease – not only the subclinical stages but also the early overt clinical stages – frequently go undetected in young children.

Table 5 Evaluation for congenital LF infection

| Study site/date [Ref.] | No. MF+/No. examined | | | |
| | Placentas | | Cord blood specimens | |
	MF+ mothers	MF− mothers	MF+ mothers	MF− mothers
Brazil 1993 [12]	0/10	0/10		
Congo 1950 [15]	3/4	0/87		
Dominican Republic 1978 [23]	1/1		1*/1	
Haiti 1993 [39]	2/21	0/56	1†/21	0/56
Haiti 1997 [42]			1*/31	0/33
India 1983 [46]			0/13	0/44
India 1984 [47]	0/4	0/4	4‡/12	0/236
Total	6/40	0/157	7/78	0/369

Note: Infection is defined as microfilaraemia (MF).
* Follow-up not reported.
† Found negative at subsequent examination at 3-weeks of age.
‡ Two infants determined negative at subsequent examinations over the 8-month period after birth; two lost to follow-up.

Table 6 Lymphatic morbidity reported with LF in children

Clinical presentation [ref.]	No. patients with disease		Diagnostic indicator
	<10-year old	10–19-year old	
Hydrocoele [5, 24, 30, 32, 52, 54, 55, 63, 66, 74, 78, 80, 86]	3 (67% ≥ II*)	130 (91% ≥ II)	Clinical assessment
Lymphoedema/elephantiasis of the limb [24, 27, 30, 32, 33, 54, 55, 63]	5 (80% ≥ II*)	52 (62% ≥ II)	Clinical assessment
Adenopathy/mass [2–6, 131]	16 1	34	Worm in biopsy† FDS‡
Hernia/epididymitis [131]		4	Worm in biopsy†
Subclinical [3, 5, 6]		20	FDS‡

* Lesions graded according to standard scale (I–IV) [Kumaraswami 2000].
† Seen by histopathology.
‡ 'Filaria Dance Sign', seen by ultrasound examination.

Other clinical pathology associated with the presence of filarial worms, such as adenopathy and lymphangitis has been demonstrated principally through histopathologic examinations (Cooray 1960; Jungmann & Figueredo-Silva 1989; Amaral *et al*. 1994; Figueredo-Silva *et al*. 1994; Faris *et al*. 1998; Dreyer *et al*. 1999b). Excisional biopsy with histopathologic diagnosis of either acute or chronic LF was made in 56 children (including 16 who were < 10-year old) presenting with soft tissue masses, but whose clinical presentations were generally not recognized as being caused by LF, despite the children's residence in LF-endemic areas (Cooray 1960; Jungmann & Figueredo-Silva 1989; Figueredo-Silva 1994). The most frequent presumptive clinical diagnoses were neoplasia, tuberculosis, or inguinal hernia; in only two of these cases was the diagnosis of LF entertained before biopsy (Jungmann & Figueredo-Silva 1989). Histologically, these biopsies reflected the spectrum of tissue and inflammatory reactions seen in LF infections, regardless of patient age. In the proximity of live worms, there were varying degrees of lymphangiectasia, generally without inflammatory changes or lymphatic obstruction; if present, the acute inflammatory response was a non-granulomatous eosinophilic, lymphocytic and plasmacytic parietal lymphangitis. *In-situ* worm death was associated with a progressive granulomatous reaction, at times including polypoid endothelial hyperplasia or granulomatous endolymphangitis with subendothelial connective tissue involvement and ultimate effacement of lymphatic architecture and fibrous hyalinized scarring. This severe damage was most commonly seen associated with worm calcification (Jungmann *et al*. 1991).

Subclinical, asymptomatic or minimally symptomatic lesions have been identified on ultrasound, principally associated with the presence of nests of living adults worms [Filarial Dance Sign (FDS)] and constituting lymphangiectasia both around and at a distance from these worm nests; this lymphatic dilatation was seen to increase with patient age (mean of 1.6 mm in < 10-year olds *vs*. 2.1 mm in > 10-year olds (Dreyer *et al*. 1999a). The scrotal area was the exclusive site for detecting FDS in boys > 14 years of age, but in younger pre-pubescent children (both male and female) the FDS was detected primarily in axillary, crural and inguinal locations (Dreyer *et al*. 1999a, 2001). Unfortunately, because of difficult technical challenges in visualizing these particular locations with ultrasound, there remains a gross under-detection of live worms in the younger, pre-pubescent children.

Other types of clinical presentation in children have been reported, but often without a specific diagnosis. These include the relatively common acute adenolymphangitis (ADL) and, less commonly, chyluria and tropical pulmonary eosinophilia (TPE). A total of 145 children < 10 years old, and 181 children aged 10–19 were reported as having ADL characterized by episodic attacks of nodular inflammation in the limbs, scrotum or other subcutaneous tissues, and with or without accompanying general malaise and fever (Bai *et al*. 1977; Raghupathy & Date 1982; Ramzy *et al*. 1994; Gyapong *et al*. 1996; Alexander *et al*. 1999). These attacks were associated with incapacitation, often lasting several days and often re-occurring (Gyapong *et al*. 1996; Alexander *et al*. 1999). LF-associated chyluria was described in four cases (10–12-year-old children), two with accompanying haematuria (Gupta *et al*. 1967; Bai *et al*. 1977; Raghupathy & Date 1982; Kohli *et al*. 1994). Three of these children were microfilaraemic and two of them had microfilariae in the urine. Finally, TPE is also described as occurring in children, with one reported case, an 11-year-old boy, presenting with recurrent bouts of cough and

dyspnea that progressed to incapacitating restrictive and obstructive lung disease (Magnussen *et al.* 1995).

Immune responses to LF infection in children

Almost all studies of antibody levels in children, either with LF infection or exposure, agree that the pattern of humoral immune responsiveness does not differ appreciably from that described in adults (in Table 1, nos. 18, 28, 35, 36, 43, 58, 64, 71, 73, 82, 83; Wamae *et al.* 1995; Dimock *et al.* 1996; Steel *et al.* 1996; Nicolas *et al.* 1999), even including the hyper-responsiveness of the tropical pulmonary eosinophilia syndrome (Magnussen *et al.* 1995). However, while the pattern of responsiveness is similar, the levels of antibodies are generally lower in children and rise progressively to those of adulthood (Chanteau *et al.* 1995). Furthermore, as also recognized in adult populations, the level of antibody response is generally higher in high-prevalence populations than in low-prevalence populations (Chanteau *et al.* 1995; Haarbrink *et al.* 1995).

