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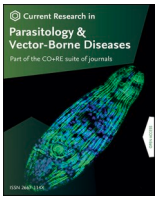

Filarial disease in the Brazilian Amazon and emerging opportunities for treatment and control

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ABSTRACT

Following the successful eradication of *Wuchereria bancrofti*, there are now just three species of conventional microfilaremic human filarial parasites endemic to the Brazilian Amazon region: *Mansonella ozzardi*, *Mansonella perstans* and *Onchocerca volvulus*. The zoonotic filarial parasite *Dirofilaria immitis* is also found in the Amazon region as are several sylvatic filarial parasites, some of which have been recorded causing zoonoses and some of which have never been recorded outside the region. *Onchocerca volvulus* is only found in the Amazonia onchocerciasis focus in the Brazilian state of Roraima where it affects the people of the Yanomami tribe living around the densely forested Venezuela border region. *Mansonella ozzardi* is by far the most common filarial parasite in Brazil and has a broad but patchy distribution throughout the western Amazon region. Recorded in the Brazilian states of Acre, Roraima, Matto Grosso, and within almost every municipality of Amazonas state, it is believed that pollution of the urban stream and river systems prevents the development of the simuliid vectors of *M. ozzardi* and explains the parasite's reduced distribution within urban areas and an absence of recent reports from the state capital Manaus. Decades of WHO-led periodic ivermectin treatment of Yanomami tribe's people have resulted in the partial suppression of *O. volvulus* transmission in this focus and has also probably affected the transmission of *M. ozzardi* in the region. *Mansonella perstans*, *O. volvulus* and very probably *M. ozzardi* infections can all be treated and most likely cured with a 4–6-week treatment course of doxycycline. The Brazilian Ministry of Health does not, however, presently recommend any treatment for mansonellosis infections and thus parasitic infections outside the Amazonia focus are typically left untreated. While the long treatment courses required for doxycycline-based mansonellosis therapies preclude their use in control programmes, new fast-acting filarial drug treatments are likely to soon become available for the treatment of both onchocerciasis and mansonellosis in the Amazon region. Filarial disease management in the Brazilian Amazon is thus likely to become dramatically more viable at a time when the public health importance of these diseases is increasingly being recognized.

1. Introduction

Over the last 80 years or so, infectious disease control programmes have made great progress in reducing the global disease burden caused by onchocerciasis and lymphatic filariasis (Rebollo and Bockarie, 2017; Brattig et al., 2021). During the same period and in parallel to this, onchocerciasis and lymphatic filariasis research has been slowly revealing the breadth and seriousness of the pathologies that these filarial diseases can cause (Crump et al., 2012; Hadermann et al., 2023). Key epidemiological studies first showed that infections with *Onchocerca volvulus* could cause blindness, then that infections were associated with an excess of mortalities, and most recently, that they are associated with epilepsy (Little et al., 2004; Crump et al., 2012; Hadermann et al., 2023). Similarly, while it has long been recognized that lymphatic filariasis can

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cause lymphedema and hydrocele, it took time before tropical pulmonary eosinophilia was also recognized as part of the lymphatic filariasis clinical profile and disease burden (Simonsen et al., 2013). Only within the last decade has the stigma and psychological trauma caused by filarial disease disfigurements begun to be included in the disease burden calculations for these diseases (Ton et al., 2015). This slow unveiling of the true pathogenicity of onchocerciasis and lymphatic filariasis, both of which have been targeted by the World Health Organization (WHO) for decades, has led many to question whether less well-studied chronic filarial diseases like mansonellosis and loiasis, which have historically been seen as benign, may also be responsible for significant but difficult-to-detect disease burdens and thus whether they may also need to be targeted for control in the future (Ta-Tang et al., 2021; Jacobsen et al., 2022).

After the WHO upgraded its filarial disease targets from controlling onchocerciasis and lymphatic filariasis to eliminating both, the areas in which it implemented mass-drug administration expanded into many regions where loiasis and onchocerciasis are co-endemic (Crainey et al., 2017; Brattig et al., 2021). As the mass administration of ivermectin in such areas is dangerous, the programme's geographical expansion has helped stimulate the development of new fast-acting, curative anti-filarial drugs, many of which have the potential to be used for treating a wide range of filarial parasites. The programme's expansion has also stimulated research interest in loiasis which ultimately led to the discovery that it is responsible for a significant disease burden, through the excess mortalities it causes (Chesnais et al., 2017; Veletzky et al., 2020). While there is still too little data yet to argue mansonellosis is also responsible for a significant disease burden, evidence that *Mansonella ozzardi* infections are associated with corneal lesions and evidence that *Mansonella perstans* could be associated with nodding syndrome is augmenting concerns that mansonellosis could also be responsible for a significant but presently hidden disease burden (Vianna et al., 2012; Ta-Tang et al., 2021; Colebunders et al., 2023; Edridge et al., 2023). Despite these growing concerns and the fact that new drugs could dramatically increase the viability of a wide range of filarial disease programmes, most filarial disease endemic regions have no formal filarial parasite surveillance or management procedures outside of those provided by the WHO's lymphatic filariasis and onchocerciasis programmes (Ta-Tang et al., 2021; Jacobsen et al., 2022).

In comparison with the health systems in most other filarial disease endemic regions, the health system in the Brazilian Amazon can be considered to have substantial infectious disease surveillance infrastructure and management resources (Bitton et al., 2019; Castro et al., 2019). The region can thus be seen as among the most likely in the world to expand the range of filarial diseases it provides treatment and control programmes (Portela et al., 2024). At present, however, the Brazilian Ministry of Health does not have any formal filarial disease management or monitoring programmes, beyond those conducted in partnership with OEPA (Ta-Tang et al., 2021; Portela et al., 2024). At a time when both the case for and the viability of new filarial disease control is dramatically strengthening, there is a need for a detailed and up-to-date picture of the epidemiological situation in the region. This review therefore sets out to provide a full account of current knowledge on the discovery, diversity, and abundance of the filarial parasites of the Brazilian Amazon before discussing their public health importance in the context of emerging new therapeutic treatment and management options.

