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Human Filariasis in Travelers and Migrants: A Retrospective 25-year Analysis at the Institute of Tropical Medicine, Antwerp, Belgium

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Background. Information on human filariasis in international travelers is scarce. We describe the epidemiology, clinical presentation, and outcome of these infections in a reference travel clinic over the past decades.

Methods. We reviewed all cases of filariasis diagnosed at the Institute of Tropical Medicine, Antwerp, Belgium, from 1994 to 2018. Diagnosis was obtained by either parasitological methods (confirmed) or strict clinical case definitions (probable). We assessed the characteristics of cases at diagnosis and response to therapy within 3–12 months.

Results. A total of 320 patients (median age: 41 years; 71% males) were diagnosed with 327 filarial infections (*Wuchereria bancrofti* = 6, *Onchocerca volvulus* = 33, *Loa loa* = 150, *Mansonella perstans* = 130, unspecified species = 8). Diagnosis was confirmed in 213/320 (67%) patients. European long-term travelers accounted for 166 patients (52%) and visitors/migrants from tropical countries for another 110 (34%). Central Africa was the likely region of acquisition for 294 (92%) patients. The number of filariasis cases decreased from 21.5/year on average in the 1990s to 6.3/year in the past decade, when loiasis became predominant. Cases reported symptoms in >80% of all filarial infections but mansonellosis (45/123 single infections; 37%). Lymphatic filariasis and onchocerciasis cases responded well to conventional therapy. However, 30% of patients with loiasis and mansonellosis experienced treatment failure (with diethylcarbamazine and levamisole-mebendazole, respectively).

Conclusions. The burden and species distribution of filariasis in travelers evolved in the past decades. Most presentations were symptomatic. Case management would benefit from more effective therapies for loiasis and mansonellosis.

Keywords. filariasis; traveler; migrant; therapy; epidemiology.

Human filariasis forms a complex of vector-borne nematode infections in which humans are the definitive hosts and that cause various diseases such as lymphatic filariasis (from *Wuchereria bancrofti* and *Brugia* spp.), onchocerciasis (*Onchocerca volvulus*), loiasis (*Loa loa*), and mansonellosis (*Mansonella perstans, M streptocerca,* and *M ozzardi*). Although the prevalence of lymphatic filariasis and onchocerciasis decreased substantially following major control efforts over the past 2 decades [1, 2], these infections remain widely distributed in the tropics. In the nonendemic setting, however, filarial infections are diagnosed in a minority of migrants and travelers returning from endemic areas. In a survey by the GeoSentinel network from 1997 to 2004, filariasis was diagnosed in 271 of 43 722 ill travelers (0.6%), and *O volvulus* was the most common identified species [3]. Another GeoSentinel study that covered the 2007–2011 period reported 113 cases of filarial infection in 42 173 medical encounters (0.3%), but did not specify the species distribution [4].

The diagnosis of filarial infection in travelers and migrants is notoriously difficult. On the one hand, microscopic detection of larval or adult worms (microfilaria and macrofilaria, respectively) has low sensitivity for all species, whereas on the other hand, antifilarial antibody detection assays usually do not distinguish between etiological species, frequently cross-react with other nematodes, and cannot differentiate past exposure from active infection. Antigen-based assays are only available for the detection of *W bancrofti* adult worms, and they have fair diagnostic performance characteristics in endemic settings [5]. Nucleic acid detection assays are not available in clinical routine. Consequently, in many instances, diagnosis relies on the combination of suggestive clinical features with indirect laboratory markers of parasitic infection such as eosinophilia, supported by a positive antifilarial antibody titer. In exposed patients with nonspecific symptoms, species diagnosis is particularly challenging because clinical presentation may overlap between filarial infections and with that of many other parasitic diseases. In some cases, response to empirical treatment may present the only diagnostic clue, but this approach also has suboptimal specificity. In addition, adequate management

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of filarial infections requires substantial expertise. Treatment regimens are species-specific, they may be complex and toxic, and have a limited evidence base, especially in travelers. Several retrospective case series from European travel clinics have been published in the past decade and these focused mainly on loiasis [6–10] and to a lesser extent on mansonellosis [11, 12].

The Institute of Tropical Medicine, Antwerp (ITMA), is the national reference center for the laboratory diagnosis and clinical management of tropical diseases in Belgium. We aimed to report on the temporal trend of human filarial infections diagnosed at our institution during a 25-year period, and to describe the presentation, diagnostic method, treatment, and outcome by filarial species.