Particularly noteworthy is the finding that children with MF or antigenaemia (especially if accompanied by MF) have high anti-filarial IgG4 responses, even in the youngest age groups (in Table 1, nos. 21, 36, 43, 64, 82, 83). Also as in adults, antibodies of other IgG subclasses (IgG1, IgG2 and IgG3) and other isotypes (IgE and IgM) appear generally lower in microfilaraemic children compared with those in endemic populations who are amicrofilaraemic (in Table 1, nos. 18, 35, 36, 43, 64, 71, 82, 83). There is, however, some suggestive data (Table 7) that this generalization, might not extend to the youngest age group of children, in whom the

Th-1-type responses (IgG1, IgG2 and IgG3) of infected children appear to be relatively greater than they are later in life. Such an observation, if substantiated by further research, would be of particular interest because of its potential direct relevance to a postulated Th-1→Th-2 shift in the pattern of immune response during the course of LF (and other helminth) infection (Maizels *et al.* 1995).

In a study of amicrofilaraemic teenage children who had grown up exposed to filariasis infection, those born to mothers who were microfilaraemic at the time that the children were born had greater levels of IgG4 antibody to filarial antigens than those born to amicrofilaraemic mothers, while IgE titres were greater in those born to amicrofilaraemic mothers; IgG1, IgG2 and IgG3 responses did not vary with maternal status (Steel *et al.* 1994). These findings imply a potential prenatal programming or influencing of subsequent immune responsiveness depending on the mother's infection status.

Another potentially important finding relates to the issue of protective immunity; specifically, *in contrast to adults*, few infected children (i.e. defined by MF or antigenaemia) have antibodies to the surface of infective larvae (L3), whereas a large percentage of adults in the same populations have such antibodies (Day *et al.* 1991b). This difference has been postulated to reflect a state of 'concomitant immunity' (i.e. protection from additional infection in those already infected) in adults but not children.

Lymphocyte responses and their clinical correlations

Table 8 presents information from four studies on lymphocyte proliferative responses to filarial antigens in children

Table 7 Relative levels of filaria-specific antibodies in 'infected'* and 'non-infected' individuals† living in LF endemic areas

Immunoglobulin Type/subclass	Children			Adults‡
	≤ 5 years	≤ 10 years	≤ 15 years	
IgG	MF+ < MF− [35]	MF+ < MF− [35]	MF+ < MF− [18, 35, 71]	No consistent trend
IgG1	MF+ > MF− [82]	MF+ < MF− [36, 82]	MF+ < MF− [83, 36]	MF+ < MF− [64, 82, 83, 99, 100]
	Ag+ ≅ Ag− [43]	Ag+ ≅ Ag− [64]		Ag+ < Ag− [64]
IgG2	Ag+ ≅ Ag− [43]	MF+ < MF− [36]	No consistent trend [36, 83]	MF+ < MF− [64, 83, 99, 101]
		Ag+ ≅ Ag− [64]		Ag+ ≤ Ag− [64, 101]
IgG3	Ag+ ≅ Ag− [43]	MF+ < MF− [36]	MF+ < MF− [36, 83]	MF+ > MF− [64, 83, 99, 100]
		Ag+ > Ag− [6]		Ag+ < Ag− [64]
IgG4	MF+ > MF− [82]	MF+ > MF− [36, 82]	MF+ > MF− [36, 83]	MF+ > MF− [64, 82, 83, 98–101]
	Ag+ > Ag− [43]	Ag+ > Ag− [64]		Ag+ > Ag− [64, 100, 101]
IgM	–	–	MF+ < MF− [18, 71]	No trend [18, 71]
IgE			MF+ < MF− [18, 35, 83]	MF+ < MF− [18, 35, 83, 98, 100]
	–	–		Ag+ < Ag− [101]

* Either Ag+ (antigenaemic) or MF+ (microfilaraemic), depending on study.
† Either Ag− (non-antigenaemic) or MF− (amicrofilaraemic), depending on study.
‡ Adults, ≥ 20 years of age.

Table 8 Lymphocyte responsiveness to filarial antigens in children

Lymphocyte source*	Clinical group†	Parameter	Relative response‡
PBMC	Children [20, 37] MF-adolescents [19]	Proliferation	MF+ < MF−
		Proliferation	MF+ mothers < MF− mothers
		IL2	MF+ mothers < MF− mothers
		IL5	MF+ mothers < MF− mothers
		IL10	MF+ mothers < MF− mothers
		INF-γ	MF+ mothers < MF− mothers
		GMCSF	MF+ mothers < MF− mothers
CBMC	Newborns [42]	Proliferation	MF+ mothers ≈ MF− mothers
		IL2	MF+ mothers ≈ MF− mothers
		IL4	MF+ mothers ≈ MF− mothers
		INF-γ	MF+ mothers ≈ MF− mothers

* PBMC: peripheral blood mononuclear cells; CBMC: cord blood mononuclear cells.
† Children in these studies were 6–10 years of age [20], ≤15 years of age [37] or 17–19 years of age [19].
‡ MF+: microfilaraemic children; MF−: amicrofilaraemic children; MF+ mothers: children whose mothers were microfilaraemic at the time of the child's birth; MF− mothers: children whose mothers were amicrofilaraemic.

(Ottesen *et al*. 1977; Hitch *et al*. 1991b, 1997; Steel *et al*. 1994). The following generalizations can be made:

- Amicrofilaraemic children in endemic populations have a consistently higher proliferative response to filarial antigens than those with MF, irrespective of age (Ottesen *et al*. 1977; Hitch *et al*. 1991b), and the same relationship holds for antigen-negativity or positivity (Hitch *et al*. 1991b).
- Responses in amicrofilaraemic children are stronger than those of amicrofilaraemic adults (Ottesen *et al*. 1977).
- Microfilaria-positive maternal status at the time of a child's birth appears to diminish the peripheral blood mononuclear cells (PBMC) proliferative response to filarial antigen even in amicrofilaraemic children 17–19 years old (Steel *et al*. 1994).
- There is no significant difference in the level of CBMC proliferation response to filarial antigen between children with microfilaraemic mothers and those with amicrofilaraemic mothers (Hitch *et al*. 1997).