2. Human filarial parasite diversity in the Brazilian Amazon

There are four filarial parasites that use humans as their definitive hosts and are widely accepted to be presently or formally endemic to the Brazilian Amazon region: *Onchocerca volvulus*, *Wuchereria bancrofti*, *M. ozzardi* and *M. perstans*. These four parasite species, which all cause microfilaremic infections, can be considered as true human filarial parasites and distinct from the filarial parasites that infect humans, but which predominantly or exclusively use animals as their definitive hosts, and which are hereafter described as zoonotic filarial parasites (Orihel, 1985; Crainey et al., 2017; Ta-Tang et al., 2018). Of these four human filarial parasites in the Amazon region, *M. ozzardi* is the only species to be considered native and *W. bancrofti* is the only species thought to have been lost (Ta-Tang et al., 2018; Martins et al., 2021). *Onchocerca volvulus* and *M. perstans* are both presently considered endemic to the Amazon region and, like *Wuchereria bancrofti*, are thought to have arrived in the Americas through the nefarious activities of the transatlantic slave trade (Crainey et al., 2016a; da Silva et al., 2017; Martins et al., 2021). A basic scheme illustrating how true human filarial infections are transmitted is shown in Fig. 1.

Besides reports of these four human filarial parasite species, there have also been several reports of atypical human microfilarial infections occurring in the Amazon region (Godoy et al., 1980; Adami et al., 2008; Arrospide et al., 2009). While molecular efforts to confirm these infections as being caused by distinct novel human filarial parasite species have hitherto failed, the possibility that these atypical microfilariae are explained by *M. ozzardi* hybrids with other filarial parasite species remains (Marcos et al., 2012; Ta-Tang et al., 2016). Although hybrids of filarial parasites have never previously been recorded, most of the techniques used for the molecular characterization of filarial infections do not allow to easily distinguish hybrids from co-infections (Marcos et al., 2012; Ta-Tang et al., 2016). If thus filarial diversity in the Amazon region is not restricted to the three distinct human filarial parasite species currently considered endemic, the most likely source of additional diversity is from parasites of African origin forming hybrids with *M. ozzardi* as the historical geographical isolation between *M. ozzardi* and these parasites would have not been expected to create the conditions for mating barriers evolving between them (Turelli et al., 2001). Of all the possible *M. ozzardi* hybrids that could be formed in the Amazon region, *M. ozzardi* × *M. perstans* hybrids are by far the most likely. Adult *M. ozzardi* and *M. perstans* are both found in the connective tissues of the mesentery; both parasites are transmitted by Ceratopogonidae vectors and are congeneric and thus genetically closely related (Daniels, 1902; Baird et al., 1987). The two parasites also have the broadest overlap in their distribution and thus the opportunities for mating and finding viable arthropod vectors for the resulting hybrids seem most probable for this combination (Ta-Tang et al., 2018; Crainey et al., 2020). Historically, the inaccessibility of adult filarial parasites and the small size of microfilariae and filarial parasite larvae has made genotyping of individual filarial parasites very challenging, and this has precluded investigations into the existence of filarial parasite hybrids and genetic exchange between human filarial parasite species more broadly. However, individual microfilariae can now be easily isolated and genotyped with the assistance of laser dissection, and thus whether human filarial parasites in the Amazon region form hybrids or exchange genetic material (and if they do - to what extent) will likely soon become known (Post et al., 2009).

3. Zoonotic filarial parasite diversity in the Brazilian Amazon

In addition to the filarial disease caused by the three human filarial parasite species that are presently considered endemic to the Brazilian Amazon, multiple sylvatic filarial parasites have also been recorded causing zoonoses in the region (Bain et al., 2011; Otranto et al., 2011; Barbosa et al., 2023). A basic scheme illustrating how these sylvatic filarial parasites can cause disease in humans is shown in Fig. 2. *Dirofilaria immitis* is probably the most common cause of human filarial zoonosis in the New World and has been detected in its canine hosts in numerous urban centers within the Brazilian Amazon (Silva et al., 2008; Soares et al., 2014; Barbosa et al., 2023). The parasite's primary hosts (stray and domestic dogs) in these regions are found abundantly and its catholic culicine vectors breed year-round meaning the region's residents are constantly exposed to *D. immitis* infection. Despite this and the fact that *D. immitis* has been endemic to the region for at least a century,