MATERIAL AND METHODS

Study Setting and Search Strategy

For this retrospective study, which covered the period from the earliest available electronic files at our center (1994) to 2018, we searched the database of the clinical laboratory of the ITMA using several queries. First, we retrieved all microscopic examinations demonstrating the presence of microfilaria of any species in blood or skin scarifications, as well as all positive *W bancrofti* antigen-based test results. Second, we identified all positive antifilarial serological results associated with eosinophilia (defined as eosinophil cell count in blood ≥500/μL). We then retrieved all medical files of the cases captured by our search criteria. Each case was critically reassessed for consistency with the established case definitions (see the following section) and included accordingly. Cases of zoonotic filariasis were not included in this study.

Participants were classified as European travelers, either short-term (arbitrarily defined as a tropical stay shorter than 6 months) or long-term (or expatriate, tropical stay >6 months); natives of tropical countries, either migrants (travel to Europe for establishment) or visitors (short-term trip); and travelers visiting friends and relatives (ie, natives of tropical countries residing in Europe who were diagnosed following a trip back to their country of origin). For the report on epidemiology, the study period was divided in 3 decades: 1994–1999 (6 years); 2000–2009 (10 years); and 2010–2018 (9 years).

Diagnosis and Case Definition of Filariasis

Diagnosis of filariasis was confirmed in case microfilaria (and in some instances adult worms) were observed or in case of positive *W bancrofti* antigen result. The *W bancrofti/Brugia* spp., *L loa*, and *M perstans/M ozzardi* microfilaria were searched for after a modified Knott concentration method [13], followed by Carazzi hematoxylin staining. The microfilarial load was quantified and results reported as the number of microfilaria per 10 mL of blood. Since 2000, the cumbersome night blood sampling for detection of *W bancrofti* microfilaria was replaced by the *W bancrofti* antigen-based immunoassay (Og4C3 Filariasis Ag ELISA, Trobio Townsville, Queensland, Australia). Microfilaria of *O volvulus* and *M streptocerca* were detected in Carazzi hematoxylin-stained specimens from skin scarifications obtained from the patient's back or from any suspect cutaneous lesion; results were expressed in a semiquantitative way (<5 microfilaria/slide reported as "+"; 5–20 as "++"; >20 as "+++").

Filariasis was considered as probable in patients presenting with positive antifilarial serological result and eosinophilia after the microscopic and serological workup had excluded any alternative parasitic diagnosis. Probable cases were then classified according to species-suggestive clinical manifestations. For lymphatic filariasis, features considered as suggestive were lymphangitis and/or orchitis and/or lymphedema; for onchocerciasis, itching and/or skin rash and/or corneal lesions; and for loiasis, Calabar swelling (migratory transient subcutaneous edema) and/or worm migration in eye or skin. Probable cases that did not manifest species-suggestive symptoms or had overlapping features were labelled as unspecified. Nonfilarial concomitant infections were retained only in confirmed filariasis cases.

The antibody-based diagnosis of filariasis was performed from 1994 to 2003 with an in-house enzyme-linked immunosorbent assay and from 2003 onwards with a commercial assay (Acanthocheilonema viteae, Bordier Affinity Products SA, Crissier, Switzerland) according to the instructions of the manufacturer. The assay's threshold for positivity was set as "weak positive" (from 2003 to 2009) and as an optical density ratio ≥1.0 (from 2009 onwards) for use in clinical settings.

Case Management

Treatment of the different types of filariasis has evolved in our center since 1994 because of emerging alternative regimens or issues of drug availability in Belgium. Briefly, after a course of anti-inflammatory drugs and antibiotics covering skin bacteria, lymphatic filariasis was treated with a 12-day course of diethylcarbamazine (DEC, 200 mg twice daily for adults) up to 2010; from 2010 onwards, a 6-week course of doxycycline (200 mg/day) targeting the *Wolbachia* endosymbionts was preferred [14]. Similarly, up to 2010, onchocerciasis was treated with a course of 200 μg/kg ivermectin, sometimes annually repeated, and since 2010, the preferred regimen has consisted of a single course of ivermectin (200 μg/kg) combined with a single 6-week course of doxycycline (200 mg/day) [14]. Loiasis was treated with a 3-week course of DEC (gradually increased to 200 mg twice daily in adults). When the microfilaremia was >25,000/10 mL of blood, DEC therapy was sometimes preceded by a single dose of ivermectin 200 μg/kg, or if microfilaremia was >500,000/10 mL, by loiapheresis [15]. Infection with *M perstans* was treated with a combination of levamisole 150 mg once on days 1, 3, and 5 and mebendazole 1500 mg/day from day 2 to day 16 up to 2014 and later with a 3-week course of