Children have comprised part of several studies of cytokine production in LF endemic populations (Dimock *et al*. 1996; Steel *et al*. 1996; Sartono *et al*. 1997), but comparative analyses between the responses of adults and children have not been presented. However, responses of uninfected adolescents living in an endemic area and distinguished by their having been born to microfilaraemic or non-microfilaraemic mothers have been described (Steel *et al*. 1994). Interestingly, those born of MF+ mothers mounted significantly lower cytokine responses (IL2, IL5,

IL10, INF-γ and granulocyte macrophage colony stimulating factor (GMCSF)) to filarial antigens than did those born to MF− mothers (Table 8). While this significant difference in responsiveness was seen at the age of adolescence, a study of newborns, born to either MF+ or MF− mothers failed to find any difference in cytokine production when cord blood lymphocytes were examined (Hitch *et al*. 1997).

Discussion

Lymphatic filariasis is now recognized as a widespread, important disease affecting as many as 120 million people worldwide, with a billion people living in areas at risk of infection (Ottesen *et al*. 1997). What has not been well appreciated, however, is the fact that it is the children in these areas who are at greatest risk, because it is during childhood that infection is first acquired and in childhood that the early damage to the lymphatic system takes place – damage that subsequently leads to the same clinical consequences (mainly early lymphoedema and hydrocoele) later in childhood that progress to the more prominent expressions of LF disease in adults. While it is clear from this review that *some* LF in children has been recognized previously, the availability of new, more sensitive diagnostic techniques has now greatly expanded our ability to detect and understand just how widespread these LF infections of children in endemic areas really are.

As demonstrated in Figure 1, across all endemicity levels the prevalence of LF infection in children is proportional to

that of the adults in each population; those under 10 have prevalence rates averaging 30% of the adult rate and 10–19-year olds have about 69% of the adult rate. Thus, much of the wide variation in childhood prevalence of LF recognized earlier and seen in the aggregated data of Figure 2 can be explained by the differences in the prevalence of infection among the adults of these reported populations.

Technical factors associated with blood sampling volume and techniques also contributed to the variability and relatively low estimates of prevalence of LF in children, but the greatest cause for misdiagnosis of LF infection in children has certainly been the relatively poor sensitivity of microfilaria detection techniques. Regardless of how much blood is examined for microfilariae, the detection of circulating antigen (now by simple finger-prick techniques) has proven to be a much more sensitive diagnostic for bancroftian filariasis than anything previously available. Indeed, as indicated in Table 3 and Figure 3, the enhanced effectiveness of antigen detection, vis-à-vis microfilaria detection, to diagnose LF infection is greatest in very young children, many of whose infections had been previously undiagnosed. Furthermore, the direct observations on the incidence of infection in very young children (Lammie et al. 1998; Weil et al. 1999) emphasize again the magnitude of the proportion of children acquiring their LF infections even before age 5 in endemic communities.

It is not clear what exactly determines which children in a population become infected and at what age, and whether there are specific risk factors for acquiring infection. Gender does not appear to affect the acquisition of infection in childhood (defined by MF [Figure 6] or by antigenaemia [Steel et al. 2001]), although it is well recognized that among the adults in endemic areas men have significantly higher infection rates (determined by MF [Fig. 6] [Brabin 1990] or antigenaemia [Steel et al. 2001]) than do women. Maternal infection (determined either by MF or antigenaemia) has been clearly shown to be a risk factor for childhood infection (Table 4), and there is convincing immunological evidence for prenatal exposure and sensitization to filarial antigens. However, many of the same studies showing maternal infection as a risk factor make the same conclusion about paternal infection (Table 4), so that the relative importance of biological, vis-à-vis environmental, risk factors still remains uncertain (Ottesen et al. 1981).

Perhaps most important in our analysis and growing understanding of LF infection in children are the questions of what *disease* is caused by these infections and how reversible it is with treatment. Interestingly, almost all of the overt clinical disease reported in children is in those >10 years of age (Table 6). Whether this observation reflects only the length of time it takes to damage lymphatic systems sufficiently to express overt clinical disease or whether there

is something 'special' about post-pubertal individuals that facilitates the development of overt disease (lymphoedema or hydrocoele) in the presence of underlying lymphatic damage is not clear. What is clear, however, is that while these 'classic' consequences of lymphatic dysfunction are not normally seen – some would argue, never seen (Dreyer et al. 2000) in the pre-pubertal years – other clinical manifestations of LF *are* seen in younger-age children. Most well documented is adenopathy which can be chronic, painless and clinically indistinguishable from neoplasia, tuberculosis and other such diagnoses that have been frequently applied to this presentation of LF (Cooray 1960; Jungmann & Figueredo-Silva 1989; Amaral et al. 1994; Figueredo-Silva et al. 1994; Faris et al. 1998; Dreyer et al. 1999b, 2001). Similarly, acute episodes of adenitis or adenolymphangitis can be seen in children of all age groups, but specific diagnostic criteria for differentiating LF from other causes of this clinical presentation have not yet been established.

In addition to the overt clinical manifestations of LF in childhood recognized previously (Table 6), after the development of ultrasonographic techniques to detect intralymphatic live adult worms (Amaral et al. 1994), it has been possible to define distinct subclinical pathology in the lymphatics of infected children (Dreyer et al. 1999a). As it is this subclinical pathology that leads to the development of overt disease, understanding these early lesions and defining their response to treatment should be of highest priority for future research efforts.

Thus far little has been written specifically on the treatment of LF in children, especially the clinical manifestations. The new, recently codified approaches to managing filarial lymphoedema and hydrocoele in adults (Addiss & Dreyer 2000; Dreyer et al. 2000) have also been used successfully with children, although little description of this has yet been published. A recent account of two young girls (6 and 10 years of age) presenting with adenopathy shown on ultrasound to be caused by living adult filarial worms, recorded the regression of both overt and identifiable subclinical pathology after diethylcarbamazine (DEC) treatment in one child and after spontaneous death of the adult parasite in the other (Dreyer et al. 2001). Formal studies are needed to extend these case-report observations and determine how effective the treatment of such children can be, either individually in the clinic or as part of community-wide mass drug administration campaigns to eliminate LF (Ottesen 2000).