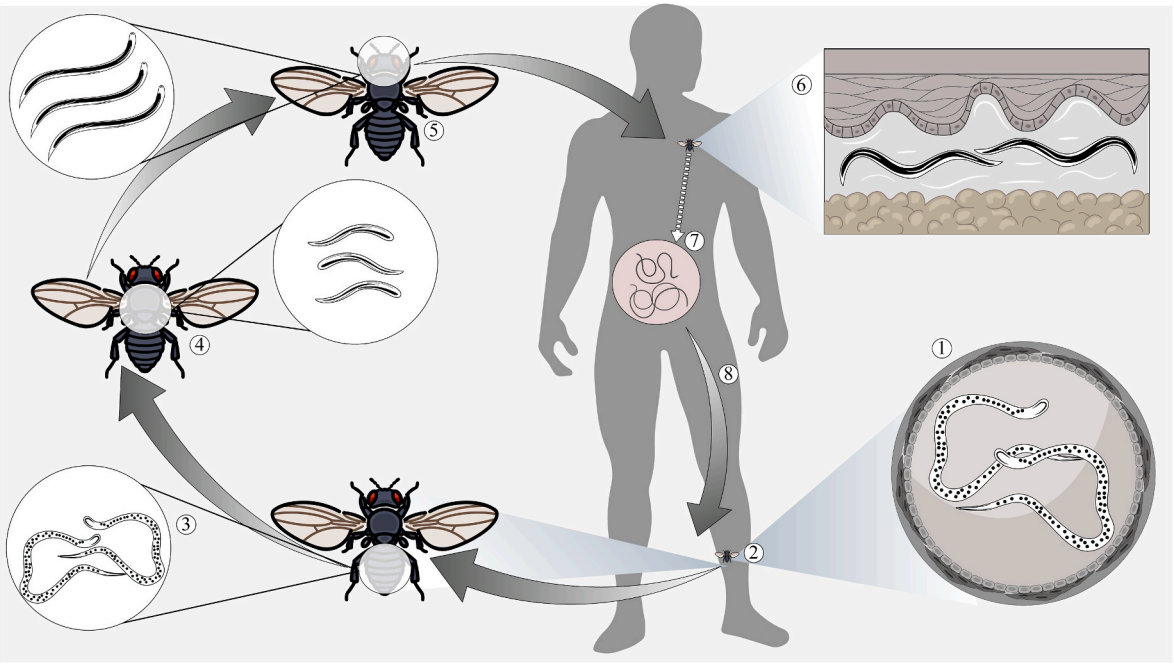

Fig. 1. A generalized scheme of how true human filarial parasites are transmitted. Numbers on the image indicate important steps in the biological life-cycle of a typical human filarial parasite: (1) Microfilariae are present in the blood or skin of an infected person; (2) Vectors take up microfilariae during the blood meal; (3) Microfilariae transform into first-stage (L1) larvae in vector's abdomen; (4) L1 larvae migrate to the vector's thorax where they develop into second-stage (L2) larvae; (5) L2 larvae transform into the infective stage (L3) and migrate to the head/mouth parts of a competent vector; (6) When an infected vector takes a subsequent blood meal, the L3 larvae enter the host and transform into L4 larvae; (7) After a period of 8–12 months, the L4 larvae transform into adult parasites and begin to reproduce sexually; (8) Fertilized female parasites release microfilariae into the bloodstream or subcutaneous tissue. This scheme is based on the transmission cycle of *Mansonella ozzardi* shown in Ferreira et al. (2021).

classic clinical reports of dirofilarial pulmonary coin-shaped lesions, which are typically detected incidentally on X-ray and CT-scans, appear never to have been made in the region (McCall et al., 2008). Clinical reports of filarial zoonoses in the region have thus far been limited to ocular manifestations, which are probably the most commonly reported presentation of zoonotic filarial infections (Orihel and Eberhard, 1998; Bain et al., 2011; Otranto and Eberhard, 2011; Otranto et al., 2011; Barbosa et al., 2023). Two reports of adult filarial parasites being recovered from the eyes of Amazon residents exist, and in both of these cases the parasites recovered were not previously known to science; one parasite belonged to the genus *Pelecitus* and the other - to the genus *Dirofilaria* (Bain et al., 2011; Otranto et al., 2011). The recent regional deployment of molecular tools to characterize filarial larvae in dipteran vectors has also led to the discovery of a novel filarial parasite species that would not have previously been identifiable based on morphological characteristics (Brilhante et al., 2020). This discovery, taken together with the discovery of new filarial parasites from case reports, suggests that there is probably a great paucity of data concerning the diversity of sylvatic filarial parasites in the Amazon region. Thus, the broad range of filarial parasites already known to the region is probably only a tiny fraction of the true diversity of the region's sylvatic filarial parasites (Conga et al., 2019a, 2019b; Silva et al., 2022; Costa et al., 2023).

4. The discovery and distribution of filarial parasites in the Brazilian Amazon

The parasite *Wuchcercia bancrofti* is named after Otto Edward Henry Wucherer who was born in Portugal but carried out medical research in Bahia (Brazil) and the Australian parasitologist Joseph Bancroft who worked in Queensland (Cook, 1993). These researchers gained their eponyms in recognition of Wucherer's early description of the parasite's microfilariae (the first made from a urine sample), and Bancroft's discovery and description of the adult parasites (Wucher, 1868; Cook, 1993). Despite the place of Brazil at the vanguard of early research on *W. bancrofti* and the fact that the elephantiasis was known to be endemic to Belem long before the 1940s, microfilariae of *W. bancrofti* were not recorded in the Brazilian Amazon until 1945 (Causey et al., 1945). Subsequent blood and vector surveys spanning the entire Brazilian Amazon region were conducted in the 1950s and confirmed the transmission of *W. bancrofti* and endemicity in the Amazon region's two largest urban centers (Manaus and Belem) but failed to find autochthonous cases anywhere else (Deane, 1949; Rachou et al., 1954a, 1954b; Lacerda and Rachou, 1956; Rachou and Lacerda, 1956). These surveys ultimately led to the introduction of targeted lymphatic filariasis control measures in Belem, but not in Manaus (Rachou, 1960; Martins et al., 2021). Despite this, arbovirus vector control measures that were implemented in Manaus and that could reasonably have been expected to have had a major impact on the local culicine vectors of lymphatic filariasis were deployed and sustained so that by the 1980s Manaus was considered by the Brazilian Ministry of Health as free of lymphatic filariasis (Martins et al., 2021; Portela et al., 2024). After rigorous microfilariae and vector surveys conducted in Belem failed to find *W. bancrofti* in the early 2000s, the Amazon region was considered to be free from lymphatic filariasis (Fontes et al., 2005, 2012). Concerns of migrant-induced regional recrudescence of lymphatic filariasis were, however, voiced in the mid-2010s (Rawlinson et al., 2014). Following a devastating earthquake in lymphatic filariasis endemic Haiti in 2010, an estimated four to six thousand Haitians sought refuge and economic prosperity in Manaus. Although a blood survey of these immigrants only found one infected person among the 244 examined individuals, concerns about recrudescence persisted because of the vector populations in the region (Rawlinson et al., 2014; Silva et al., 2017; Martins et al., 2021). However, a recent city-wide blood survey in Manaus failed to detect *W. bancrofti* in more than 3700 examined individuals and although other urban centers in the Amazon region have grown larger