Table 1. Epidemiological, Clinical, Laboratory, and Management Features of International Travelers Diagnosed With Filarial Infection (n = 320) at the Institute of Tropical Medicine, Antwerp, 1994–2018

	Lymphatic Filariasis (n = 6)	Onchocerciasis (n = 33)	Loiasis (n = 150)	Mansonellosis (n = 123)[a]	Unspecified Filariasis (n = 8)	Total (n = 320)
Epidemiological features						
Male	4 (67%)	25 (76%)	93 (62%)	99 (80%)	6 (75%)	227 (71%)
Median age in y (min; max)	45.5 (31;75)	37 (10;70)	41 (17;80)	50 (15;82)	41 (9;65)	41 (9;82)
Type of traveler						
European short-term traveler	2 (33%)	3 (9%)	16 (11%)	4 (3%)	2 (25%)	27 (8%)
European long-term traveler	2 (33%)	16 (48%)	58 (39%)	85 (69%)	5 (62%)	166 (52%)
Visiting friends and relatives traveler	…	3 (9%)	12 (8%)	1 (1%)	1 (12%)	17 (5%)
Native of tropical countries, migrant or visitor	2 (33%)	11 (33%)	64 (43%)	33 (27%)	…	110 (34%)
Likely region of acquisition						
Central Africa	2 (33%)	25 (78%)	148 (98%)	110 (89%)	8 (100%)	293 (92%)
West Africa	1 (17%)	7 (21%)	2 (2%)	12 (10%)	…	22 (7%)
East Africa	…	1 (3%)	…	…	…	1 (0.3%)
Other continent	3 (50%)	…	…	1 (1%)	…	4 (1%)
Median duration of exposure[b] in weeks (min; max)	260 (20; >500)	150 (3; >500)	50 (2; >500)	250 (4; >500)	68 (4; >500)	100 (2; >500)
Diagnostic certainty						
Parasitological confirmation	3 (50%)	11 (34%)	76 (51%)	123 (100%)	…	213 (67%)
Mean microfilarial load/10 mL (range) Median microfilarial load/10 mL (Q1–Q3)		[c]	5070 (0–100,000) 0 (0–930)	731 (2–40,600) 34 (15–140)	…	
Probable cases	3 (50%)	22 (66%)	74 (49%)	…	8 (100%)	107 (33%)
Reason for testing						
Clinical manifestations	5 (83%)	32 (97%)	126 (84%)	45 (37%)	2 (25%)	210 (65%)
Asymptomatic eosinophilia	1 (17%)	1 (3%)	19 (13%)	33 (27%)	6 (75%)	60 (19%)
Screening postexposure	…	…	5 (3%%)	45 (37%)	…	50 (16%)
Clinical presentation						
Asymptomatic	1 (17%)	1 (3%)	24 (16%)	78 (64%)	6 (67%)	110 (35%)
Generalized/focal itching	1 (17%)	26 (81%)	46 (30%)	25 (19%)	2 (22%)	100 (31%)
Generalized/focal rash	…	17 (53%)	14 (9%)	8 (6%)	…	39 (12%)
Lymphadenitis/orchitis	3 (50%)	…	1 (1%)	…	…	4 (1%)
Lymphedema	2 (33%)	3 (9%)	7 (5%)	1 (1%)	…	13 (4%)
Calabar swelling	…	1 (3%)	86 (57%)	10 (8%)	…	97 (30%)
Worm in eye	…	…	30 (20%)	…	…	30 (9%)
Cutaneous larva migrans	…	…	5 (3%)	…	…	5 (2%)
Respiratory symptoms	…	1 (3%)	6 (4%)	8 (6%)	1 (11%)	16 (5%)
Nonspecific systemic symptoms	…	…	10 (7%)	3 (2%)	2 (22%)	15 (5%)
Laboratory data						
Eosinophil cell count, median (Q1–Q3)	1875 (480–4792)	1240 (780–2810)	1545 (807–2892)	480 (260–1130)	4395 (1682–6760)	1095 (480–2542)
Eosinophil cell count, range	210–5340	90–18990	10–69200	30–9730	1140–8130	10–69200
Eosinophil cell count in blood > 500/µL	5 (83%)	30(91%)	135 (90%)	60 (49%)	8 (100%)	238 (74%)
Eosinophil cell count in blood > 1000/µL	3 (50%)	22 (67%)	103 (69%)	35 (28%)	8 (100%)	171 (54%)
Elevated immunoglobulin E, n/n tested	2/3 (66%)	13/16 (81%)	69/92 (75%)	48/60 (80%)	3/4 (75%)	135/175 (77%)
Positive antifilarial serology	4 (67%)	31 (94%)	133/146 (91%)	84/113 (68%)	8 (100%)	259/306(81%)