Indeed, although we now recognize that LF is a frequent and common infection of children in all LF-endemic areas and that it causes both subclinical lymphatic damage and eventual overt clinical disease, an enormous number of questions (both conceptual and practical) remains to be answered. The most immediate concern the optimal

approach to treatment and prevention, both of overt clinical disease and of the subclinical lymphatic damage of early infections. It is critically important to learn how to reverse these early lesions and thereby prevent future development of lymphoedema and hydrocoele in older children and adults. Treatment studies may be sufficient to define the reversibility of such lesions, but studies on the pathogenesis of lymphatic dysfunction are also necessary in order to provide the necessary insight for continuing to optimize therapeutic strategies in the future. It will also be important to identify whether or not the same renal pathology seen in microfilaraemic adults (Dreyer *et al.* 1992) is also a part of the clinical disease induced by LF in children. Further, as LF-induced lymphadenopathy and lymphadenitis still cannot be distinguished from the much more common viral and bacterial causes of these presentations, guidelines for the differential diagnosis of this problem in children must be established. Also, as already described with other filarial infections (Cooper *et al.* 1998), LF in children might alter their immunological responses either to other concurrent infections or to vaccine immunizations. As such possibilities are of critical public health importance, further studies on the immune responses of infected children to LF and other immunogens are extremely important.

Protecting children from LF infection and disease should be a primary goal of programmes to eliminate LF (Ottesen 2000). Studies to look at the value of the treatment regimens being advocated for LF elimination programmes to provide effective prophylaxis to children need to be undertaken. Similarly, the role of maternal infection as a risk factor for childhood infection should be explored, because a positive finding would make imperative the treatment of women of childbearing age if appropriate drug regimens could be established. Further, the definition of those immune parameters that could protect children from LF infection might offer a long-term ancillary tool for global efforts to eliminate LF that are based primarily on mass-drug administration. Finally, as children may well form the sentinel populations needed to assess the effectiveness of efforts to interrupt transmission during LF elimination programmes, it is important that the limits and usefulness of antigen detection methods to assess the acquisition of infection by young children be clearly defined.

Certainly, many questions remain unanswered, but it is clear already that LF infection in childhood is an issue that can no longer be disregarded. The best ways to treat and prevent infection must be established immediately, so that optimal care for the children in endemic areas can be assured. Not only should this care come from specific LF elimination programmes, but it should also come as a result of inclusion of this important childhood infection in programmes aimed at other health needs of school-age and pre-school age children. As many such programmes are currently active, it should be possible to achieve very significant additional health benefits from a very small added cost to these programmes. Indeed, this opportunity to coordinate the efforts to respond effectively to a broad range of childhood infections, including LF, now provides an essential public health challenge to all of those with concern for the health of children throughout the world.

Acknowledgements

References

Addiss DG & Dreyer G (2000) Treatment of lymphatic filariasis. In: *Lymphatic Filariasis* (ed. TB Nutman) Imperial College Press, London, pp. 151–199.

Alexander ND, Perry RT, Dimber ZB et al. (1999) Acute disease episodes in a *Wuchereria bancrofti*-endemic area of Papua New Guinea. *American Journal of Tropical Medicine and Hygiene* **61**, 319–324.

Amaral F, Dreyer G, Figueredo-Silva J et al. (1994) Live adult worms detected by ultrasonography in human Bancroftian filariasis. *American Journal of Tropical Medicine and Hygiene* **50**, 753–757.

Bai KI, Sastry VN & Subbaiha DV (1977) Chyluria in childhood. *Indian Paediatrics* **14**, 229–230.

Bloomfield RD, Suarez JR & Malangit AC (1978) Transplacental transfer of Bancroftian filariasis. *Journal of the National Medical Association* **70**, 597–598.

Brabin L (1990) Sex differentials in susceptibility to lymphatic filariasis and implications for maternal child immunity. *Epidemiology and Infection* **105**, 335–353.

Chanteau S, Glaziou P, Plichart C et al. (1995) *Wuchereria bancrofti* filariasis in French Polynesia: age-specific patterns of microfilaremia, circulating antigen, and specific IgG and IgG4 responses according to transmission level. *International Journal of Parasitology* **25**, 81–85.

Cooper PJ, Espinel I, Paredes W et al. (1998) Impaired tetanus-specific cellular and humoral responses following tetanus vaccination in human onchocerciasis: a possible role for interleukin-10. *Journal of Infectious Diseases* **178**, 1133–1138.

Cooray GH (1960) Some observations on filarial infection in Ceylon with special reference to its histopathology. *Indian Journal of Malariology* **14**, 617–632.

Day KP, Grenfell B, Spark R et al. (1991b) Age specific patterns of change in the dynamics of *Wuchereria bancrofti* infection in Papua New Guinea. *American Journal of Tropical Medicine and Hygiene* **44**, 518–527.

Dimock KA, Eberhard ML & Lammie PJ (1996) Th1-like antifilarial immune responses predominate in antigen-negative persons. *Infection and Immunity* 64, 2962–2967.

Dissanayake S, de Silva LV & Ismail MM (1980) IgM antibody to filarial antigens in human cord blood: possibility of transplacental infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 74, 542–544.

Dreyer G, Ottesen EA, Galdino E et al. (1992) Renal abnormalities in microfilaremic patients with Bancroftian filariasis. *American Journal of Tropical Medicine and Hygiene* 46, 745–751.

Dreyer G, Norões J, Addiss D et al. (1999a) Bancroftian filariasis in a paediatric population: an ultrasonographic study. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 93, 1–4.

Dreyer G, Santos A, Norões J et al. (1999b) Proposed panel of diagnostic criteria, including the use of ultrasound, to refine the concept of 'endemic normals' in lymphatic filariasis. *Tropical Medicine and International Health* 4, 575–579.

Dreyer G, Norões J, Figueredo-Silva J & Piessens WF (2000) Pathogenesis of lymphatic disease in bancroftian filariasis. *Parasitology Today* 16, 544–548.