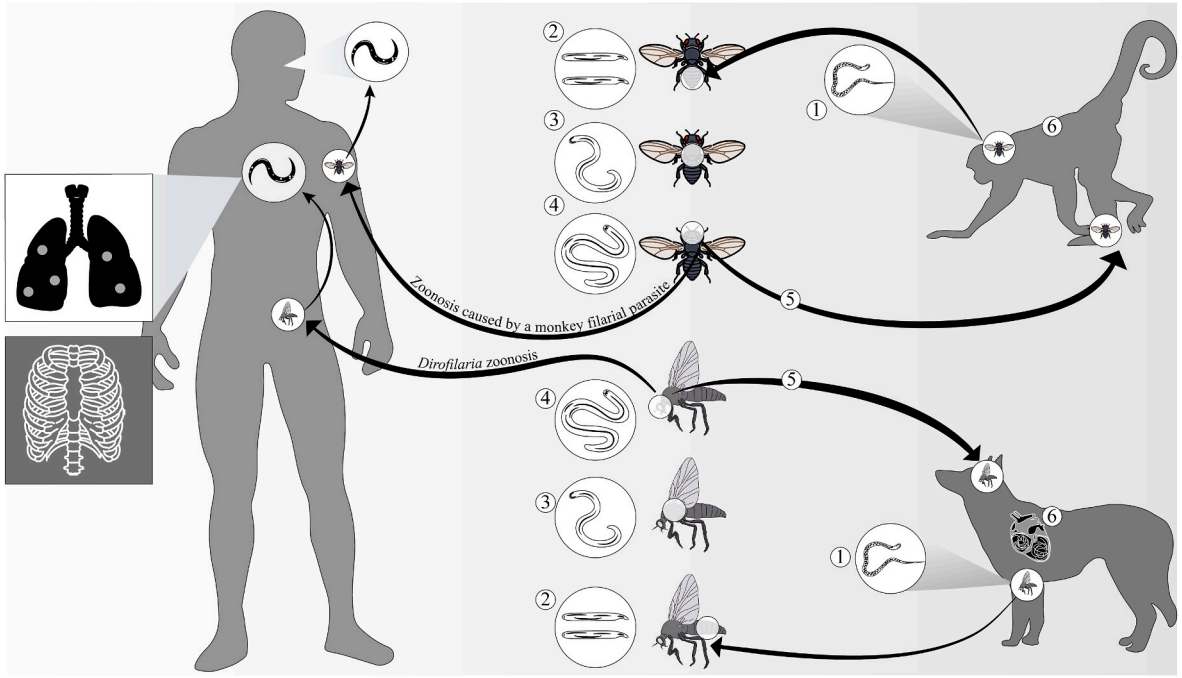

Fig. 2. A generalized scheme of how zoonotic filarial parasites cause disease in humans. The image shows two distinct scenarios. In the first scenario, i.e. zoonosis caused by a monkey filarial parasite, a filarial parasite from a non-human primate enters a non-permissive human host and partially develops into an adult filarial parasite before localizing around the eye socket. In the second scenario, i.e. zoonosis caused by *Dirofilaria*, *D. immitis* larvae are shown entering a human, where they can partially develop and then accumulate and calcify in the lungs, where they can subsequently appear on X-ray exams as coin-shaped lesions. Although the two types of parasites cause different zoonoses in humans, they share very similar life-cycles. Numbers on the image indicate important parasite life-cycle stages. The two scenarios only differ at step (6) when the L4 larvae of the parasites transform into adults and begin reproducing sexually within a definitive host's body. While adult female *D. immitis* localize and release microfilariae from the heart of their canine hosts, adult female non-primate filarial parasites typically localize and release microfilariae from the abdominal cavity or subcutaneous tissues of the definitive host. The life-cycle steps (1) to (5) for both parasites are essentially the same: (1) The vector takes up microfilariae present in the bloodstream during the blood meal; (2) Microfilariae transform into L1 larvae in vector's abdomen; (3) L1 larvae migrate to vector's thorax and develop into L2 larvae; (4) L2 larvae transform into the infective stage (L3) and migrate to the head and mouth parts of a competent vector; (5) L3 larvae enter their definitive host and begin transformation into L4 larvae.

than the sizes of Manaus and Belem at the time when they were first recorded as endemic, blood surveys in such regions have also proven all negative (Korte et al., 2013; Martins et al., 2021). Feared recrudescence of lymphatic filariasis has therefore not yet materialized in the Brazilian Amazon and thus while the region continues to have environmental conditions suitable for the sustainability of lymphatic filariasis foci, it presently remains free of them (Korte et al., 2013; Martins et al., 2021).

Although it was once proposed that microfilaremic *O. volvulus* infections were reported in Brazil at around the same time they were first recorded in Africa (O'Neill, 1875; Corrêa and Moraes, 1979), the first report of an autochthonous case of onchocerciasis in Brazil was not made until the 1960s and the Amazonia onchocerciasis focus (AOF) was not characterized until the 1970s (Moraes and Dias, 1972; Moraes et al., 1974; Corrêa and Moraes, 1979). The validity of a second Brazilian onchocerciasis focus in the central-west region of the country, purportedly spread by the activities of illegal gold mining, was questioned shortly after it was reported (Maia-Herzog et al., 1999, 2000; Richards et al., 2000; Shelley, 2002). However, while it remains controversial as to whether the Minaçu onchocerciasis focus was a short-lived satellite focus (as the lymphatic filariasis focus in Manaus seems to have been) or was simply artifactual, there is presently no controversy that the AOF is now the only active onchocerciasis focus in Brazil (Shelley, 2002; Crainey et al., 2017; Sauerbrey et al., 2018). Although this focus only affects ~30,000 people of the Yanomami tribe (~15,000 on either side of the political border), the nomadic hunter-gatherer lifestyle of this population and the vast size of the dense forested territory of the AOF (which straddles the border with Venezuela) has made onchocerciasis elimination in this focus extremely challenging (Shelley, 2002; Botto et al., 2011; Sauerbrey et al., 2018; Grillet et al., 2019). Consequently, onchocerciasis control and elimination in the AOF has progressed less quickly than in all other Latin American onchocerciasis foci, and today the AOF is the only onchocerciasis focus in Latin America where *O. volvulus* transmission is still considered to be ongoing (Crainey et al., 2017; Sauerbrey et al., 2018).

