A SYSTEMATIC REVIEW OF THE EPIDEMIOLOGY OF MANSONELLIASIS

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Abstract

Although infection with any of the three types of *Mansonella* species that affect humans is often asymptomatic, a large portion of the world’s population is at risk of this vectorborne filarial nematode infection. No previous global review of the epidemiology of mansonelliasis has been conducted. A systematic review of the literature was conducted. Original research articles that provided population-based mansonelliasis prevalence rates were identified by searching the PubMed database using pre-defined eligibility criteria. Data from each of the forty-six included studies were extracted and compared. Mansonelliasis is a common infection in some parts of west and central Africa and Latin America, with significant variation in prevalence rates over small geographic spaces. The risk of infection increases with age and may be higher in males than females. Despite many similarities, the three agents that cause mansonelliasis have distinct biological, clinical, and epidemiological characteristics. Knowledge about mansonelliasis is important for making differential diagnoses, identifying the possible risks of co-infection with multiple filariases, and addressing the concerns of at-risk populations.

Keywords: mansonelliasis; filariasis; mansonella; epidemiology

Introduction

Mansonelliasis is one of several filarial nematode infections for which humans are the definitive host. This puts it in the same category as several parasitic infections of importance to global public health, including onchocerciasis, lymphatic filariasis, dracunculiasis, and loiasis. The three agents that cause mansonelliasis – *Mansonella perstans*, *M. streptocerca*, and *M. ozzardi* – vary in features such as anatomy and periodicity, the vectors that transmit the agent to humans, the clinical signs and symptoms they cause, and the world regions where they are endemic. While some of these major filarial infections have garnered international attention – onchocerciasis (river blindness) (Gardon et al., 1997) and dracunculiasis (Guinea worm) (Barry, 2007; Cairncross et al., 2002) have been the focus of global eradication efforts – mansonelliasis has been neglected.

This paper is the first systematic global review of the epidemiologic literature on all three forms of mansonelliasis. A systematic search strategy was used to identify 46 original scientific articles of the prevalence of mansonelliasis. These publications report on studies from 18 countries in Africa and Latin America. After providing a brief background on the key features of each of the three types of mansonelliasis, this paper provides a comparison of the epidemiology of these infections, with an emphasis on at-risk populations and geographic regions. Up-to-date epidemiological information is essential for making differential diagnoses, planning public health interventions, and advancing research in the field.

Background on Mansonelliasis

Agent and Vector Characteristics

Three types of *Mansonella*, which are filarial nematodes (roundworms), are known to infect humans: *M. perstans* (formerly *Dipetalonema perstans*), *M. streptocerca* (formerly *Dipetalonema streptocerca*), and *M.
**Clinical Characteristics**

Table 1 highlights key differences in signs and symptoms, diagnosis, and treatment between the three species. Infection with any of the three is often asymptomatic. Symptoms that do occur are related to the preferred location of the agent: *M. perstans* are typically found in body cavities, *M. streptocerca* in dermal and subcutaneous tissue, and *M. ozzardi* in subcutaneous tissues (Garcia, 2007; Heymann, 2004). Symptoms of infection with *M. perstans* may include pectoral and chest pains, periodic dizziness, joint and back pain, and ocular symptoms (Anosike et al., 2005b; Bregani et al., 2006; Bregani et al., 2007). Infection with *M. streptocerca*, which is found under the skin, is associated with cutaneous edema (build-up of fluid in the skin), thickening of the skin, formation of hypopigmented macules (flat blotches) and papules (raised bumps), and pruritus (itchiness) (Heymann, 2004; Fischer et al., 1997). *M. ozzardi* may cause symptoms that include skin rashes, headaches, fever, pruritus, lymphedema (swelling of the arms or legs), and joint pain (CDC, 2008; Garcia, 2007).

