The Role of Albendazole in Programmes to Eliminate Lymphatic Filariasis

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Citing earlier advances in the treatment of lymphatic filariasis [particularly the effectiveness of single-dose diethylcarbamazine (DEC) in reducing microfilaraemia and its enhanced effectiveness when co-administered with single-dose ivermectin], Eric Ottesen, Mahroof Ismail and John Horton consider recent studies on the antifilarial activity of albendazole that have led to the current recommendations for its use in single-dose regimens in conjunction with either DEC or ivermectin for large-scale control/elimination programmes. Furthermore, the potential of albendazole as a macrofilaricide for treating individual patients with lymphatic filarial infections is emphasized as one of a number of important research questions that remain to be explored.

The introduction of dramatically effective treatment regimens to decrease microfilaraemia has been primarily responsible for the recent designation of lymphatic filariasis as a disease that can be eliminated[1] and for the resolution by the World Health Assembly to eliminate lymphatic filariasis as a public health problem globally[2]. Granted, there are important biological criteria that help make elimination of this disease feasible; in particular, the lack of any animal reservoir either for *Wuchereria bancrofti* (responsible for 90% of lymphatic filariasis), or for most *Brugia* infections; and the fact that transmission of infection is inefficient, with no amplification of infection in the mosquito vectors[2]. Technical innovations too, have been important: most notably, a diagnostic test that is simple, sensitive and specific, and that is based on an anytime-of-day, finger-prick, antigen-detection test[3]. Nevertheless, without effective treatment tools, elimination of lymphatic filariasis would not even be conceivable.

New treatment strategies

The first important breakthrough in the development of new treatment regimens came from early studies to determine whether single-dose ivermectin was as effective and safe a microfilaricide in lymphatic filariasis as it had already proved to be for onchocerciasis[4]. Although the answer to this question was 'yes', of equal importance was the finding that single doses of the older medication, diethylcarbamazine (DEC), had long-term effectiveness (ie. reduction of blood microfilaria levels for up to one year after treatment) that was equal, not only to that of single-dose ivermectin[5–7], but also to that of the two-week course of DEC[8] that had long been recommended as necessary for treating lymphatic filariasis! Thus, the use of single-dose, once-yearly treatment to reduce microfilaraemia in endemic populations was recognized as being an effective strategy throughout the world, just as it had been shown to be decades ago in many Pacific Island countries, where single-dose DEC had been the mainstay of filariasis control programmes[9,10].

The next major advance was the recognition that two-drug treatment (initially, single doses of DEC and of ivermectin, administered concurrently) was significantly more effective than treatment with either drug alone, yielding up to 99% clearance of microfilaraemia up to one year after treatment[4,11,12]. These findings were especially welcome because they raised the possibility that this two-drug regimen might effectively interrupt transmission of lymphatic filariasis. However, significant concerns remained, the most important of which was that DEC makes any multidrug regimen unsafe for community-wide use in Africa or elsewhere where onchocerciasis or loiasis might coexist with bancroftian filariasis; the reason being that DEC can induce severe (even fatal) reactions in patients with either of these other infections; this is a result of the excessively rapid killing of the microfilariae, with consequent severe inflammatory reactions in heavily infected patients[13,14]. In addition, ivermectin was a new drug, then unregistered for use in lymphatic filariasis, and not widely available other than through the Mectizan® Donation Program for the control of onchocerciasis in Africa and other endemic regions[15].

Subsequent studies established that: (1) albendazole [already widely recognized as a powerful antiparasitic agent for many other types of infection (Table 1)] co-administered with ivermectin was equally effective as DEC in combination with ivermectin against

Table 1. Broad antiparasite effectiveness of albendazole or ivermectin used alone as a single dose[a,b]

Parasite/infection	Albendazole	Ivermectin
Ascaris	4+	4+
Trichuris	1+/3+	1+/3+
Hookworm	4+	1+
Strongyloides	2+	4+
Larva migrans (cutaneous)	3+	4+
Onchocerciasis	0/1+	4+[c]
Cysticercosis	[d]	0
Echinococcosis	[d]	0
Giardia/Trichomonads	[d]	0
Microsporidia/Cryptosporidia	[d]	0
Lice	0	3+
Scabies	0	4+

[a] Albendazole dose, 400 mg (for each person); ivermectin dose, 150–200 $\mu g\ kg^{-1}$.

