inappropriate, confusing and misleading to have different health communities (for humans and animals) involved with infectious agents and insect vectors, applying clearly defined terms so loosely and inaccurately. Editors should also assume responsibility for maintaining terminological precision.

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1471-4922/$ - see front matter
doi:10.1016/j.pt.2004.06.004

Lymphatic filariasis and *Brugia timori*: prospects for elimination

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Brugia timori **is a pathogenic filarial nematode of humans, replacing the closely related species** ***Brugia malayi*** **on some islands in eastern Indonesia. Recent studies on Alor island show that, locally,** ***B. timori*** **is still of great public health importance, causing mainly acute filarial fever and chronic lymphedema. PCR-based assays to detect parasite DNA, in addition to assays for detecting specific antibodies that have been originally developed for** ***B. malayi*****, can be used efficiently as diagnostic tools for** ***B. timori*****. In the framework of the Global Program to Eliminate Lymphatic Filariasis, a single annual dose of diethylcarbamazine, in combination with albendazole, was found to reduce the prevalence and density of microfilaraemia persistently. Therefore, elimination of** ***B. timori*** **appears to be achievable.**

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Available online 19 June 2004

Brugia timori is a filarial nematode of humans, closely related to *Brugia malayi* [1,2], and is a causative agent of lymphatic filariasis in Timor and neighbouring islands of Indonesia. The successful control of *B. timori* in parts of Flores island using multiple doses of diethylcarbamazine (DEC) was reported in the 1980s [3]. However, this was not extended to other parts of Flores or to other islands. Today, *B. timori* is still abundant locally and is a frequent cause of morbidity. The target of the Global Program to Eliminate Lymphatic Filariasis (GPELF) is to eliminate disease caused by *Wuchereria bancrofti*, *B. malayi* and *B. timori* worldwide, by the year 2020 [4]. To achieve this goal, an increased knowledge of *B. timori* and its differences and similarities to the other lymphatic filarial parasites is needed.

Distribution of *B. timori*

Brugia timori is restricted to the eastern islands of the lesser Sunda archipelago (Nusa Tenggara Timur), where it replaces *B. malayi*. Microfilariae (Mf) of the *B. timori* type were first described from East Timor [1]. The official description of the species was based on specimens collected in northeast Flores [2]. The species also occurs on Sumba, Lembata, Pantar, Alor and other small islands of the archipelago. The prevalence of microfilaraemia in the island inhabitants can reach up to 25%. In some areas, such as central Alor, 40% of the residents show signs of infection and >80% have antifilarial antibodies [5,6]. On Flores, *B. timori* was found co-endemic with *W. bancrofti* mainly in coastal lowland areas with irrigated rice paddies. Therefore, *B. timori* was described to be a lowland species [7]. Recent studies from Alor showed that *B. timori* occurs in rice-farming areas also in altitudes of ~800 m, whereas *W. bancrofti* was found in the coastal areas with dry land agriculture [6]. *Anopheles barbirostris* is the only known natural vector of *B. timori*, but culicine mosquito species, such as *Aedes togoi*, were found to support development under experimental conditions [8]. On Alor and Flores, *An. barbirostris* breeds close to the rice fields in small water holes besides the rivers used for irrigation. On both islands, *Anopheles subpictus*, the vector of *W. bancrofti*, is found in the coastal areas, where it breeds in small ponds with brackish water. The global number of *B. timori* infections is not known, but it is assumed that <800 000 individuals are infected (i.e. extremely small when compared with infections with *W. bancrofti* and *B. malayi*) [6].

Diagnosis of *B. timori* infection

The Mf of *B. timori* can be distinguished from those of *B. malayi* and *W. bancrofti* by their large size (~310 μm), the long nucleus-free anterior end and the larger number of small, single row nuclei in the posterior end (Figure 1a). The sheath usually cannot be stained by Giemsa [9]. The adult male worms of *B. timori* have more subventral adanal papillae when compared with those in *B. malayi*, and the females have larger ovejectors (see Table 1) [2].