**Diagnosis and Treatment**

Diagnosis and treatment also vary by species (Table 1). Blood smears that look for microfilariae are the easiest way to diagnose *M. perstans* and *M. ozzardi* (CDC, 2008). *M. streptocerca* microfilariae do not circulate in the blood, so it is necessary to take a skin snip (CDC, 2008). Care must be taken to differentiate mansonelliasis from onchocerciasis or other filarial infections (Fischer et al., 1997). Treatment must be specific to the infective agent. *M. perstans* is most effectively treated with mebendazole; ivermectin is not effective against *M. perstans*, but is the drug of choice for treating *M. ozzardi* (Garcia, 2007; Heymann, 2004). Both diethylcarbamazine (DEC) and ivermectin have been used to treat *M. streptocerca* infection (Garcia, 2007).

**Methods**

Systematic reviews of the literature minimize the selection bias that may occur in narrative reviews that select articles by hand rather than by using a strict set of inclusion criteria. This methodical approach yields a valid and comparable set of research articles which together can reveal trends and gaps in the published research literature.

A systematic review of original research articles focusing on the prevalence of mansonelliasis was conducted using PubMed, a database from the U.S. National Institutes of Health that searches all MEDLINE citations along with several other databases and older publications (Figure 1). A search for “mansonelliasis” yielded 173 results. The abstracts and/or full-texts of these articles were screened for eligibility. Of the 173 articles, 127 were ineligible: 30 that included only individuals with mansonelliasis and did not provide any population-based statistics, 26 that examined the vectors of infection rather than the human hosts, 22 that reported solely on laboratory techniques and diagnostic methods, 18 that evaluated treatment for mansonelliasis, 16 that focused on a disease other than mansonelliasis and only mentioned mansonelliasis in the commentary, and 15 additional articles that did not report population-based prevalence rates.

All of the 46 remaining articles were located and read, and information about the study country, study years, sample size, age range of participants, and prevalence was recorded. All languages were eligible for inclusion, and the 46 eligible articles were in English (39), Spanish (3), Portuguese (3), and French (1).
Table 1: Agent characteristics [CDC, 2004; Garcia, 2007; Heymann, 2004].

| Agent                     | Mansonella perstans | Mansonella streptocerca | Mansonella ozzardi |
|---------------------------|---------------------|-------------------------|-------------------|
| Adult Size                | 4-8 cm x 0.06 mm    | 2 cm x 0.01 mm          | 3-5 cm x 0.07-0.15 mm |
| Microfilarial Characteristics | 100-200 μm x 5 μm; blunt rounded tail; body nuclei extend to tip of tail | 180-240 μm x 2.5-5 μm; curved hooked “Shepherd’s crook” tail; body nuclei extend to tip of tail | 170-240 μm x 3-4 μm; long thin pointed tail; body nuclei do not extend to tip of tail |
| Vector                    | Culicoides spp. (biting midges) | Culicoides spp. (biting midges) | Culicoides spp. (biting midges) and Simulium spp. (blackflies) |
| Hosts                     | humans, gorillas, and monkeys | humans and monkeys | humans |
| Signs / Symptoms           | usually asymptomatic | often asymptomatic; may cause chronic pruritus (itchiness) and thick papules on skin | often asymptomatic; may cause malaise |
| Common Adult Locations     | body cavities       | subcutaneous tissues     | subcutaneous tissues |
| Common Microfilarial Locations | blood               | skin                    | blood |
| Diagnosis                  | peripheral blood smear | skin snip             | blood smear |
| Recommended Treatment      | mebendazole         | DEC (diethylcarbamazine) / ivermectin | ivermectin |
| Geographic Range           | Africa and the Americas | West and central Africa | the Americas |

Results

The goals of the systematic review were to identify the areas of the world where mansonielliasis has been studied, to identify the prevalence rate in affected communities, and to list the risk factors that have been identified for each species. These findings are presented below and in Tables 2, 3, and 4.