Table 1. Continued

	Lymphatic Filariasis (n = 6)	Onchocerciasis (n = 33)	Loiasis (n = 150)	Mansonellosis (n = 123)[a]	Unspecified Filariasis (n = 8)	Total (n = 320)
Initial management						
Unknown (immediate lost to follow-up)	0	0	3	6	2	11
Initial therapeutic abstention	0	0	9	32	1	42
Treatment administered at diagnosis	6	33	138	85	5	267
Diethylcarbamazine 12 days	5	…	…	…	…	5
Doxycycline 6 weeks	1	…	…	…	…	1
Ivermectin	…	32	…	…	…	32
Ivermectin + doxycycline 6 weeks (single course)	…	1	…	…	…	1
Diethylcarbamazine 3 weeks	…	…	114	3	3	120
Ivermectin + diethylcarbamazine 3 weeks	…	…	22	4	2	28
Levamisole-mebendazole 16 days	…	…	…	78	…	78
Albendazole 3 weeks	…	…	2[d]	…	…	2

All results are n or n/n, %, except if otherwise specified; Q1–Q3 means interquartile range.

[a]Seven patients were diagnosed with *M perstans* in coinfection with onchocerciasis (n = 1) or loiasis (n = 6).

[b]Only determined in European short- and long-term travelers.

[c]Microfilarial loads in skin scarifications were "+" in 7 cases and "++" in 4.

[d]Administered because diethylcarbamazine was no longer available in Belgium.

DEC (same regimen as loiasis). Since late 2016, DEC has no longer been available in Belgium, and a 3-week course of albendazole (400 mg twice daily) was used instead to treat loiasis and mansonellosis [16–18]. Any concomitant infection was treated accordingly at diagnosis.

A follow-up visit was offered at least once, 3–12 months after the first consultation, whether a specific treatment had been administered or not. In the absence of reexposure, any persistence of symptoms, eosinophilia, or microfilaria by microscopy after therapy was considered as clinical, laboratory, or parasitic treatment failure, respectively. Additional treatments could then be administered at the physician's discretion. All efforts were made to follow-up cases until a final cure, preferentially at our institute.

Statistical Analysis

For all cases of confirmed or probable filariasis, relevant longitudinal data were extracted from the medical files, deidentified, and entered in a Microsoft Access 2010 database. Variables included demographic data, month, and year of first diagnosis; travel history; reason for testing; clinical presentation; absolute blood eosinophil count; presence and density of blood/skin microfilaria; antifilarial antibody test results; other active infections confirmed by parasitology; administered treatment(s); reported adverse events; posttherapy clinical and laboratory assessment; and outcome. Analysis was performed with SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Differences were compared using Student *t* test or Mann-Whitney *U* test, when appropriate, for continuous variables and χ^2 and Fisher exact tests for categorical variables. *P* values < .05 indicated statistical significance.

Ethics Statement

This was a retrospective analysis of data collected during routine clinical care over a 25-year period, conducted after ethical clearance by the institutional review board of ITMA. Laboratory and clinical data were retrieved from medical files through an encoded link and were deidentified for analysis according to Belgian legislation. No written informed consent was obtained from individual participants, but an assumed consent (opt out) procedure has been established since 2007 at the ITMA covering surveillance use of clinical and laboratory data.