Mansonellosis is by far the most common filarial disease in the Brazilian Amazon and *M. ozzardi* is by far the most common causative agent, with *M. perstans* only known to occur in the extreme north of the region (Lima et al., 2016; Ta-Tang et al., 2018; Crainey et al., 2020). First recorded in Brazil's Amazonian border regions with Guyana by Daniels (1898) only a year after the first description of the parasite by Sir Patrick Manson, *M. ozzardi* is found widely, though not uniformly, throughout Brazil's western Amazon region (Daniels, 1898; Ta-Tang et al., 2018; Crainey et al., 2022). Although the parasite has been recorded in the Brazilian states of Roraima, Acre, Matto Grosso, and within almost every municipality of the Amazonas State, there are regions of Rondonia and Para states that ostensibly have similar vector fauna and environmental conditions to those in Amazonas State but are apparently free from *M. ozzardi* (Deane, 1949; D'Andretta et al., 1969; Moraes et al., 1985; Basano et al., 2011; Adami et al., 2013; Abrahim et al., 2019). It has been suggested that the absence of *M. ozzardi* from surveyed regions of Rondonia might be explained by resident populations receiving a form of immunization to *M. ozzardi* infections through exposure to bites from insects infected with sylvatic filarial parasites (Ta-Tang et al., 2018). However, it has recently been shown that residents of *M. ozzardi*-endemic Sao Gabriel do Cachoeira are routinely being exposed to infectious stage L3 larvae of *Mansonella mariae* (a species that infects a range of non-human primate species), suggesting that if immunization from exposure to sylvatic filarial

parasites occurs at all, it probably does not provide complete protection for everyone (Sato et al., 2008; Bain et al., 2015; Silva et al., 2022). In *M. ozzardi*-endemic municipalities of the Amazonas State, urban populations have significantly lower prevalences than rural populations (Medeiros et al., 2009; Martins et al., 2010). It is thought this is because polluted urban rivers and streams preclude the development of the juvenile stages of the parasite's simuliid vectors (Ta-Tang et al., 2018). An absence of simuliid vectors in the Amazonas State capital Manaus, may thus, very well explain a paucity of recent reports of *M. ozzardi* among the city's residents (Couceiro et al., 2007, 2012). The absence of *M. ozzardi* in Belem is, however, more likely explained by a wider regional absence of the parasites from the eastern Amazon region rather than by urbanization (Causey et al., 1945). In addition to *M. ozzardi* having a patchy distribution in the Amazon region, its prevalence is also highly variable (Lima et al., 2016; Ta-Tang et al., 2018). Within the State of Amazonas for example, light-microscope-based thick blood smear microfilariae surveys have recorded prevalences above 50% among some indigenous Amazonian communities in Labrea and a prevalence as low as 6.3% in an urbanized area of Tefé (Medeiros et al., 2008, 2014). However, these data are likely underestimates of the true regional prevalence of *M. ozzardi*, as PCR testing of blood samples from endemic areas has shown that light microscope-based microfilariae blood surveys miss many "sub-microscopic" infections (Medeiros et al., 2015). Light microscope-based diagnoses of mansonellosis infections typically only examine 20–40 μl of blood, while PCR diagnoses typically utilize > 200 μl. It is, therefore, possible that "sub-microscopic" *M. ozzardi* infections are simply infections with low microfilarial counts. It is, however, also possible that submicroscopic infections have a more complex explanation. Microfilariae are far more difficult to encounter in patients with the sowda form of onchocerciasis than in patients with generalized onchocerciasis (Gallin et al., 1995; Hoerauf et al., 2002). The sowda manifestation is associated with a hyperimmune response to *O. volvulus* infection and the IL13 gene variant Arg110Gln (Hoerauf et al., 2002). The same IL13 variant Arg110Gln is also significantly more common among people with submicroscopic *M. ozzardi* infections in the Brazilian Amazon than among people with patent *M. ozzardi* infections. Thus, it could be that submicroscopic infections are caused by a hyperimmune response to *M. ozzardi* infection clearing the microfilariae but leaving traces of their DNA in the blood of infected individuals (Santos, unpublished data).

Dirofilaria immitis was the first zoonotic filarial parasite to be recorded in the Amazon region after a team of British colonial researchers, based at the historical Liverpool School of Tropical Medicine (LSTM) field laboratory in Manaus, performed a parasite survey on regional stray dogs (Gordon and Young, 1922). Since then, this parasite has been recorded in numerous urban centers throughout the Amazon region (Silva et al., 2008; Soares et al., 2014; Barbosa et al., 2023). Interestingly, most of these reports indicated that the parasite occurs more in peri-urban areas rather than in urban centers (Soares et al., 2014; Barbosa et al., 2023). The urban regions of Manaus where *D. immitis* was first recorded a century ago thus now appear to be free of the parasite, whereas the peri-urban regions of the modern city, which were all primary rainforest when the first report of the parasite was published, seem to be where *D. immitis* is now most abundant (Gordon and Young, 1922; Barbosa et al., 2023). These peri-urban regions are also the regions where most contacts between humans and sylvatic filarial parasites are expected to occur because of the proximity to the forest habitat used by most of the known hosts of sylvatic filarial parasites (Conga et al., 2019a, 2019b; Costa et al., 2023). As the Amazon region's unrelenting reforestation continues and rainforest-urban interface regions expand with the consequential urbanization, more contact between sylvatic filarial parasites and Amazon region residents and more cases of zoonotic filarial infections can thus be expected to occur (Feng et al., 2017; Lowe et al., 2020; Silva et al., 2022; Costa et al., 2023).