Dreyer G, Figueredo-Silva J, Carvalho K et al. (2001) Lymphatic filariasis in children: adenopathy and its evolution in two young girls. *American Journal of Tropical Medicine and Hygiene* 64 (in press).

Eberhard ML, Hitch WL, McNeeley DF et al. (1993) Transplacental transmission of *Wuchereria bancrofti* in Haitian women. *Journal of Parasitology* 79, 62–66.

Faris R, Hussain O, El Setouhy M et al. (1998) Bancroftian filariasis in Egypt: visualization of adult worms and subclinical lymphatic pathology by scrotal ultrasound. *American Journal of Tropical Medicine and Hygiene* 59, 864–867.

Figueredo-Silva J, Dreyer G, Guimaraes K et al. (1994) Bancroftian lymphadenopathy: absence of eosinophils in tissues despite peripheral blood hypereosinophilia. *Journal of Tropical Medicine and Hygiene* 97, 55–59.

Forsyth KP, Spark R, Kazura J et al. (1985) A monoclonal antibody-based immunoradiometric assay for detection of circulating antigen in Bancroftian filariasis. *Journal of Immunology* 134, 1172–1177.

Gupta S, Prui RK & Sen SB (1967) Chyluria in childhood. *Indian Paediatrics* 4, 445–450.

Gyapong JO, Gyapong M & Adjei S (1996) The epidemiology of acute adenolymphangitis due to lymphatic filariasis in northern Ghana. *American Journal of Tropical Medicine and Hygiene* 54, 591–595.

Hightower AW, Lammie PJ & Eberhard ML (1993) Maternal filarial infection – a persistent risk factor for microfilaremia in offspring? *Parasitology Today* 9, 418–421.

Hitch WL, Lammie PJ, Walker EM et al. (1991b) Antifilarial cellular responses detected in a Haitian paediatric population by use of a microblastogenesis assay. *Journal of Infectious Diseases* 164, 811–813.

Hitch WL, Eberhard ML & Lammie PJ (1997) Investigation of the influence of maternal infection with *Wuchereria bancrofti* on the humoral and cellular responses of neonates to filarial antigens. *Annals of Tropical Medical Parasitology* 91, 461–469.

Jungmann P & Figueredo-Silva J (1989) Bancroftian filariasis in the metropolitan area of Recife (Pernambuco State, Brazil): clinical aspects in histologically diagnosed cases. *Brazilian Journal of Medical Biological Research* 22, 687–690.

Jungmann P, Figueredo-Silva J & Dreyer G (1991) Bancroftian lymphadenopathy: a histopathologic study of fifty-eight cases from Northeastern Brazil. *American Journal of Tropical Medicine and Hygiene* 45, 325–331.

Kohli V, Gulati S & Kuman L (1994) Filarial chyluria. *Indian Paediatrics* 31, 451–454.

Kumaraswami V (2000) The clinical manifestation of lymphatic filariasis. In: *Lymphatic Filariasis* (ed. TB Nutman) Imperial College Press, London, pp. 103–125.

Lammie PJ, Hitch WL, Walker Allen EM et al. (1991) Maternal filarial infection as risk factor for infection in children. *Lancet* 337, 1005–1006.

Lammie PJ, Hightower AW & Eberhard ML (1994) Age-specific prevalence of antigenemia in a *Wuchereria bancrofti*-exposed population. *American Journal of Tropical Medicine and Hygiene* 51, 348–355.

Lammie PJ, Reiss MD, Dimock KA et al. (1998) Longitudinal analysis of the development of filarial infection and antifilarial immunity in a cohort of Haitian children. *American Journal of Tropical Medicine and Hygiene* 59, 217–221.

Magnussen P, Makunde W, Simonsen PE et al. (1995) Chronic pulmonary disorders, including tropical pulmonary eosinophilia, in villages with endemic lymphatic filariasis in Tanga region and in Tanga town, Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 89, 406–409.

Maizels RM, Sartono E, Kurniawan A et al. (1995) T-cell activation and the balance of antibody isotypes in human lymphatic filariasis. *Parasitology Today* 11, 50–56.

More SJ & Copeman DB (1990) A highly specific and sensitive monoclonal antibody-based ELISA for the detection of circulating antigen in Bancroftian filariasis. *Tropical Medical Parasitology* 41, 403–406.

Nicolas L (1997) New tools for diagnosis and monitoring of bancroftian filariasis parasitism: the Polynesian experience. *Parasitology Today* 13, 370–375.

Nicolas L, Langy S, Plichart C et al. (1999) Filarial antibody responses in *Wuchereria bancrofti* transmission area are related to parasitological but not clinical status. *Parasite Immunology* 21, 73–80.

Ottesen EA (2000) The global programme to eliminate lymphatic filariasis. *Tropical Medicine and International Health* 5, 591–594.

Ottesen EA, Weller PF & Heck L (1997) Specific cellular immune unresponsiveness in human filariasis. *Immunology* 33, 413–421.

Ottesen EA, Mendell NR, MacQueen JM et al. (1981) Familial predisposition to filarial infection – not linked to HLA-A or -B locus specificities. *Acta Tropica* 38, 205–216.

Raghupathy P & Date A (1982) Chyluria of possible filarial aetiology in a South Indian child. *Annals of Tropical Paediatrics* 2, 199–200.

Ramzy RM, Hafez ON, Gad AM et al. (1994) Efficient assessment of filariasis endemicity by screening for filarial antigenaemia in a

sentinel population. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **88**, 41–44.

Rao KR, Venkatanaryana M, Naidu YD *et al.* (1984) Transplacental transmission in bancroftian filariasis. *Indian Journal of Medical Research* **79**, 495–496.

Sanjeevi CB & Narayanan PR (1989) Antifilarial and anti PPD antibodies in cord blood. *Indian Journal of Pediatrics* **56**, 207–211.

Sartono E, Kruize YC, Kurniawan A *et al.* (1997) Depression of antigen-specific interleukin-5 and interferon-γ responses in human lymphatic filariasis as a function of clinical status and age. *Journal of Infectious Diseases* **175**, 1276–1280.