Molecular differentiation of *B. timori* from *B. malayi* is not straightforward. Around 10% of the *B. malayi* genome contain a repetitive DNA sequence containing a *Hha* I restriction site. The *Hha* I repeat is a proven target for PCR diagnostics, which can separate *B. malayi* from the animal parasite *Brugia pahangi*, but is unable to distinguish *B. malayi* from *B. timori* [10]. The easiest way to distinguish *B. malayi* from *B. timori* is restriction fragment length polymorphism (RFLP) of the mitochondrial cytochrome *c* oxidase subunit 2. The *B. malayi* genome project is currently undertaking full genome sequencing of the TRS strain of *B. malayi* (http://www.tigr.org/tdb/e2k1/bma1/). This zoophilic isolate from peninsular Malaysia was initially pathogenic to humans, but was also found to be infective to monkeys, cats and other animals. The TRS strain of *B. malayi* has been reared for many generations in laboratory hosts before being used for genome sequencing. Comparative sequence analyses might help to identify DNA sequences that vary between *B. timori*, the zoophilic strains of *B. malayi* and the anthropophilic strains of *B. malayi* that do not successfully infect animal hosts.

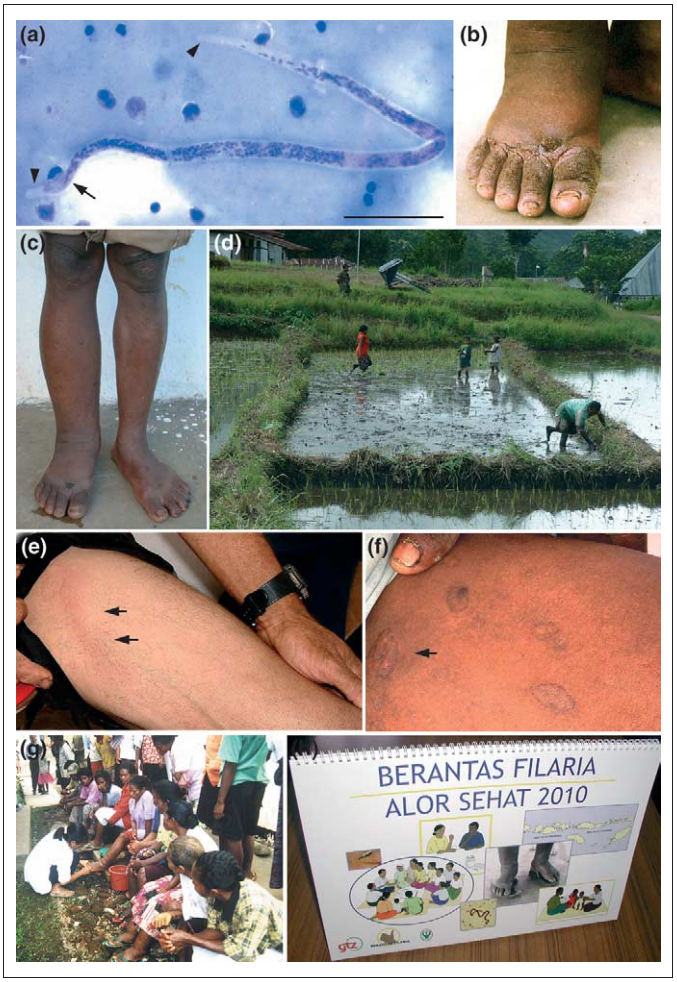

Figure 1. *Brugia timori* on Alor island, eastern Indonesia. **(a)** Giemsa-stained microfilaria of *B. timori* with an unstained sheath (arrows) and nucleus-free anterior end (arrow). Scale bar = 50 μm. **(b)** Lymphedema and mossy lesion of the right foot caused by *B. timori*. **(c)** Typical lymphedema of the leg below the knee caused by *B. timori*. **(d)** Farmers in a *B. timori*-endemic area working in their rice paddies. **(e)** Acute adenolymphangitis (arrows) observed 6–24 h after treatment with a single dose diethylcarbamazine (6 mg kg^{-1}) combined with albendazole (400 mg). **(f)** Filarial abscess caused by *B. timori* (arrow) next to urtical lesions. **(g)** Demonstration of local hygiene to reduce morbidity caused by *B. timori*. **(h)** Flip-chart for health education developed by Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ) for the lymphatic filariasis control programme on Alor (photo courtesy by GTZ).