5. Human filarial parasite abundance in the Brazilian Amazon

It is estimated that there are presently around 51 million people infected with parasites causing lymphatic filariasis (*W. bancrofti*, *Brugia malayi* or *Brugia timori*) and that around 21 million people are infected with *O. volvulus*, causing onchocerciasis (Ehrens et al., 2022a). Assuming infection prevalence of around 20%, there are a little over 5000 people in the Amazon region infected with *O. volvulus*, almost all of whom are people of the Yanomami tribe (Sauerbrey et al., 2018). Even excluding the possibility of infections in the Pacific region (as there have been no credible reports from the region for almost a century) and accounting for the fact that onchocerciasis and lymphatic filariasis control programmes have very likely had a significant impact on *Mansonella streptocerca* prevalence levels, it is still very likely that more than 200 million people are presently living with chronic mansonellosis infections (Crainey et al., 2016b; Ta-Tang et al., 2021). Given this, it is perhaps not surprising that mansonellosis infections are by far the most common form of human filarial infection in the Brazilian Amazon and indeed, in the Amazon region in general. Assuming that urban centers with populations greater than 100 thousand people are free of *M. ozzardi* and that endemic regions have overall prevalences of around ~19%, there are around 26 million people infected with *M. ozzardi* globally. Of these, around 12 million live in the Amazon region, and around 1.4 million live in the Brazilian Amazon. Updating the widely cited *M. perstans* infection estimates by Simonsen et al. (2011) with the 2022 World Bank population data, it can be assumed that today more than 186 million Africans are living with chronic *M. perstans* infections and that this figure is set to grow. As *M. perstans* infections typically occur at far lower prevalence levels in Latin America than they do in Africa and because their geographical distribution is restricted to certain regions of the Brazilian, Colombian, Guyanian, Suriname and Venezuelan Amazon regions, there are likely only around 1 million *M. perstans* infections in the New World (Daniels, 1898; Beaver et al., 1976; Kozek et al., 1983). The geographical range of *M. perstans* is particularly restricted in Brazil, where it occurs with extremely low prevalence in the state of Roraima and the extreme northwest of the Amazonas State (Crainey et al., 2020). An estimate of between 50,000 and 100,000 *M. perstans* infections in Brazil is thus probably not very conservative.

6. Public health importance of filarial parasites in the Brazilian Amazon

With the loss of lymphatic filariasis, onchocerciasis is now the only filarial disease in the Brazilian Amazon to be targeted for control (Sauerbrey et al., 2018; Martins et al., 2021). In part because most mansonellosis infections are asymptomatic and in part because the symptoms hitherto linked to mansonellosis are considered mild, mansonellosis is not targeted for control anywhere within the Brazilian Amazon or indeed outside it (Ta-Tang et al., 2021; Ferreira et al., 2023; Portela et al., 2024). Although it has been suggested that *M. perstans* may cause nodding syndrome and the partial development of *M. ozzardi* in arbovirus vectors like *Aedes aegypti* could affect the transmission of arboviruses and even that chronic mansonellosis infections could affect vaccine efficiency, the public health importance of mansonellosis in the Brazilian Amazon has historically been considered limited to how it can impact the monitoring and ultimately the control of onchocerciasis (Shelley et al., 2001; Post et al., 2003; Vaughan et al., 2007; Ta-Tang et al., 2010; Edridge et al., 2023). The microfilariae of both *M. perstans* and *M. ozzardi* can be found in the skin but cannot be easily distinguished from microfilariae of *O. volvulus* threatening the reliability of light-microscope based skin-snip surveys of onchocerciasis (Post et al., 2003; Ta et al., 2018; Nana-Djeunga et al., 2019). Some simuliid vectors of *O. volvulus*, and most notably *Simulium oyapockense*, also transmit *M. ozzardi* and other zoonotic filariae, rendering classical microscopic dissection of vectors unreliable for measuring transmission rates (Shelley et al., 2010; Romão Ribeiro da Silva et al., 2019; Silva

et al., 2022). While immunological tools such as the Ov-16 antibody test (which detects exposure to infectious L3 larvae of *O. volvulus*), have proven extremely valuable for monitoring of *O. volvulus* transmission in both African and other Latin American onchocerciasis foci, there are concerns that residents' exposure to infectious *M. ozzardi* and or zoonotic filarial parasites in the Brazilian Amazon region could render these tools ineffective in the AOF (Shelley and Coscarón, 2001; Luz et al., 2014; Botto et al., 2016; Silva et al., 2022). While using DNA-based diagnostic techniques can overcome many of these obstacles, the impact that mansonellosis can have on onchocerciasis control monitoring in the AOF is undoubtedly non-trivial and not helping with the elimination of onchocerciasis from Latin America (Alhassan et al., 2015; Poole et al., 2019; Ta-Tang et al., 2021).