*Mansonella perstans* is found in both Africa and the Americas, but has primarily been studied in Africa (Table 2). The prevalence in endemic areas varies greatly even within small geographic regions. For example, a 2003 study of school children in Uganda showed variation in school-level prevalence ranging from 0.4% to 72.8% (Onapa et al., 2005), and a 2005-2006 study in Uganda found a rate of 57.7% in one community and 76.5% in a neighboring community (Asio et al., 2009). Other studies from Uganda have found village prevalence rates as low as 2% (Onapa et al., 2001) and 21% (Hillier et al., 2008) and as high as 96% (Fischer et al., 1997). A study in Cameroon found village prevalence rates ranging from 55% to 100% (Wanji et al., 2003), while another study from Cameroon found a lower prevalence rate of 26.6% (Mommers et al., 1994). A study of villages in Congo found village prevalence rates ranging from 22.0% to 89.5% (Noireau et al., 1989) and a study in Burkina Faso found village rates ranging from 3.5% to 14% (Kyelem et al., 2003). Prevalence rates from other studies in West and Central Africa demonstrate a similarly wide infection rate, ranging from 3.2% to 47% in Nigeria (Agholade and Akinboye, 2001; Akogun, 1992; Anosike et al., 1992, 2005b; Arene and Adu, 1986; Udonsi, 1986, 1988; Ufomadu et al., 1991; Useh and Ejezie, 1995) and 6.0% in Sierra Leone (Gbakima and Sahr, 1996) to 49.1% in Gabon (Van Hoegaerden et al., 1987), 66.3% in Guinea (Vila Montlleo, 1990), and 75% in Mali (Keiser et al., 2003). The only recent study from Latin America was conducted among an indigenous population in Venezuela and found a prevalence of 11.3% (Gómez and Guerrero, 2000). A study from Colombia found a prevalence of 6% in affected communities in the 1980s (Kozek et al., 1983).

Co-infection with *M. perstans* and other filarial infections appears to be common. 42.3% of onchocerciasis patients in a study in Togo were co-infected with *M. perstans* (Schulz-Key et al., 1993), 36.9% of participants in a study in Cameroon were infected with both *M. perstans* and *O. volvulus* (Wanji et al., 2003), 14% of participants in a study in Gabon had both *M. perstans* and *L. loa* (Van Hoegaerden et al., 1987), 10.1% of persons with *M. perstans* infection in a study from Nigeria also had *L. loa* (Ufomadu et al., 1991), and 9% of participants in a study conducted in the Congo were infected with both *M. perstans* and *L. loa* and 7% had both
M. perstans and M. streptocerca (Noireau et al., 1989). Given the concern that has been raised about filarial co-infection with other agents, this may be an area of concern (Boussinesq et al., 2003; Gardon et al., 1997).

Search PubMed for “mansonelliasis”

n = 173

Remove studies that include only cases (n = 30)

n = 143

Remove animal/vector studies (n = 26)

n = 117

Remove laboratory/diagnostic studies (n = 22)

n = 95

Remove treatment/therapeutic studies (n = 18)

n = 77

Remove studies not focusing on mansonelliasis (n = 16)

n = 61

Remove studies that do not report prevalence (n = 15)

n = 46

Included studies (n = 47)

M. perstans (25)

M. streptocerca (3)

M. ozzardi (18)

Figure 1: Search strategy.

Most studies that examined differences in M. perstans prevalence by sex found no difference between males and females (Agbolade et al., 2001; Asio et al., 2009; Boussinesq et al., 2003; Gbakima and Sahr, 1996; Ufomadu et al., 1991; Useh et al., 1995) although several other studies observed a higher rate in males than females (Anosike et al., 2005b; Mommers et al., 1994; Noireau et al., 1989; Wanji et al., 2003). Studies of the association between age and infection consistently found a higher rate in adults than children (Agbolade et al., 2001; Anosike et al., 2005b; Asio et al., 2009; Gbakima and Sahr, 1996; Keiser et al., 2003; Mommers et al., 1994; Noireau et al., 1989; Ufomadu et al., 1991; Wanji et al., 2003).