RESULTS

From January 1994 to December 2018, 320 patients were diagnosed with a total of 327 different filarial infections. Diagnosis was confirmed in 213/320 (67%) cases. Median age of the study participants was 41 years (range: 9–82 years), and 227 (71%) were male (Table 1). The largest groups of patients were European long-term travelers (n = 166, 52%), followed by natives of tropical countries, either migrants or visitors (n = 110, 34%). The vast majority had likely acquired infection in Central

Africa (n = 293, 92%), with a few cases having been exposed in other African regions (n = 23) or outside Africa (India, n = 2; Philippines, n = 1; Brazil, n = 1). Of the 327 filarial infections, 6 were due to *W bancrofti*, 33 to *O volvulus*, 150 to *L loa*, 130 to *M perstans,* and 8 were considered as unspecified. Mixed filarial infection was confirmed by microscopy in 7 patients (*O volvulus/M perstans*, n = 1; *L loa/M perstans*, n = 6). No other filarial species was identified.

The number of filariasis cases and the species distribution varied substantially during the study period. The total number of cases declined from an average number of 21.5/year in 1994–1999, to 13.4/year in 2000–2009, and to 6.3/year in 2010–2018 ($P < .001$). We observed a substantial decrease in mansonellosis cases and stable numbers of filariasis caused by other species (Figure 1). In the most recent period, loiasis represented 65% (37/57) of the case load compared with 27% (35/129) in 1994–1999 ($P < .001$).

Reasons for diagnostic testing were clinical manifestations in 210 (65%) of the 320 participants, asymptomatic eosinophilia in 60 (19%), and screening because of long-term exposure in another 50 (16%). Contrary to filariasis caused by other species, the majority of mansonellosis cases were asymptomatic (Table 1). In symptomatic cases, the most frequent complaints were Calabar swelling, which occurred almost exclusively in loiasis, and itching, which was reported more by onchocerciasis cases, and was occasionally associated with skin rash. Respiratory asthma-like symptoms and nonspecific systemic complaints (fever sensation, body ache, severe asthenia) were occasionally reported. Other concomitant active infections included strongyloidiasis (n = 23), other intestinal helminthiases (n = 31; hookworms, 13; *Trichuris trichiura*, 11; *Ascaris lumbricoides*, 5; and *Taenia saginata*, 2), malaria (n = 7), schistosomiasis (n = 4), and giardiasis (n = 4). Eosinophilia was almost always present in the study participants, except in mansonellosis cases (only 50%). In loiasis cases, median eosinophil count/μL was higher in western travelers (2180; interquartile range [IQR]: 1190, 3480) compared with that of natives of tropical countries (1190; IQR: 712, 1887, $P < .001$). In contrast, median microfilaremia was lower in the former group (0/10 mL; IQR: 0, 132) than in the latter participants (2180/10 mL; IQR: 1190, 3480, $P < .001$). For mansonellosis, both median eosinophil count and microfilaremia/10 mL were similar in both travelers' groups (440 vs 575, and 33 vs 40, respectively; P = NS for both comparisons).

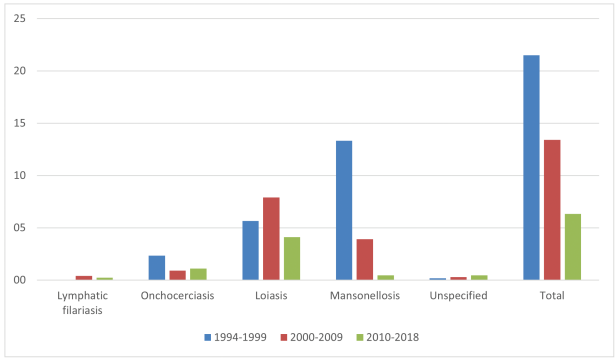

Figure 1. Average annual numbers of filariasis cases (per species and total) diagnosed from 1994 to 2018, according to the study periods.

Treatment was offered to 267 of the 309 patients for whom initial management data were available. Abstention was frequent in mansonellosis cases. Table 1 shows the different treatments administered according to the species diagnosis; DEC (either or not preceded by ivermectin), levamisole-mebendazole, and ivermectin alone were the main regimens, used in decreasing order.

Adverse events were reported in 25/148 (16.9%) patients treated with DEC ± ivermectin and in 4/78 (5.1%) levamisole-mebendazole recipients. These consisted mainly of itching/rash/swelling (n = 16) and fever/muscle ache (n = 5). Two loiasis patients treated with DEC had to be hospitalized (1 with seizure and the second with dyspnea) after treatment initiation. Both recovered quickly after a short intravenous course of corticosteroids. All other patients with adverse events were treated with oral corticosteroids, to which they rapidly responded.