Beyond the indirect public health importance of mansonellosis, there is also an increasing concern that the disease may have a significant but hitherto undetected burden (Ta-Tang et al., 2021; Ferreira et al., 2023; Portela et al., 2024). Very significant disease burdens were detected when epidemiological studies searched for excess mortalities associated with onchocerciasis and loiasis infections and as a consequence of these discoveries, researchers are now calling for dedicated WHO-funded loiasis control programmes (Little et al., 2004; Chesnais et al., 2017; Veletzky et al., 2020; Jacobsen et al., 2022). While epidemiological studies of mansonellosis that have been performed to date have associated corneal lesions, headaches and fevers to infections, the data hitherto collected are not suitable for standard disease burden calculations and no studies that would have uncovered an excess of mortality associated with mansonellosis have yet been reported (Adami et al., 2008; Vianna et al., 2012; Martins et al., 2021). Similarly, other pathologies such as wheezing and epilepsy that might be expected to be associated with filarial infections and indeed some of which have been reported in *M. ozzardi* case reports, have not yet been the subjects of epidemiological investigations (Nutman et al., 1987; Ta-Tang et al., 2021).

Thus, while historically clinicians have been reluctant to recommend mansonellosis treatment and the Brazilian Ministry of Health continues not to provide any treatment guidance for mansonellosis infections, leading clinicians are increasingly aware that the benign perception of mansonellosis could easily be explained by data paucity and are therefore increasingly recommending treatment for mansonellosis both in the Brazilian Amazon and beyond (Ferreira et al., 2023; Hochberg et al., 2023; Portela et al., 2024).

The absence of clinical dirofilarial disease reports from the Amazon region despite the compelling evidence supporting the broad distribution of the causative parasites and their prolonged endemicity in the Brazilian Amazon suggests that there have likely been numerous undetected zoonotic *D. immitis* infections (Silva et al., 2008; Soares et al., 2014; Barbosa et al., 2023). The principal public health concern about these infections is that, when seen on X-ray and CT-scans, they can provoke expensive, invasive, and unnecessary clinical investigations (McCall et al., 2008). To date, there are no estimates of how much such investigations are costing the Brazilian National Health Service (SUS), but the wide distribution of the parasite and the lack of regional case reports suggest costs could be significant (Barbosa et al., 2023; Portela et al., 2024). Outside of the clinical manifestations caused by dirofilariasis, ocular manifestations of zoonotic filarial parasites are probably the most commonly detected forms of zoonotic filarial infection and have been detected in the Amazon region (Bain et al., 2011; Otranto et al., 2011). Such infections, however, appear to occur only very rarely and thus probably do not have a significant disease burden associated with them (Orihel and Eberhard, 1998; Otranto and Eberhard, 2011).

7. Existing and emerging treatment and control options for the filarial parasites in the Brazilian Amazon

The World Health Organization control efforts in the AOF are focused on the mass drug administration (MDA) of ivermectin, which is done two to four times a year (Sauerbrey et al., 2018; Grillet et al., 2019). Although this approach has been in operation for decades, and transmission of onchocerciasis has been halted in some areas, the transmission of *O. volvulus* is still on-going in other areas, and this has led to the targeted use of doxycycline in certain hyperendemic regions (Crainey et al., 2017; Sauerbrey et al., 2018; Grillet et al., 2019). Presently there are no dedicated mansonellosis or zoonotic filarial control programmes either inside or outside the Brazilian Amazon; however, the activities of the WHO in the AOF are likely to have had a major impact on mansonellosis in the region (Ta-Tang et al., 2021). The ivermectin treatments used by the onchocerciasis control programme of the WHO are highly effective at clearing microfilariae of *M. ozzardi* and thus this programme's efforts to break transmission of *O. volvulus* are likely to have affected the transmission of *M. ozzardi* similarly (Ta-Tang et al., 2018; Ferreira et al., 2023). The programme's doxycycline treatments are also likely to have cured *M. ozzardi* and *M. perstans* infections from all the Yanomami people that were treated in this way (Coulibaly et al., 2009; Debrah et al., 2019). The limited extent to which the programme has used doxycycline, however, means the effect it has had on mansonellosis in the region is also likely to have been limited. Because the microfilariae of *M. perstans* are not susceptible to ivermectin, the transmission and prevalence of this parasite species is unlikely to have been affected by the WHO's use of ivermectin (Ta-Tang et al., 2018, 2021; Ferreira et al., 2023).

Soil-transmitted helminths (STH) are also endemic in the Brazilian Amazon (Gonçalves et al., 2016; Oliveira et al., 2016). These infections are typically treated with benzimidazoles (like mebendazole and albendazole) or ivermectin and with mebendazole dosages that would be expected to clear *M. perstans* microfilariae, but only if treatment regimens were sustained for at least two weeks (Asio et al., 2009; Ferreira et al., 2023). Thus, it is likely that STH treatments in the Amazon region have to date only minimally impacted the transmission of *M. perstans* and may even have promoted *M. perstans* drug resistance (Jourdan et al., 2018; Ta-Tang et al., 2018; Ferreira et al., 2023). Mansonellosis control programmes that cycled (every six months) between 14 days of mebendazole treatment and 1–3 days of ivermectin treatment could not only be expected to have major impact on mansonellosis transmission, but also on local STH prevalence (Jourdan et al., 2018; Ferreira et al., 2023). However, the long treatment times required to deliver curative ivermectin doses for STH infections and microfilaricidal doses of mebendazole for *M. perstans* infections, make the logistics of STH and mansonellosis dual control programmes arguably impractical. Further, this problem is compounded by the fact that neither mebendazole nor ivermectin have clear macrofilaricidal activities, meaning the six monthly cycling between treatment regimens would need to be sustained for at least 10–15 years (the natural lifespan of the adult filarial parasites) in order to eliminate mansonellosis from a targeted area. While onchocerciasis and lymphatic filariasis control programmes in Africa have clearly demonstrated the viability of sustaining mass drug administration programmes for periods in excess of 10–15 years, these programmes typically used single dose treatments and delivered very clear health benefits that would have not be delivered by a STH-mansonellosis control programme (Hotez and Lo, 2020; Brattig et al., 2021; Ta-Tang et al., 2021). Whether such a sustained campaign would be considered viable for mansonellosis control in the Brazilian Amazon or anywhere else is thus questionable. Recently, however, the broad spectrum antihelminthic drug oxfendazole has been shown to possess macrofilaricidal activity against *L. sigmodontis* and has completed phase I clinical trials for onchocerciasis treatment (Ehrens et al., 2022b; Ferreira et al., 2023; Risch et al., 2023). The drug is now in clinical trials to test its efficacy against *M. perstans*, *L. loa* and *Trichuris trichiura*, and may cure *M. perstans* infections with as little as five days of treatment (Risch et al., 2023). Thus, it may be possible in the future to create more viable dual-acting synergistic SHT-mansonellosis programmes combing this drug with other antihelminthics like ivermectin.