[b] Qualitative scoring system 0–4+; 0, no recognized activity; 4+, highly effective in killing that parasite or causing very marked reductions (>95%) in stool egg counts (for intestinal helminths).

[c] Killing effect against microfilariae only.

[d] Effective against these infections but requiring multiple doses.

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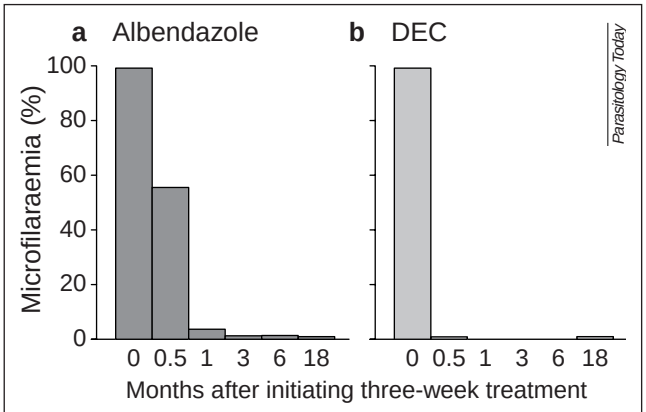

Fig. 1. Microfilarial clearance induced by three weeks of treatment in adult men with *Wuchereria bancrofti* infection using either high-dose albendazole (800 mg day^{-1}; *N* = 15) (a) or standard-dose diethylcarbamazine (DEC; 6 mg kg^{-1} per day) (*N* = 12) (b). Values for each time point are geometric means of each patient's residual microfilaraemia (expressed as a percentage of his pretreatment level). All patients had microfilaria counts >100 ml^{-1}, and the mean values for the two groups were comparable [633 ± 150 (SEM) for the albendazole group and 566 ± 120 for the DEC group]. Microfilaraemia was quantified by counting parasites in 60 µl of blood. Although clearance was more rapid with DEC, there was no significant difference in microfilarial clearance between the groups at three, six or 18 months after treatment. Note that at 18 months, only ten patients per group were available for follow-up. (Figure redrawn using data from Ref. 20.)

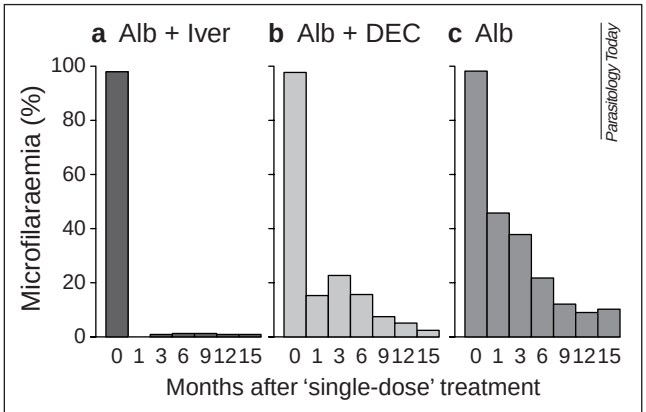

Fig. 2. Microfilarial clearance induced by 'single-dose' treatment of patients with *Wuchereria bancrofti* infection using single administrations of albendazole (Alb; 600 mg) and ivermectin (Iver; 400 µg kg^{-1}) given together (*N* = 13) (a), albendazole (600 mg) plus diethylcarbamazine (DEC; 6 mg kg^{-1}) given together (*N* = 13) (b), or albendazole (600 mg) alone (*N* = 12) (c). Values for each time point are geometric means of each patient's residual microfilaraemia (expressed as a percentage of his pretreatment level; these ranged from 67 to 8280 microfilariae per ml among the patients but were comparable for the three study groups). Microfilaraemia was quantified by Nucelepore® filtration of 1 ml of blood. At 15 months, there was no significant difference between the microfilarial reductions in the two groups receiving two-drug treatment (Alb + Iver or Alb + DEC), but the reductions in both of these groups were significantly greater than that in the group receiving albendazole alone. (Figure redrawn using data from Ref. 17.)