Table 1. Summary of diagnostic and ecological differences between *Brugia malayi* and *Brugia timori*[a]

	Brugia malayi	*Brugia timori*
Microfilariae		
Mean length	220 μm	310 μm
Cephalic space	Length to width ratio = 2:1	Length to width ratio = 3:1
Sheath	Stained pink with Giemsa	Stained pale pink with Giemsa
Terminal nuclei	4-5 in a single row	5-8 in a single row
Mean length of Innenkörper[b]	31 μm	60 μm
Adult worms		
Females	Body length to ovejector length ratio = 360:1	Body length to ovejector length ratio = 170:1
Male adanal papillae	3-4 on a side, regularly spaced	3-5 on a side, irregularly spaced
Genetic markers	Cytochrome *c* oxidase subunit 2 with *Hpa*I restriction site	Cytochrome *c* oxidase subunit 2 without *Hpa*I restriction site
Ecology	Various ecotypes (anthropophilic or zoophilic); transmitted *by Anopheles* or *Mansonia* spp.; some strains with animal reservoirs; nocturnally periodic, subperiodic or aperiodic	One ecotype (anthropophilic); transmitted by *Anopheles*; no animal reservoir known; nocturnally periodic
Geographic distribution	India, southeast Asia	Lesser Sunda archipelago of eastern Indonesia, East Timor

[a]Data from Refs [2,6,9,10].
[b]The inner body, zone with a less dense pattern of nuclei.

The similarity of the *Hha*I repeat of *B. timori* and *B. malayi* makes it possible to detect DNA of *B. timori* in humans and vectors by PCR-based assays targeting this repeat that were originally developed for the detection of *B. malayi* [10]. These assays can be useful for the xenomonitoring of *B. timori* in mosquito populations and for the detection of Mf in humans, expecially in combination with serological assays [11].

Like *B. malayi* and many other filarial parasites, *B. timori* harbors *Wolbachia* endobacteria, which can be a target for chemotherapy [10]. Comparison of the 16S ribosomal DNA (rDNA) and the genes coding for one of the *Wolbachia* surface proteins (WSP-1) and for the cell division protein filamentous temperature-sensitive mutant Z (FtsZ) of *Wolbachia* from *B. timori* and *B. malayi* reveals few nucleotide differences. However, these differences support the assumption that each sibling species is infected with a different strain of endobacteria. With additional information emanating from the *B. malayi*–*Wolbachia* genome project (http://tools.neb.com/wolbachia/), other surface-associated proteins of the *B. timori*–*Wolbachia* can be identified to investigate a possible role of *Wolbachia* in the speciation of *Brugia* parasites that infect humans.

Antigens and antibodies against *B. timori*

Antigenic characterization of *B. timori* has been very limited relative to *B. malayi* and *B. pahangi*, but the information available indicates a close antigenic similarity among all three species. Surface proteins of *B. timori* adults and infective larvae, labelled with radioactive iodine, show a similar pattern on one-dimensional sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE) to surface proteins from *B. malayi* and *B. pahangi* [12]. The adult profile contains a major component of 29–30 kDa, which in *B. malayi* and *B. pahangi* is known to be glutathione peroxidase [13]. These antigens are recognized by sera from *B. timori*-infected subjects [14] and appear to be serologically crossreactive because antibodies against *B. malayi* are equally reactive with surface antigens from adult worms of the three *Brugia* species [12]. More recently, in the era of molecular cloning, similar results have been noted with a recombinant antigen (BmRI) from *B. malayi* which showed 100% (97 positive out of 97 cases) recognition by antibodies from patients with *B. timori* [11]. Thus, no *B. timori*-specific antigenic determinants have yet been identified.