Figure 2 shows the cure rates per treatment regimen as assessed at 3–12 months posttreatment in travelers who did not have repeat exposure in filaria-endemic areas. Data were not available for 51 of the 320 initial participants (16%). All 6 patients with lymphatic filariasis were cured (1 with the 6-week doxycycline regimen). A similarly favorable evolution was observed for onchocerciasis cases at 3–12 months after a single course of ivermectin, but a subgroup of 8 patients (including 3 with repeat exposure) clinically relapsed later on and required 1–5 additional annual courses of ivermectin. Cure rates were only 70% in loiasis cases treated with DEC ± ivermectin and 65% in patients with mansonellosis given levamisole/mebendazole (Figure 2). Most were retreated with the same respective regimen. No further persistence or relapse of symptoms or eosinophilia were reported, except in 3 loiasis patients who each required 3 DEC courses in total. Of note, most loiasis and one-half of the mansonellosis patients who were not treated immediately after diagnosis still had evidence of active infection at reassessment (Figure 2). All persistent infections were treated at that time and achieved cure.

DISCUSSION

In this large case series from a reference travel clinic, the vast majority of filariasis was diagnosed in expatriates returning and migrants arriving from Central Africa. The absolute number of filariasis cases steadily decreased over the past 25 years; loiasis became predominant in the past decade, whereas the number of mansonellosis cases sharply declined. One-third of the identified cases would have been missed if diagnosis had

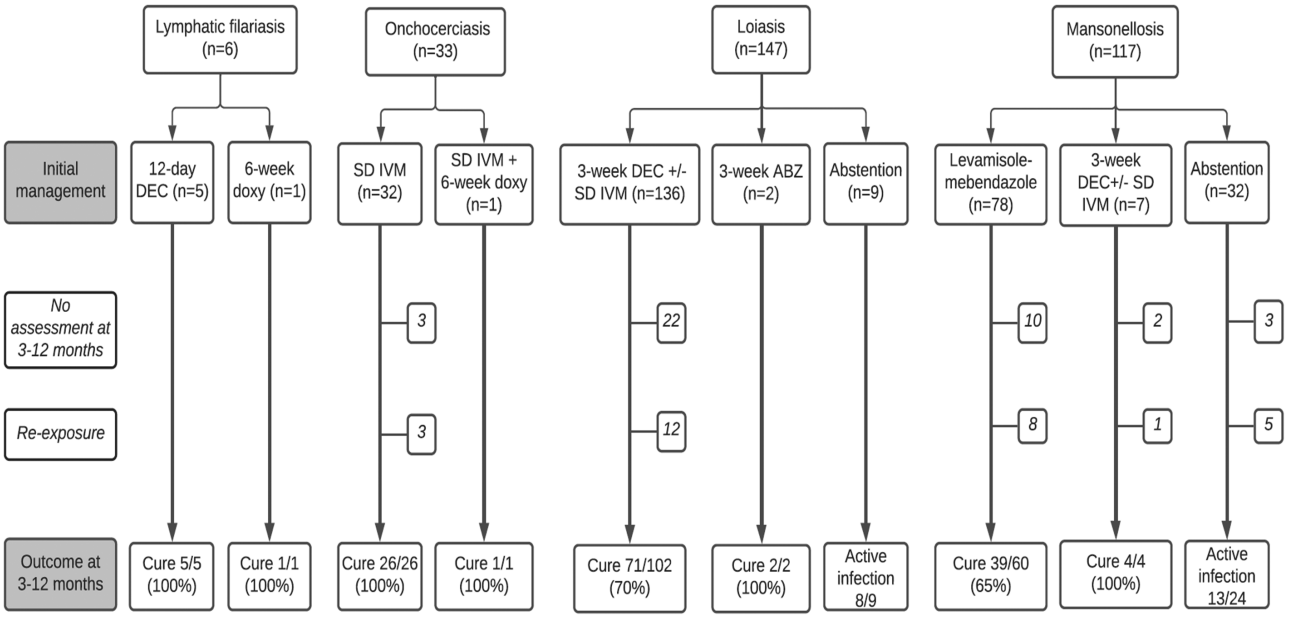

Figure 2. Initial management and outcome of filarial monoinfections in not reexposed international travelers at the Institute of Tropical Medicine, Antwerp, 1994–2018.

relied on microscopy only. Almost all participants presented with clinical symptoms and/or had eosinophilia, except those with mansonellosis. Species-specific therapy varied a great deal during the study period and was quite unsatisfactory for loiasis and mansonellosis, both in terms of tolerability and effectiveness.