W. bancrofti infection[16,17] (and, thus, provided a two-drug regimen that could be used with much greater safety in Africa); and (2) albendazole could also be used safely in combination with DEC to treat lymphatic filariasis elsewhere in the world[18]. All of the treatment tools necessary for developing a global strategy to eliminate lymphatic filariasis by interrupting transmission[18] were then available.

The use of albendazole in lymphatic filariasis

While earlier work had shown albendazole to be effective against brugian filariasis in laboratory animals[19], Jayakody *et al.*[20] conducted the first formal study of the effectiveness of albendazole in *W. bancrofti* infections in humans. Following dosage regimens used earlier for treating echinococcosis[21], high doses of albendazole (400 mg twice daily) were given for three weeks to 15 microfilaraemic men, and the results were compared with those of 12 other microfilaraemic men of comparable age and weight treated for three weeks with DEC (6 mg kg^{-1} per day). Although the microfilaricidal activity of the albendazole regimen was dramatic (Fig. 1), 11 of these 15 men experienced a syndrome of acute pain, fever and inflammation of the scrotal sac and adjacent tissue, presumably induced by dying parasites. Similar reactions are seen in individuals after DEC treatment, and have been shown to reflect the macrofilaricidal activity of the drug[22,23]. However, the frequency and severity of reactions in these long-term, high-dose albendazole-treated individuals discouraged further study of this treatment regimen at the time, even though the effectiveness of albendazole against *W. bancrofti* infections had been clearly established.

Single doses of albendazole (600 mg), however, especially in combination with either ivermectin (400 µg kg^{-1}) or DEC (6 mg kg^{-1}), proved to have both long-term effectiveness and safety in decreasing microfilaraemia in *W. bancrofti* infections[17] (Fig. 2). These findings were corroborated at the lower drug dosages (albendazole, 400 mg; ivermectin, 200 (µg kg^{-1}) used commonly for treating intestinal helminths and onchocerciasis, respectively, both in 'short-term'[16] and in further long-term (M.M. Ismail *et al.*, unpublished) evaluations. Indeed, the effectiveness of these regimens may persist for more than two years (M.M. Ismail, unpublished), and additional studies are under way to define more precisely the full duration of the activity of these regimens, in order to reduce the levels of microfilariae in the blood to near zero.

Although the experience with *Brugia malayi* infections in humans is less extensive, the available evidence also indicates a microfilaricidal effectiveness of 98–99% one year after two-drug, single-dose treatment with either albendazole + DEC or ivermectin + DEC[39]; furthermore, the addition of albendazole or ivermectin resulted in no additional adverse reactions compared with DEC treatment alone.

In addition to the significant microfilaricidal activity induced by these drug combinations[11,12,16,17], circulating filarial antigen levels, presumably reflecting the presence of viable adult worms[24], were seen to fall progressively (Fig. 3), and most dramatically in the patients receiving the single-dose combination of albendazole + DEC[17]. DEC alone can be macrofilaricidal[22,23] and cause progressive reduction in circulating antigen levels[25–27], whereas ivermectin probably does not[17,27]. It is also clear from the earlier studies that prolonged high doses of albendazole are macrofilaricidal[20]; thus,