The key advantage of using doxycycline (a drug targeting the filarial parasite's bacterial endosymbionts) to treat mansonellosis infections

instead of classical antihelminthic treatments such as mebendazole or ivermectin is that doxycycline is curative and probably effective for all types of mansonellosis infections that occur in the Amazon, i.e. those caused by *M. ozzardi*, *M. perstans*, as well as mansonellosis co-infections (Ta-Tang et al., 2021; Ferreira et al., 2023). The key disadvantage is that treatments require the drug to be administered daily for four to six weeks, which makes control programmes using these drugs logistically complex and financially challenging to implement (Ta-Tang et al., 2021; Ferreira et al., 2023). Because this long treatment time affects the viability of antibiotic-based filarial control programmes, a great amount of effort and financial resources have been invested in identifying alternative *Wolbachia*-targeting drugs with shorter treatment times (Bakowski and McNamara, 2019; Johnston et al., 2021). Thus, a number of curative short-course anti-*Wolbachia* drugs for onchocerciasis and lymphatic filariasis are now available at various stages of clinical trials (Johnston et al., 2021; Ehrens et al., 2022b). Two anti-*Wolbachia* drugs (CC6166 and Corallopyronin A) are presently in phase I clinical trials and could help to bring down treatment times significantly, possibly to seven days or less. It thus seems likely that elimination by MDA of both onchocerciasis and mansonellosis in the Brazilian Amazon and beyond is now closer than ever before (Bakowski and McNamara, 2019; Ta-Tang et al., 2021; Ferreira et al., 2023). Anti-*Wolbachia* drugs could also potentially be used synergistically to control other neglected tropical diseases of the Amazon region and potentially in combination with classical antihelminthic drugs like ivermectin too. Antibiotic-based MDA programmes are already used for trachoma, yaws disease and scabies control, which are all endemic to the Brazilian Amazon.

The outdoor biting habits and the size and inaccessibility of river oviposition sites in the Amazon region make vector control inviable for mansonellosis; for the same reason it is regarded inviable for onchocerciasis and thus it is unlikely that vector control will ever become an important part of filarial control in the Amazon region (Shelley, 2002; Ta-Tang et al., 2021). Although the recent application of next-generation sequencing (NGS) of regional filarial parasite DNA could help in the development of a mansonellosis vaccine, this seems further away for mansonellosis than for onchocerciasis or even dirofilariasis (Crainey et al., 2018, 2020; Geary, 2023; Sinha et al., 2023). Chemically arrested *D. immitis* infections and exposure to irradiated *D. immitis* can provide protection against dirofilarial infections in dogs and studies into the molecular basis of this protection have led to the identification of candidate molecules for *D. immitis* vaccine development (Geary, 2023). Genetically modified immunocompromised mice are now greatly facilitating our understanding of the molecular interplay between filarial parasites and their hosts' immune systems and together with recent advances in mRNA vaccine development could help to accelerate vaccine availability for all filarial parasites in the Amazon region (Geary, 2023; Marriott et al., 2023).

8. Conclusions

The present filarial disease landscape in the Brazilian Amazon has been shaped by the introduction of African filarial parasites and urbanization of the region. Questions remain about whether there is genetic exchange between filarial species of African origin and native New World species and whether such exchange could affect the efficacy of some regional filarial disease treatments. New possible synergies between traditional antihelminthic drugs and emergent curative filarial treatments are creating new opportunities for filarial disease management both within the Brazilian Amazon and beyond. Most immediately for the Brazilian Amazon region, new short-course therapeutics could help accelerate the elimination of onchocerciasis. Perhaps more importantly for the region, however, these same drugs could radically reduce the cost and increase the practically of the treatment of all types of Amazon region mansonellosis (i.e. infections caused by *M. ozzardi*, *M. perstans* or *M. ozzardi* + *M. perstans* co-infections). These new emerging therapies, together with a growing awareness that chronic filarial diseases can cause significant but difficult to detect disease burdens, brings an urgent need for a better understanding of the epidemiology and disease burden of mansonellosis in the Amazon region. As well as a clear need to determine if excess mortalities or neurological or respiratory pathologies are associated with mansonellosis, there is a need for mansonellosis epidemiological data that can be used for disease burden calculations so its public health importance can be measured against other infection diseases that occur in the region. Recent reports of *D. immitis* in the city of Manaus (after an absence of reports for more than a century) highlight the regional neglect of monitoring filarial zoonoses, which are likely to increase as regional deforestation creates more interface regions between the rainforest (where sylvatic filarial parasite reservoirs most commonly occur) and the Amazon region's urban populations. The need to determine if zoonotic filarial disease cause pathologies that are presently being overlooked is thus also growing.

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Cleudecir Siqueira Portela: Conceptualization, Data curation, Methodology, Writing - review & editing. **Cláudia Patrícia Mendes de Araújo:** Conceptualization, Methodology, Writing - review & editing. **Patrícia Moura Sousa:** Conceptualization, Writing - review & editing. **Carla Letícia Gomes Simão:** Conceptualization, Writing - review & editing. **João Carlos Silva de Oliveira:** Conceptualization, Writing - review & editing. **James Lee Crainey:** Conceptualization, Writing - original draft, Writing - review and editing. All authors read and approved the final manuscript.

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