Important limitations apply to this single-center retrospective analysis. First, diagnosis relied either on insensitive parasite-based methods or on strict clinical case definitions. An unknown number of cases with undetectable microfilaria, or cases presenting with coinfection, and/or less typical features has likely been missed. It is also possible that some patients who attended other Belgian health facilities were not referred, somewhat limiting the generalizability of our findings. Also, the possibility of false-positive cases cannot be dismissed (eg, if another unrecognized helminthic infection caused suggestive symptoms, eosinophilia, and serological cross-reactivity). We cannot rule out species misclassification because manifestations may overlap. In addition, the evolution of traveler profiles and posttravel screening practice over time may have influenced the capture and distribution of filariasis cases. Finally, complete collection of follow-up and outcome data were hampered by the retrospective design, the high mobility of the study population, and the rather mild course of some filarial infections. On the other hand, this study provides a large clinical description of human filariasis in the nonendemic setting, with a fair retention rate and a consistent, state-of-the-art management by expert physicians.

Despite the wide global distribution of *W bancrofti*, very few cases were observed throughout the long study period. Lymphatic filariasis has only been anecdotally reported in travelers [19, 20]. The risk of acquisition is considered as very limited even during long-term travel because of the low efficiency of pathogen transmission [21, 22]. The decreasing prevalence should make this condition even rarer in travelers, precluding robust effectiveness studies on new anti-*Wolbachia* therapy in this population. Most onchocerciasis cases were diagnosed clinically in this series because conventional microscopy lacks sensitivity, especially in the nonendemic setting. The declining frequency of cases in our center is probably also related to the decreasing prevalence in endemic areas [23]. A single dose of ivermectin, which is exclusively microfilaricidal, was effective in most cases. Even in patients who were not reexposed, repeat doses of ivermectin were sometimes required. Persistent infection in this group possibly relates to the recurrent microfilaria release by adult worms that have a long lifespan. Here also, the effectiveness of doxycycline treatment could not be assessed properly [24], whereas the potential added-value of moxidectin still needs to be evaluated [25].

In line with other reports, loiasis remains an important consideration in travel medicine [7–10]. We observed similar features of loiasis as described previously, including the striking differences in laboratory profile between nonimmune travelers and natives of filaria-endemic countries [26]. In our study also, the conventional 3-week DEC course was found suboptimal in controlling infection [27], but comparisons with other series was impaired by the lack of harmonized therapy of loiasis across European travel clinics [28]. Very limited evidence from endemic and nonendemic settings suggest that prolonged courses (21–28 days) of high doses of albendazole (800 mg daily for adults) might be an effective alternative to DEC [17, 29, 30], but robust trials are lacking.

Finally, mansonellosis, the least invalidating filarial infection in this series, has sharply decreased as a travel-associated pathology. The reason for this decline is unclear because no targeted control activities are deployed in areas of endemicity. In our institution, it is possibly related to the decreasing number of long-term travelers such as missionaries who were exposed in Central Africa. The actual frequency of mansonellosis may have been underestimated as diagnosis was exclusively based on microscopy because symptoms were nonspecific or absent, and both eosinophilia and serology had limited sensitivity [11, 12, 26]. No therapy has demonstrated robust parasitological effectiveness against mansonellosis [31], and the combination treatment levamisole-mebendazole, in use for years in our center but no longer available, was not optimal. The best therapeutic strategy remains poorly defined. Although the presence of *Wolbachia* endosymbionts in *M perstans* appears inconsistent across studies [32], several field trials showed a clinical benefit in using doxycycline as therapy [33, 34]. A multicentric exploration of endosymbiosis in travel-associated mansonellosis could inform on the potential usefulness of this treatment.

In conclusion, the burden of human filariasis is steadily decreasing in travel medicine with a foreseeable loss of clinical and parasitological expertise. Development of more sensitive diagnostic and monitoring tools is an urgent research priority. There is also a pressing need for robust multicentric trials that evaluate alternative therapies, especially for loiasis and mansonellosis.

Notes

Author contributions. Concept: E. B., R. H., J. C., and P. S.; clinical data collection: E. B., R. H., S. V. D. B., U. M., I. B., S. D., C. T., J. V. G., J. C., and P. S.; laboratory analysis: A. M. F. and M. V. E.; chart review: E. B.; data analysis: E. B.; first draft manuscript: E. B., R. H., J. C., and P.S.; revision of the manuscript: all authors.

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