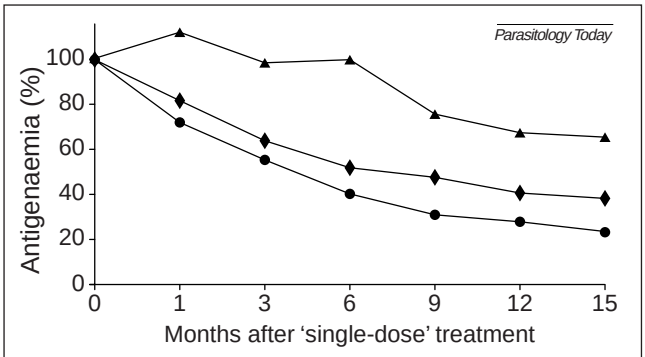

Fig. 3. Progressive reduction in antigenaemia (expressed as the mean percentage of the pretreatment antigen level for each patient) induced by 'single-dose' treatment of patients with *Wuchereria bancrofti* infections using albendazole alone (600 mg) (N = 12) (closed triangle), albendazole (600 mg) plus ivermectin (400 μg kg^{-1}) (N = 13) (closed diamond), or albendazole (600 mg) plus DEC (6 mg kg^{-1}) (N = 13) (closed circle). Antigen levels were consistently lower in the 'albendazole + DEC' group than in the 'albendazole + ivermectin' group over the entire 15 months of follow-up, and reached statistical significance at the 12- and 15-month time points. (Data redrawn from Ref. 17.)

the evidence from the circulating antigen levels in Fig. 3 suggests that even a single dose of albendazole (although perhaps not having discernible macrofilaricidal activity on its own) might significantly enhance the effects of DEC on adult worm viability or function.

'Beyond-filariasis' benefits

Albendazole is as effective and safe a drug for treating intestinal helminth infections (including hookworms) as any available, and it has effects on other parasites as well[28,29] (Table 1). Therefore, its inclusion in two-drug treatment regimens for the control or elimination of lymphatic filariasis might result in a public health impact far greater than the elimination of lymphatic filariasis alone, especially because the filariasis elimination strategy (described in detail in Ref. 18) calls for the community-wide treatment in endemic areas of all those 'at risk' of infection, not just those with documented filariasis. Furthermore, when albendazole is used in combination with ivermectin, the public health benefit is even broader. Not only is ivermectin itself effective against many intestinal nematodes and even ectoparasites, such as scabies and lice[30] (Table 1), it also 'complements' the activity of albendazole such that the effectiveness of the two drugs against *Trichuris* infections is significantly greater than that of either drug alone[31,32]. Furthermore, significantly enhanced nutritional benefits (height and weight gain in selected study populations) have been seen after treatment with this combination[31]. Extrapolation from earlier work predicts that such nutritional benefits from the concurrent effectiveness on geohelminth infections will also result in both greater cognitive development among children and greater productivity (ie. fewer work days lost among adults) in treated populations[33,34].

Because many of these 'ancillary benefits' of albendazole and ivermectin can be directly perceived by individuals receiving treatment for filariasis, the compliance within these at-risk populations targeted for lymphatic filariasis elimination should be appreciably enhanced. Indeed, enhanced compliance (and, hence, the number of successful treatments for all infected individuals, regardless of whether they recognize their filarial infections or are entirely asymptomatic) will be especially important, as the percentage of the population 'covered' is predictably the most important factor in determining the success of mass control/elimination programmes[35] (Box 1).

Box 1. Programme to Eliminate Lymphatic Filariasis (PELF)

The PELF aims: (1) to stop the spread of infection (ie. interrupt transmission); and (2) to alleviate the suffering of affected individuals (ie. control morbidity).

Interruption of filariasis transmission has been achieved previously through a number of strategies including community-wide treatment, selective treatment of diagnosed individuals and vector control efforts. Recent discovery of the dramatic, prolonged reductions in microfilaraemia induced by two-drug, single-dose treatment regimens [selecting among albendazole, diethylcarbamazine (DEC) and ivermectin] has led to the development of a new elimination strategy based on once-yearly, two-drug treatment intervention during 4–6 years for entire populations where lymphatic filariasis is endemic. Although both albendazole and DEC have some macrofilaricidal effectiveness, the strategy is based primarily on the intent to reduce microfilaraemia in the community to levels below which transmission cannot be sustained, and to keep it at these levels for the duration of fecundity in the adult worms (estimated at 4–6 years).