Wuchereria bancrofti infections in humans can be reliably detected by the circulating filarial antigen (ICT) assay, which tests the sera of afflicted individuals [15]. The same antigen reacts with monoclonal antibodies (mAbs) to a phosphorylcholine (PtdCho). For reasons that have not become apparent, the ICT test or the PtdCho-based assay do not perform well in *B. malayi* infections of humans [16], although the antigen can be detected in experimentally infected animals [17]. It is noteworthy that a PtdCho-based circulating antigen assay was effective at detecting active infections in sera from *B. timori* cases from Flores [3].

Clinical signs of infection

The most striking clinical sign of lymphatic filariasis caused by *B. timori* is lymphedema of the leg below the knee (Figure 1b, c) [18]. In an area with 25% of individuals tested positive for Mf, ~12% of the examined inhabitants showed lymphedema [6]. Of the individuals with lymphedema, 90% were negative for Mf. Lymphedema of the arms was also observed, but this condition is rare and is not a characteristic of lymphatic filariasis. Hydroceles or genital elephantiasis were never observed among 800 men examined in *B. timori*-endemic areas on Alor. It is known from other endemic areas that brugian filariasis usually does not cause genital disease.

On Alor, clinical signs of lymphatic filariasis caused by *B. timori* and *W. bancrofti* showed almost no overlap. In the *B. timori*-endemic areas, only lymphedema were observed, whereas in the *W. bancrofti*-endemic areas, hydroceles and no lymphedema were found [6]. This could be explained by differences in the parasite biology (e.g. by a different location of the adult worms within the lymphatic system) or by other factors. Bacterial superinfections that take advantage of the damaged lymphatic system are

assumed to contribute to the progression of lymphedema in bancroftian filariasis [19]. Body hygiene could help to prevent this progression. Different professions and socio-cultural habits in the coastal areas and in the rice-farming areas in the center of the island could influence pathogenesis of lymphedema. The majority of the populations in the highland valleys work bare-foot in the swampy rice-fields (Figure 1d). Without health education to motivate them, these farmers are loath to wash their feet if they have skin lesions because of the pain during this process.

Other clinical signs of *B. timori* infection comprise acute fever attacks, lymphangitis, abscesses and scars [6]. The prevalence of these clinical signs appears to be similar to that reported in *B. malayi* infections. In a village in northwestern Flores, *B. timori* was reported to be responsible for abscess formation in many individuals [20]. This village had many transmigrants, who were urged to move from mostly filariasis non-endemic areas on the densely populated island Java to less populated islands within Indonesia. The island Alor has few transmigrants and, without antifilarial treatment, abscess formation was rarely observed during our field surveys. Although the clinical signs caused by *B. timori* are less spectacular than those for bancroftian filariasis, the high prevalence of mild or moderate lymphedema not only in older adults, but also in younger adults and children, makes the infection a serious public health problem in many endemic areas.

Treatment and side effects

Mass drug administration (MDA) to control *B. timori* in Indonesia was first performed on an annual basis in the late 1970s using DEC for nine consecutive days with total doses of 2500 mg for the first year, and 2750 mg for the second year. About 200 individuals were treated in western Flores and the prevalence of Mf-positive individuals decreased in one year from 30% to 2.5% [21]. In the first year, 88% of the treated individuals showed general and/or local adverse effects; however, during re-treatment when the Mf densities dropped, the side effects were remarkably mild even with a higher dosage of DEC [21]. Additional studies on DEC mass treatment were performed in other villages in the same endemic area using 5 mg kg^{-1} DEC for ten consecutive days, followed by selective treatment of cases with microfilaraemia or lymphedema [3]. Despite the efficacy of DEC, its adverse effects on first treatment remained a disincentive to its use in many locales.

To find a regimen more adaptable and sustainable for filariasis control in Indonesia, a low dosage of DEC to be administered by local villagers was introduced [22]. Villagers (cadres) who were trained in drug distribution and recognition of adverse reactions distributed 100 mg DEC weekly for 18 months to all residents with the exception of infants, pregnant women, the elderly and those with debilitating disorders. The purpose of the low dosage regimen was to minimize adverse reactions to the drug and to boost the villagers' confidence in self-reliance. The prevalence of people with Mf decreased in two villages to $<1\%$ and the majority of patients with lymphedema became clinically asymptomatic. Mild adverse reactions were encountered only during the first few weeks of treatment [3]. Although successful, the low-dose regimen did demand a high input in training of personnel and regular monitoring of drug delivery.