Mansonella streptocerca occurs in west and central Africa, and has been the focus of relatively few studies (Table 3). As was found for M. perstans, the prevalence rate appears to vary widely within endemic areas. A study in western Uganda in the mid-1990s found that the village prevalence ranged from 5% to 89% (Fischer et al., 1997). A study from the 1980s conducted in the Central African Republic found a prevalence of 13.5% (Okelo et al., 1988) and a study in Nigeria from the early 1990s found a prevalence of 0.5% (Anosike and Onwuliri, 1994). Additional studies are required to establish the geographic range where this agent is endemic and to identify risk factors.
Table 2. Epidemiological studies of *M. perstans*.

| Country    | Study Year | Sample Size | Age Range (years) | Prevalence | Reference          |
|------------|------------|-------------|-------------------|------------|--------------------|
| Colombia   | --         | 604         | --                | 6%         | Kozek, 1983        |
| Burkina Faso | 2001     | 3303        | ≥ 1               | 6%         | Kyelem, 2003       |
| Cameroon   | 1992       | 466         | ≥ 0.5             | 27%        | Mommers, 1994      |
| Cameroon   | --         | 1458        | ≥ 15              | 70%        | Wanji, 2003        |
| Congo      | 1985-1986  | 2313        | ≥ 1               | 29%        | Noireau, 1989      |
| Gabon      | 1984-1985  | 411         | 9-70              | 49%        | Van Hoegaerden, 1987 |
| Guinea     | 1989       | 829         | ≥ 10              | 66%        | Vila Montilleo, 1990 |
| Mali       | 2003-2004  | 373         | --                | 3%         | Anosike, 2005a     |
| Mali       | 1996-2000  | 755         | ≥ 5               | 9%         | Anosike, 2005b     |
| Mali       | 1997-1998  | 373         | 4-55              | 3%         | Agbolade, 2001     |
| Mali       | 1988-1991  | 4183        | 0-70              | 29%        | Anosike, 1992      |
| Mali       | 1993       | 840         | ≥ 1               | 15%        | Useh, 1995         |
| Mali       | 1989       | 2552        | --                | 11%        | Akogun, 1992       |
| Mali       | 1984-1987  | 940         | 3-80              | 8%         | Ufomadu, 1990      |
| Nigeria    | --         | 845         | --                | 13%        | Udonsi, 1988       |
| Nigeria    | 1983-1984  | 1674        | ≥ 1               | 47%        | Arene, 1986        |
| Nigeria    | --         | 1351        | ≥ 1               | 46%        | Udonsi, 1986       |
| Guinea     | 1993       | 630         | 5-70              | 6%         | Gbakima, 1996      |
| Togo       | --         | 182         | --                | 42%        | Schulz-Key, 1993   |
| Uganda     | 2005-2006  | 1566        | ≥ 1               | 65%        | Asio, 2009         |
| Uganda     | 2003-2005  | 2499        | 14-47             | 21%        | Hillier, 2008      |
| Uganda     | 2003       | 12207       | 5-19              | 61%        | Onapa, 2005        |
| Uganda     | 1998       | 3548        | --                | --         | Onapa, 2001        |
| Uganda     | 1994-1995  | 233         | ≥ 14              | 96%        | Fischer, 1997a     |
| Uganda     | 1991-1993  | 1543        | ≥ 14              | 49%        | Fischer, 1996      |

Table 3. Epidemiological studies of *M. streptocerca*.

| Country       | Study Year | Sample Size | Age Range (years) | Prevalence | Reference          |
|---------------|------------|-------------|-------------------|------------|--------------------|
| Central African Republic | --       | 267         | 1-100             | 14%        | Okelo, 1988        |
| Nigeria       | 1990-1992  | 1349        | 0-70              | 0.5%       | Anosike, 1994      |
| Uganda        | 1994-1995  | 806         | ≥ 14              | 61%        | Fischer, 1997a     |