Simonsen PE, Lemnge MM, Msangeni HA *et al.* (1996) Bancroftian filariasis: the patterns of filarial-specific immunoglobulin G1 (IgG1), IgG4, and circulating antigens in an endemic community of northeastern Tanzania. *American Journal of Tropical Medicine and Hygiene* **55**, 69–75.

Steel C, Guinea A, McCarthy JS *et al.* (1994) Long-term effect of prenatal exposure to maternal microfilaraemia on immune responsiveness to filarial parasite antigens. *Lancet* **343**, 890–893.

Steel C, Guinea A & Ottesen E (1996) Evidence for protective immunity to bancroftian filariasis in the Cook Islands. *Journal of Infectious Diseases* **174**, 598–605.

Steel C, Ottesen EA & Nutman TB (2001) Worm burden and host responsiveness in *Wuchereria bancrofti* infection: use of antigen detection to refine earlier assessments from the South Pacific. *American Journal of Tropical Medicine and Hygiene* **64** (in press).

Wamae CN, Lammie PJ & Muttunga JN (1995) Bancroftian filariasis: profile of serum antifilarial antibody and circulating parasite antigen. *East African Medical Journal* **72**, 492–494.

Weil GJ, Hussain R, Kumaraswami V *et al.* (1983) Prenatal allergic sensitization to helminth antigens in offspring of parasite-infected mothers. *Journal of Clinical Investigation* **71**, 1124–1129.

Weil GJ, Jain DC, Santhanam S *et al.* (1987) A monoclonal antibody-based enzyme immunoassay for detecting parasite antigenemia in Bancroftian filariasis. *Journal of Infectious Diseases* **156**, 350–355.

Weil GJ, Ramzy RM, Chandrashekar R *et al.* (1996) Parasite antigenaemia without microfilaraemia in Bancroftian filariasis. *American Journal of Tropical Medicine and Hygiene* **55**, 333–337.

Weil GJ, Lammie PJ & Weiss N (1997) The ICT filariasis test: a rapid-format antigen test for diagnosis of Bancroftian filariasis. *Parasitology Today* **13**, 401–404.

Weil GJ, Ramzy RM, El Setouhy M *et al.* (1999) A longitudinal study of Bancroftian filariasis in the Nile Delta of Egypt: baseline data and one-year follow-up. *American Journal of Tropical Medicine and Hygiene* **61**, 53–58.

Appendix I

This review was originally written in Vancouver format, i.e. with references cited as numbers in the text and with a bibliography ordered by ascending numbers. TM & IH uses Harvard format, but in the interest of better readability we retained the Vancouver system where the authors described single characteristics of large groups of papers analysed. For technical reasons those papers which are not referenced in the text in Harvard style must appear separately, in an appendix rather than being part of the References section.

Addiss DG, Eberhard ML & Lammie PJ (1994) 'Filarial' adenolymphangitis without filarial infection. *Lancet* **343**, 597.

Alexander ND & Grenfell BT (1999) The effect of pregnancy on *Wuchereria bancrofti* microfilarial load in humans. *Parasitology* **119**, 151–156.

Alexander ND, Kazura JW, Bockarie MJ *et al.* (1998) Parental infection confounded with local infection intensity as risk factors for childhood microfilaraemia in bancroftian filariasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **92**, 23–24.

Beye HK, Edgar SA, Kessel JF *et al.* (1952) Preliminary observations on the prevalence, clinical manifestation and control of filariasis in the Society Islands. *American Journal of Tropical Medicine and Hygiene* **1**, 637–661.

Blumberg B, McGiff J & Guicherit I (1951) Filariasis in Moengo (Surinam) in 1950. *Doc Neerl Indones Morb Trop* **3**, 368–372.

Braga C, Albuquerque MF, Silva MR *et al.* (1998) Risk factors for the occurrence of bancroftian filariasis infection in children living in endemic areas of northeast Brazil. *Journal of Tropical Paediatrics* **44**, 87–91.

Briceno Rossi AL & Hewitt R (1949) Treatment of Bancroftian filariasis with 'Hetrazan' in Puerto Cabello, Venezuela. *Southern Medical Journal* **42**, 978–981.

Burnett GF & Mataika JU (1961) Mass-administration of diethylcarbamazine citrate in preventing transmission of aperiodic human filariasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **55**, 178–187.

Campello TR, Ferreira RS, Pires ML *et al.* (1993) A study of placentas from *Wuchereria bancrofti* microfilaraemic and amicrofilaraemic mothers. *Journal of Tropical Medicine and Hygiene* **96**, 251–255.

Chadee DD, Tilluckdharry CC, Rawlins SC *et al.* (1995) Mass chemotherapy with diethylcarbamazine for the control of Bancroftian filariasis: a twelve-year follow-up in northern Trinidad, including observations on *Mansonella ozzardi*. *American Journal of Tropical Medicine and Hygiene* **52**, 174–176.

Chandra G & Hati AK (1996) Filariasis survey in a rural area of West Bengal. *Journal of Communicable Disease* **28**, 206–208.

Chandrashekar R, Rao UR & Subrahmanyam D (1990) Antibody-mediated cytotoxic effects *in vitro* and *in vivo* of rat cells on infective larvae of Brugia malayi. *International Journal of Parasitology* **20**, 725–730.

Chaturvedi P, Advani B, Khan AA *et al.* (1991) Congenital filarial lymphoedema. *Indian Journal of Paediatrics* **58**, 378–380.

Chaturvedi P, Gawdi AM, Parkhe K *et al.* (1993) Arthritis in children: an occult manifestation of Bancroftian filariasis. *Indian Journal of Paediatrics* **60**, 803–807.

Chaturvedi P, Harinath BC, Reddy MV et al. (1995) Filarial antibody detection in suspected occult filariasis in children in an endemic area. *Journal of Tropical Paediatrics* 41, 243–245.

Chlebowsky HO & Zielke E (1980) Studies on Bancroftian filariasis in Liberia, West Africa. III. Efficacy of repeated treatment with diethylcarbamazine and vector control on the microfilarial reservoir in a rural population. *Tropenmedizin und Parasitologie* 31, 181–193.

Das PK, Sirvidya A, Vanamail P et al. (1997) *Wuchereria bancrofti* microfilaraemia in children in relation to parental infection status. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 91, 677–679.