Providing tremendous impetus to this initiative has been the recent (1998) decision by the global healthcare company SmithKline Beecham to collaborate with the WHO in the lymphatic filariasis elimination effort through the donation of a number of important resources but, most especially, all of the albendazole needed to ensure the success of the elimination programme worldwide. Even more recent is the decision by Merck & Co, Inc. to support this programme and the WHO's efforts to eliminate lymphatic filariasis by expanding their Mectizan® (ivermectin) Donation Program for onchocerciasis control to include treatment of lymphatic filariasis in Africa, where onchocerciasis may be coendemic. These donations have brought the cost of the medications required for this programme to zero or near zero (cost of DEC currently is US $0.01–0.02 per person). The creation of additional partnerships with other private, public and international organizations has strengthened further the prospects for success of these lymphatic filariasis elimination efforts.

To alleviate the suffering resulting from lymphatic filariasis, efforts must be made to educate communities and affected patients about the recent discovery of the enormous value that intensive local hygiene has, both for improving the damage that has already occurred and for preventing the debilitating acute episodes of inflammation that accompany and exacerbate this damage. The technical approaches to achieving this goal of the PELF are distinctly different from those focused on interrupting transmission, but it is clear that both goals must be addressed to assure programme success. Eliminating transmission is an important preventive measure that will protect the subsequent generations of children from acquiring filarial infection and its debilitating clinical consequences – principally, lymphoedema, elephantiasis and genital damage. Alleviating the suffering of those already affected is an important therapeutic measure ensuring immediate medical care for the neediest of patients and demonstrating commitment to improving public health not only in the future, but also today as well.

Optimizing albendazole use

A great deal has been learned during the past decade about the effective use of all three of the available antifilaria drugs: DEC, ivermectin and albendazole. However, not only is further research needed to optimize treatment intervals for the two-drug combinations used already (see above), but co-administration of single doses of all three drugs has not yet been tried. This might have benefits exceeding those of any of the two-drug combinations already studied, especially as all three drugs have different mechanisms of action[29,30,36]. Indeed, such multidrug treatment is being increasingly recognized as the most effective approach to many infectious diseases (such as tuberculosis, leprosy and AIDS).

Of particular concern for any public health programme that relies on broad, community-wide drug treatment strategies is the potential for the development of drug resistance. Accordingly, the development of tools and techniques to detect such potential resistance, and strategies to prevent its development should be a research priority. Certain strategies have already been defined to slow the development of resistance both to anthelmintics of veterinary importance[37] and, of course, to antibacterial agents in humans. Use of drug combinations in the filariasis elimination programmes might help to prevent the development of resistance to the individual drugs over the 4–6 year duration of the once-yearly treatment programmes[18]; clearly, this is a subject that merits further investigation.

From a public health perspective, the strategy to eliminate lymphatic filariasis requires intervention in endemic communities once a year for a defined period estimated at 4–6 years[8]. While albendazole and ivermectin have already demonstrated broad-spectrum effectiveness against geohelminths and other organisms, it is clear that even greater cost-effectiveness could be achieved if other disease control activities (eg. schistosomiasis control, malaria control or even micronutrient supplementation), could also be integrated with these once-yearly community interventions. Research both at the field-implementation level and at the clinical level to ensure safety of co-administered drugs is needed before such potentially cost-effective approaches can be undertaken and evaluated.

Treatment options for the individual

The outstanding advances in drug treatment options for lymphatic filariasis made over the past decade have focused almost entirely on ridding populations of microfilaraemia, in order to interrupt transmission. While 'simple' hygiene-oriented means of treating individual patients to minimize and even reverse the progression of elephantiasis and other expressions of lymphatic pathology have been developed, with unexpectedly good results for the patients[38], curing the infections of individuals (by killing the adult worms) has received very little attention to date. Indeed, current recommendations on how best to treat individual patients are inadequate. However, with the newer tools available, such as ultrasonography for direct visualization of adult worms[22] and antigen detection for indirect assessment of their functional activity[24], with the past and recent experience with DEC as a 'partially macrofilaricidal' drug[22,23], and with the clear implications that albendazole can be macrofilaricidal[17,20], there are now many avenues open to productive research to define how best to treat individuals with lymphatic filarial infections. Such information represents a major gap in our understanding of how to manage filarial infections, one that must be filled to complement the activities of the increasing number of filariasis elimination programmes anticipated for implementation over the next 20 years in all endemic regions[18].