As an efficient and more sustainable MDA strategy, the GPELF recommends a single annual dose of 6 mg kg^{-1} DEC combined with 400 mg albendazole for five years [4]. This regimen was evaluated for the first time for *B. timori* on Alor island [23]. The drug combination resulted in no additional adverse reactions compared with DEC treatment and had the same efficacy on Mf density. Compared with the treatment of *W. bancrofti* infection, the microfilaricidal effect of DEC on *B. timori* infection is more rapid and associated with more adverse reactions [23]. The frequency and severity of adverse reactions were correlated with the Mf density of *B. timori*. With the help of antipyretics and antihistamines, general reactions, which were mainly fevers, headaches, myalgia and itching, resolved in no more than two days, whereas local reactions such as adenolymphangitis lasted longer (Figure 1e,f). The monitoring of long-term effects of the DEC combined with albendazole treatment on *B. timori* patients in relation to Mf density and adverse reactions are still in progress [24]. The preliminary results show that this MDA strategy leads to a strong decline of prevalence of *B. timori* microfilaraemia.

Prospects for elimination

Recent studies showed that tools developed for the control and monitoring of *B. malayi* infection can be also used for *B. timori* [5,10,11,23,24]. The limited distribution of this parasite on islands and its low global prevalence implicates *B. timori* as the first candidate for elimination in the framework of the GPELF. Another advantage that aids elimination of this parasite is the fact that no animal reservoir is known for *B. timori*, although it was suspected to be originally a parasite of wild monkeys [25]. Compared with the transmission of filarial parasites by culicine mosquitoes, the transmission by *Anopheles* is less efficient, which could also help to interrupt transmission [26]. In Alor, because malaria and *B. timori* are transmitted by the same *Anopheles* species, control of *B. timori* might also profit from integrated malaria control. Because of the frequent and obvious clinical signs such as lymphedema, endemic communities are prone to control efforts and this can help to sustain compliance during MDA. For example, the total coverage during the first treatment round on Alor was 75% (A. Krentel, pers. commun.). The only drawback is the fact that *B. timori* is distributed in extremely remote, economically disadvantaged and poor areas in Indonesia. With poor or no roads available, the necessary filariasis-related health education (Figure 1g,h) and the annual distribution of drugs can present difficult logistic and financial problems, which might place the entire intervention programme at risk. However, the focusing of filariasis intervention on small and isolated areas in the early stage of GPELF can help to provide a success necessary to sustain the global programme. There is a good opportunity to eliminate *B. timori* and it is hoped that the exploration of its biology will then become only of academic interest.

Acknowledgements
We thank Paul Rückert, Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ), Kupang, Indonesia, Paul Manoempil, District Health Administration, Kalabahi, Alor and their teams for their encouragement during the field work. We thank Eric A. Ottesen, Rollins School for Public Health, Atlanta, and Dietrich W. Büttner, Bernhard Nocht Institute, Hamburg, for critically reading the manuscript. The studies were supported by grants of WHO/TDR, GlaxoSmithKline and GTZ. The studies would have been not possible without the help and understanding of the study population in Mainang village.

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doi:10.1016/j.pt.2004.06.001

Genomics meets transgenics in search of the elusive *Cryptosporidium* drug target

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Cryptosporidium **is an important pathogen of humans, and a challenging model for the laboratory. The parasite genome sequence, accessible through a comprehensive database, now provides exciting opportunities for urgently needed advances. Comparative genomics, combined with the genetic system in the related parasite** ***Toxoplasma gondii*****, outlines a detailed** ***Cryptosporidium parvum*** **metabolic map and facilitates cell biological analyses. New targets for** ***Cryptosporidium*** **drug and vaccine development can be identified and validated based on this approach.**

In recent years, *Cryptosporidium* has been one of the most troublesome agents of water-borne disease in developed countries. A series of epidemic outbreaks caused by *Cryptosporidium parvum and Cryptosporidium hominis* have occurred across the world, some at a massive

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Available online 19 June 2004