Day KP, Spark R, Garner P et al. (1991a) Serological evaluation of the macrofilaricidal effects of diethylcarbamazine treatment in bancroftian filariasis. *American Journal of Tropical Medicine and Hygiene* 44, 528–535.

De Rook H (1959) Filariasis in the village of Inanwatan (South Coast of the Vogelkop, Netherlands New Guinea). *Tropical Geographical Medicine* 11, 313–331.

Desowitz RS & Hitchcock JC (1974) Hyperendemic bancroftian filariasis in the Kingdom of Tonga: the application of the membrane filter concentration technique to an age-stratified blood survey. *American Journal of Tropical Medicine and Hygiene* 23, 877–879.

Dunyo SK, Appawu M, Nkrumah F et al. (1996) Lymphatic filariasis on the coast of Ghana. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 90, 634–638.

Dzodzomenyo M, Dunyo SK, Ahorlu CK et al. (1999) Bancroftian filariasis in an irrigation project community in southern Ghana. *Tropical Medicine and International Health* 4, 13–18.

Estambale BB, Simonsen PE, Knight R et al. (1994) Bancroftian filariasis in Kwale District of Kenya. I. Clinical and parasitological survey in an endemic community. *Annals of Tropical Medical Parasitology* 88, 145–151.

Freedman DO, Nutman TB & Ottesen EA (1989) Protective immunity in bancroftian filariasis. Selective recognition of a 43-kD larval stage antigen by infection-free individuals in an endemic area. *Journal of Clinical Investigation* 83, 14–22.

Grove DI, Valeza FS & Cabrera BD (1978) Bancroftian filariasis in a Philippine village: clinical, parasitological, immunological, and social aspects. *Bulletin of the World Health Organization* 56, 975–984.

Gubler DJ & Bhattacharya NC (1974) A quantitative approach to the study of Bancroftian filariasis. *American Journal of Tropical Medicine and Hygiene* 23, 1027–1036.

Gyapong JO, Omane-Badu K & Webber RH (1998) Evaluation of the filter paper blood collection method for detecting Og4C3 circulating antigen in bancroftian filariasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 92, 407–410.

Haarbrink M, Terhell A, Abadi K et al. (1995) IgG4 antibody assay in the detection of filariasis. *Lancet* 346, 853–854.

Hairston NG & Meillon BD (1968) On the inefficiency of transmission of *Wuchereria bancrofti* from mosquito to human host. *Bulletin of the World Health Organization* 38, 935–941.

Hassan MY (1959) The filariasis campaign in Kedah. *Medical Journal of Malaysia* 14, 36–46.

Helmy H, Weil GJ, Faris R et al. (2000) Human antibody responses to *Wuchereria bancrofti* infective larvae. *Parasite Immunology* 22, 89–96.

Hitch WL, Lammie PJ & Eberhard ML (1989) Heightened anti-filarial immune responsiveness in a Haitian pediatric population. *American Journal of Tropical Medicine and Hygiene* 41, 657–663.

Hitch WL, Hightower AW, Eberhard ML et al. (1991a) Analysis of isotype-specific antifilarial antibody levels in a Haitian pediatric population. *American Journal of Tropical Medicine and Hygiene* 44, 161–167.

Institute Against Parasitic Diseases of Guangdong Province GPC (1998) *The Filariasis Situation in Guangdong Province, China.* IAPD, Guangdong, pp. 39–50 (three studies included in this publication).

Kazura JW, Spark R, Forsyth K et al. (1984) Parasitologic and clinical features of bancroftian filariasis in a community in East Sepik Province, Papua New Guinea. *American Journal of Tropical Medicine and Hygiene* 33, 1119–1123.

Kazura JW, Bockarie M, Alexander N et al. (1997) Transmission intensity and its relationship to infection and disease due to *Wuchereria bancrofti* in Papua New Guinea. *Journal of Infectious Diseases* 176, 242–246.

Kenny M & Hewitt R (1949) Treatment of Bancroftian filariasis with Hetrazan in British Guiana. *American Journal of Tropical Medicine* 29, 89–114.

Langhammer J, Birk HW & Zahner H (1997) Renal disease in lymphatic filariasis: evidence for tubular and glomerular disorders at various stages of the infection. *Tropical Medicine and International Health* 2, 875–884.

Maciel A, Rocha A, Marzochi KB et al. (1996) Epidemiological study of Bancroftian filariasis in Recife, Northeastern Brazil. *Memorias Instituto Oswaldo Cruz* 91, 449–455.

Mahanty S, Day KP, Alpers MP et al. (1994) Antifilarial IgG4 antibodies in children from filaria-endemic areas correlate with duration of infection and are dissociated from antifilarial IgE antibodies. *Journal of Infectious Diseases* 170, 1339–1343.

Maizels RM & Lawrence RA (1991) Immunological tolerance: the key feature in human filariasis? *Parasitology Today* 7, 271–276.

Marshall CL & Yasukawa K (1966) Control of bancroftian filariasis in the Ryukyu Islands: preliminary results of mass administration of diethylcarbamazine. *American Journal of Tropical Medicine and Hygiene* 15, 934–942.

McCarthy DD (1959) Filariasis in the Cook Islands. *New Zealand Medical Journal* 58, 738–748.

McGregor IA, Hawking F & Smith DA (1952) The control of filariasis with Hetrazan: a field trial in a rural village (Keneba) in the Gambia. *British Medical Journal* 2, 908–918.

McMahon JE, Magayauka SA, Kolstrup N et al. (1981) Studies on the transmission and prevalence of Bancroftian filariasis in four coastal villages of Tanzania. *Annals of Tropical Medical Parasitology* 75, 415–431.

Meyrowitsch DW, Simonsen PE & Makunde WH (1995) Bancroftian filariasis: analysis of infection and disease in five endemic communities of north-eastern Tanzania. *Annals of Tropical Medical Parasitology* 89, 653–663.

Michael E, Bundy DA & Grenfell BT (1996) Re-assessing the global prevalence and distribution of lymphatic filariasis. *Parasitology* **112**, 409–428.

Ottesen EA (1989) Filariasis now. *American Journal of Tropical Medicine and Hygiene* **41**, 9–17.