References

1 Centers for Disease Control and Prevention (1993) **Recommendations of the international task force for disease eradication.** *Morb. Mortal. Wkly Rep.* 42, 1–38
2 Ottesen, E.A. (1998) in *Infectious Diseases and Public Health* (Angelico, M. and Rocchi, G., eds), pp 58–64, Balaban Publishers
3 Weil, G.J., Lammie, P.J. and Weiss, N. (1997) **The ICT filariasis test: a rapid format antigen test for diagnosis of bancroftian filariasis.** *Parasitol. Today* 13, 401–404
4 Chodakewitz, J. (1995) **Ivermectin and lymphatic filariasis: a clinical update.** *Parasitol. Today* 11, 233–235
5 Kazura, J. *et al.* (1993) **Comparison of single-dose diethylcarbamazine and ivermectin for treatment of bancroftian filariasis in Papua New Guinea.** *Am. J. Trop. Med. Hyg.* 49, 804–811
6 Addiss, D.G. *et al.* (1993) **Comparative efficacy of clearing-dose and single high-dose ivermectin and diethylcarbamazine against *Wuchereria bancrofti* microfilaremia.** *Am. J. Trop. Med. Hyg.* 48, 178–185
7 Dreyer, G. *et al.* (1995) **Treatment of bancroftian filariasis in Recife, Brazil: a two-year comparative study of the efficacy of single treatments with ivermectin or diethylcarbamazine.** *Trans. R. Soc. Trop. Med. Hyg.* 89, 98–102
8 Andrade, L.D. *et al.* (1995) **Comparative efficacy of three different diethylcarbamazine regimens in lymphatic filariasis.** *Trans. R. Soc. Trop. Med. Hyg.* 89, 319–321
9 Laigret, J., Fagneaux, G. and Tura, E. (1980) **Chimiothérapie de masse par la diéthylcarbamazine en doses espacées: effets obtenus à Tahiti sur la microfilarémie à *Wuchereria bancrofti*, var. *pacifica*.** *Bull. WHO* 58, 779–783
10 Kimura, E., Penaia, L. and Spears, G.F. (1985) **The efficacy of annual single-dose treatment with diethylcarbamazine citrate against diurnally subperiodic bancroftian filariasis in Samoa.** *Bull. WHO* 63, 1097–1106
11 Moulia-Pelat, J.P. *et al.* (1995) **Combination ivermectin plus diethylcarbamazine, a new effective tool for control of lymphatic filariasis.** *Trop. Med. Parasitol.* 46, 9–12
12 Ottesen, E.A. and Ramachandran, C.P. (1995) **Lymphatic filariasis infection and disease: control strategies.** *Parasitol. Today* 11, 129–131
13 Oomen, A.P. (1969) **Fatalities after treatment of onchocerciasis with diethylcarbamazine.** *Trans. R. Soc. Trop. Med. Hyg.* 63, 548
14 Carme, B. *et al.* (1991) **Five cases of encephalitis during treatment of loiasis with diethylcarbamazine.** *Am. J. Trop. Med. Hyg.* 44, 684–690
15 Hopkins, D. and Richards, F. (1997) in *1997 Medical and Health Annual* (Bernstein, E., ed.), pp 8–23, Encyclopaedia Britannica Medical and Health Annual
16 Addiss, D.G. *et al. (1997)* **Randomised placebo-controlled comparison of ivermectin and albendazole alone and in combination for *Wuchereria bancrofti* microfilaraemia in Haitian children.** *Lancet* 350, 480–484
17 Ismail, M.M. *et al.* (1998) **Efficacy of single dose combinations of albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis.** *Trans. R. Soc. Trop. Med. Hyg.* 92, 94–97
18 Ottesen, E.A. *et al.* (1997) **Strategies and tools for the control/elimination of lymphatic filariasis.** *Bull. WHO* 75, 491–503
19 Mak, J.W., Sim, B.K.L. and Yen, P.K.F. (1984) **Filaricidal effect of albendazole against subperiodic *Brugia malayi* infection in the leaf-monkey, *Presbytis melalophos*.** *Trop. Biomed.* 1, 121–123
20 Jayakody, R.L., De Silva, C.S.S. and Weerasinghe, W.M.T. (1993) **Treatment of bancroftian filariasis with albendazole: evaluation of efficacy and adverse reactions.** *Trop. Biomed.* 10, 19–24
21 Horton, R.J. (1997) **Albendazole in treatment of human cystic echinococcosis: 12 years of experience.** *Acta Trop.* 64, 79–93
22 Noroes, J. *et al.* (1997) **Assessment of the efficacy of diethylcarbamazine on adult *Wuchereria bancrofti in vivo*.** *Trans. R. Soc. Trop. Med. Hyg.* 91, 78–81
23 Ottesen, E.A. (1985) **Efficacy of diethylcarbamazine in eradicating infection with lymphatic-dwelling filariae in humans.** *Rev. Infect. Dis.* 7, 341–356
24 Weil, G.J. *et al.* (1987) **A monoclonal antibody-based enzyme immunoassay for detecting parasite antigenaemia in bancroftian filariasis**. *J. Infect. Dis.* 156, 350–355
25 McCarthy, J.S. *et al.* (1995) **Clearance of circulating filarial antigen as a measure of the macrofilaricidal activity of diethylcarbamazine in *Wuchereria bancrofti* infection.** *J. Infect. Dis.* 172, 521–526