Ottesen EA (1992) The Wellcome Trust lecture. Infection and disease in lymphatic filariasis: an immunological perspective. *Parasitology* **104** (Suppl.), S71–S79.

Ottesen EA, Weller PF, Lunde MN *et al.* (1982) Endemic filariasis on a Pacific Island. II. Immunologic aspects: immunoglobulin, complement, and specific antifilarial IgG, IgM, and IgE antibodies. *American Journal of Tropical Medicine and Hygiene* **31**, 953–961.

Ottesen EA, Duke BO, Karam M *et al.* (1997) Strategies and tools for the control/elimination of lymphatic filariasis. *Bulletin of the World Health Organization* **75**, 491–503.

Pani SP, Balakrishnan N, Srividya A *et al.* (1991) Clinical epidemiology of bancroftian filariasis: effect of age and gender. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **85**, 260–264.

Paniagua F, Garces JL, Granados C *et al.* (1983) Prevalence of bancroftian filariasis in the city of Puerto Limon and the province of Limon, Costa Rica. *American Journal of Tropical Medicine and Hygiene* **32**, 1294–1297.

Panicker KN, Krishnamoorthy K, Sabesan S *et al.* (1991) Comparison of effects of mass annual and biannual single dose therapy with diethylcarbamazine for the control of Malayan filariasis. *Southeast Asian Journal of Tropical Medicine and Public Health* **22**, 402–411.

Peel E & Van Oye E (1950) Transplacental transmission of microfilariae (negative findings). *Annales de la Societe Belge de Medecine Tropicale* **30**, 59–64.

Putrali J, Kaleb YM, Van Peenen PF *et al.* (1975) Mass treatment of Malayan filariasis in the Gumbasa irrigation area of Central Sulawesi. *Southeast Asian Journal of Tropical Medicine and Public Health* **6**, 206–210.

Raccurt CP, Mojon M & Hodges WH (1984) Parasitological, serological, and clinical studies of *Wuchereria bancrofti* in Limbe, Haiti. *American Journal of Tropical Medicine and Hygiene* **33**, 1124–1129.

Rajagopalan PK, Das PK, Subramanian S *et al.* (1989) Bancroftian filariasis in Pondicherry, South India: 1. Pre-control epidemiological observations. *Epidemiology and Infection* **103**, 685–692.

Ramaiah KD, Ramu K, Kumar KN *et al.* (1996) Epidemiology of acute filarial episodes caused by *Wuchereria bancrofti* infection in two rural villages in Tamil Nadu, South India. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **90**, 639–643.

Sabry M (1991) A quantitative approach to the relationship between *Wuchereria bancrofti* microfilaria counts by venous blood filtration and finger-prick blood films. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **85**, 506–510.

Sajidiman H, Desowitz RS & Darwis F (1975) Studies on filariasis in the Pacific. 5. *Brugia malayi* filariasis in treated and untreated populations of South Borneo. *Southeast Asian Journal of Tropical Medicine and Public Health* **6**, 190–194.

Sasa M (1963) Pilot experiments in the control of bancroftian filariasis in Japan and Ryukyu. *Bulletin of the World Health Organization* **28**, 437–454.

Sasa M & Mitsui G (1964) Frequency distribution of the microfilarial densities of people in the endemic areas of Bancroftian filariasis in the Amami Islands, South Japan. *Japanese Journal of Experimental Medicine* **34**, 17–28.

Simonsen PE & Meyrowitsch DW (1998) Bancroftian filariasis in Tanzania: specific antibody responses in relation to long-term observations on microfilaremia. *American Journal of Tropical Medicine and Hygiene* **59**, 667–672.

Simonsen PE, Meyrowitsch DW, Makunde WH *et al.* (1995) Bancroftian filariasis: the pattern of microfilaremia and clinical manifestations in three endemic communities of Northeastern Tanzania. *Acta Tropica* **60**, 179–187.

Sinha AP, Nanda DK, Singh MV *et al.* (1959) Day and night filaria surveys in some persons with periodic *W. bancrofti* before and after diethylcarbamazine therapy. *Indian Journal of Malariology* **13**, 159–162.

Terhell AJ, Houwing-Duistermaat JJ, Ruiterman Y *et al.* (2000) Clustering of *Brugia malayi* infection in a community in South-Sulawesi, Indonesia. *Parasitology* **120**, 23–29.

Tewari SC, Hiriyan J & Reuben R (1995) Epidemiology of subperiodic *Wuchereria bancrofti* infection in the Nicobar Islands, India. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **89**, 163–166.

Turner P, Copeman B, Gerisi D *et al.* (1993) A comparison of the Og4C3 antigen capture ELISA, the Knott test, an IgG4 assay and clinical signs, in the diagnosis of Bancroftian filariasis. *Tropical Medical Parasitology* **44**, 45–48.

Van Dijk WJOM (1961) Mass treatment of *Wuchereria bancrofti* filariasis with diethylcarbamazine: a trial at Inanwatan, Western New Guinea. *Tropical Geographical Medicine* **13**, 143–159.

Wamae CN, Gatika SM, Roberts JM *et al.* (1998) *Wuchereria bancrofti* in Kwale District, Coastal Kenya: patterns of focal distribution of infection, clinical manifestations and anti-filarial IgG responsiveness. *Parasitology* **116**, 173–182.

Weller PF, Ottesen EA, Heck L *et al.* (1982) Endemic filariasis on a Pacific island. I. Clinical, epidemiologic, and parasitologic aspects. *American Journal of Tropical Medicine and Hygiene* **31**, 942–952.

WHO (1993) Expert committee on filariasis lymphatic filariasis: diagnosis and pathogenesis. *Bulletin of the World Health Organization* **71**, 135–141.

Yazdanbakhsh M (1990) Molecular biological approaches towards immunodiagnosis of filariasis. *Parasitology Today* **6**, 207–208.

Zhang S, Li B & Weil GJ (1999) Human antibody responses to *Brugia malayi* antigens in brugian filariasis. *International Journal of Parasitology* **29**, 429–436.

Zielke E & Chlebowsky HO (1979) Studies on Bancroftian filariasis in Liberia, West Africa. I. Distribution and prevalence in the north-western savanna area. *Tropenmedizin und Parasitologie* **30**, 91–96.