26 Eberhard, M.L. *et al.* (1997) **Clearance of *Wuchereria bancrofti* antigen after treatment with diethylcarbamazine or ivermectin.** *Am. J. Trop. Med. Hyg.* 57, 483–486
27 Nicolas, L. (1997) **Reduction of *Wuchereria bancrofti* adult worm circulating antigen after annual treatments of diethylcarbamazine combined with ivermectin in French Polynesia.** *J. Infect. Dis.* 175, 489–492
28 Albonico, M. *et al.* (1994) **A randomized controlled trial comparing mebendazole and albendazole against *Ascaris*, *Trichuris* and hookworm infections.** *Trans. R. Soc. Trop. Med. Hyg.* 88, 585–589
29 De Silva, N., Guyatt, H. and Bundy, D. (1997) **Anthelmintics: a comprehensive review of their clinical pharmacology.** *Drugs* 53, 769–788
30 Ottesen, E.A. and Campbell, W.C. (1994) **Review: ivermectin in human medicine.** *Antimicrob. Chemother.* 34, 195–203
31 Beach, M.J. *et al.* (1999) **Assessment of combined ivermectin and albendazole for treatment of intestinal helminths and *Wuchereria bancroft* infection in Haitian schoolchildren.** *Am. J. Trop. Med. Hyg.* 60, 479–486
32 Ismail, M.M. and Jayakody, R.L. **Efficacy of albendazole and its combinations with ivermectin or diethylcarbamazine (DEC) in the treatment of *Trichuris trichiura* infections in Sri Lanka.** *Ann. Trop. Med. Parasitol.* (in press)
33 Nokes, C. *et al.* (1992) **Moderate to heavy infections of *Trichuris trichiura* affect cognitive function in Jamaican schoolchildren.** *Parasitology* 104, 539–547
34 Stephenson, L.S. *et al.* (1993) **Physical fitness, growth and appetite of Kenyan school boys with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections are improved four months after a single-dose of albendazole.** *J. Nutr.* 123, 1036–1046
35 Remme, J.H.F., Alley, E.S. and Plaisier, A.P. (1995) in *Epidemic Models: Their Structure and Relation to Data* (Mollison, D., ed.), pp 372–392, Cambridge University Press
36 Maizels, R.M. and Denham, D.A. (1992) **Diethylcarbamazine (DEC): immunopharmacological interactions of an anti-filarial drug.** *Parasitology* 105, S49–S60
37 Dobson, R.J., LeJambre, L. and Gill, J.H. (1996) **Management of anthelmintic resistance: inheritance of resistance and selection with persistent drugs.** *Int. J. Parasitol.* 26, 993–1000
38 Addiss, D.G. and Dreyer, G. in *Lymphatic Filariasis* (Nutman, T.B., ed.), Imperial College Press (in press)
39 Shenoy, R.K. *et al.* **Treatment of microfilaraemia of asymptomatic Brugian filariasis with single doses of ivermectin, diethylcarbamazine or albendazole in various combinations.** *Ann. Trop. Med. Parasitol.* (in press)

Human Dirofilariasis in the European Union

A. Muro, C. Genchi, M. Cordero and F. Simón

The dog parasites Dirofilaria immitis *and* D. (Nochtiella) repens*, well known as zoonotic agents, are widely distributed in southern Europe. Although both species are canine parasites, infection with immature worms has been found in humans, who develop nodules, mainly in subcutaneous tissue or in lung parenchyma arising from branches of the pulmonary artery. In humans, the parasites do not usually reach the adult stage and microfilaremia is absent, as has been shown by diagnosis using invasive methods for removing the nodules. In this article, Antonio Muro, Claudio Genchi, Miguel Cordero and Fernando Simón review the current situation concerning the clinical and epidemiological aspects, immune response and diagnosis of human dirofilariases.*

In Europe, canine and feline dirofilariases are widely distributed throughout the southern countries[1,2], but are less frequent or completely absent in the north (Fig. 1). Italy is the European country with the highest reported presence of dirofilariases[3], while Cherbourg (France)[4] represents the northern limits of the species. Some cases of canine cardiopulmonary dirofilariasis have been reported in Austria and Germany in dogs that had previously visited countries in southern Europe[5,6]. The distribution of *Dirofilaria* worms is not homogeneous; the highest prevalences occur in river valleys and humid areas, where the environmental conditions are more favourable for the breeding of vectors.

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Mosquito density and the abundance of microfilaraemic dogs are the most important risk factors regarding human infections. Species of the genuses *Aedes*, *Anopheles* and *Culex* have been considered competent vectors for both the *Dirofilaria* species[2,7]. The introduction of new species, such as *Ae. albopictus*, recently 'imported' into Italy[8], the adaptability of some mosquito species (such as *Cx. pipiens*) to widely different environmental conditions, and their propensity to feed on humans and on domestic carnivores[7] play an important role in the spread of infection.

The retrospective study of previously published human cases documents the emergence of infection by these species. More than 270 cases in the European Union have been reported[9,10]. Most of them were attributed to *D.* (*Nochtiella*) *repens*; only ten were caused by *D. immitis*. The country where most cases have been diagnosed is Italy (66%), followed by France (21.7%), Greece (8%) and Spain (4%). Women are affected more often than men. Age-group distribution shows a higher incidence of cases after 40 years of age in both sexes and for both parasites. A number of cases have been diagnosed in northern Europe, but they have been attributed to infections acquired while travelling in southern countries. However, studies carried out in an endemic area of western Spain, where the prevalence of canine infection is 33%, have shown that 21% of the human population develops antibodies of different isotypes against *D. immitis*[11,12]. This indicates that human contact with these parasites is more frequent than is shown by the number of reported clinical cases and that most individuals do not develop symptoms.

From a clinical point of view, pulmonary dirofilariasis manifests itself with various clinical symptoms (Box 1). Apart from the classic presentation of stable solitary pulmonary nodules, transitory pulmonary nodules have been shown to be another manifestation of the disease[13,14]. Moreover, dirofilariasis has been defined as

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