Mansonella ozzardi infection, also known as mansonellosis, occurs only in the Americas (Table 4). In the past ten years, the results of cross-sectional studies from Brazil (Cohen et al., 2008; Garrido and Campos, 2000; Medeiros et al., 2008), Bolivia (Bartoloni et al., 1999), and Venezuela (Gómez and Guerrero, 2000) have been published. Most of the studies in Brazil and Venezuela were conducted in communities located along rivers in the Amazon basin and focused on indigenous groups. The prevalence rates ranged from 9.9% (Gómez and Guerrero, 2000) to 18.9% (Cohen et al., 2008) to 28.2% (Garrido and Campos, 2000) to 30.2% (Medeiros et al., 2008). Older studies from Brazil found prevalence rates ranging from 4% (Shelley, 1975) to 27% (Lage, 1964). The Bolivian study also focused primarily on an indigenous population, and found a total prevalence of 0.7% in one town and 26% in a neighboring town of 26% (Bartoloni et al., 1999), which suggests the same diverse range of prevalence rates found for the other species. Prevalence rates from studies of rural areas in Venezuela ranged from 11% (Beaver et al., 1976) to 22% (Le Bras et al., 1978) to 30% (Formica and Botto, 1990) to 36% (Medrano et al., 1992) to 58% (Godoy et al., 1980). In a study from the 1970s, about 16% (Raccurt et al., 1980) of inhabitants surveyed from Bayeux, Haiti, were found to be infected with *Mansonella ozzardi*. In Colombia, prevalence rates ranged from 3% (Kozek et al., 1984) to 13% (Kozek et al., 1983) to 49% (Lightner et al., 1980). These studies consistently found that risk of infection increased with age (Bartoloni et al., 1999; Le Bras et al., 1978; Medeiros et al., 2008; Nathan et al., 1979). Although one study from Trinidad in
the 1970s indicated an increased risk of infection in males (Nathan et al., 1979), more recent studies from Bolivia (Bartoloni et al., 1999) and Brazil (Medeiros et al., 2008) found no differences in prevalence by sex. Thus, aside from age no risk factors have been firmly established.

Table 4: Epidemiological studies of *M. ozzardi*.

| Country     | Study Year | Sample Size | Age Range (years) | Prevalence | Reference               |
|-------------|------------|-------------|-------------------|------------|-------------------------|
| Bolivia     | 1997       | 594         | 0-85              | 26%        | Bartoloni, 1999         |
| Brazil      | 2007       | 129         | ≥ 2               | 30%        | Mederios, 2008          |
|             | 2006       | 543         | --                | 19%        | Cohen, 2008             |
|             |            | 496         | --                | 28%        | Garrido, 2000           |
|             |            | 386         | --                | 4%         | Shelley, 1975           |
|             |            | 262         | --                | 27%        | Lage, 1964              |
| Colombia    | --         | 347         | 8-70              | 49%        | Lightner, 1980          |
| Haiti       | --         | 627         | --                | 3%         | Kozek, 1984             |
|             | --         | 604         | --                | 13%        | Kozek, 1983             |
| Mexico      | 1956       | 329         | --                | 61%        | Biagi, 1956             |
| Trinidad    | 1983-1989  | 4,488       | ≥ 5               | 5%         | Nathan, 1979            |
|             | 1977       | 146         | ≥ 6               | 22%        | Le Bras, 1978           |
|             |            | 187         | --                | 10%        | Beaver, 1976            |
| Venezuela   | 1983-1989  | 423         | --                | 36%        | Medrano, 1992           |
|             | 1999       | 139         | --                | 58%        | Godoy, 1980             |
| --          | 1983-1989  | 146         | ≥ 6               | 22%        | Le Bras, 1978           |
| --          |            | 187         | --                | 10%        | Beaver, 1976            |

Discussion

While the three agents that cause mansonnelliasis share these similarities, they are distinct infections with unique agent, clinical, and epidemiological characteristics. Although infection is usually asymptomatic, millions of people worldwide – especially those in rural areas – are at risk. This systematic review shows that mansonnelliasis may be a common infection in parts of Latin American and west and central Africa, with significant variation in prevalence rates over small geographic spaces, but the review also highlights the lack of current information about the prevalence of mansonnelliasis in most areas likely to at risk. Also, although the review indicates that the risk of infection increases with age and may be higher in males than females, there is a need for additional work to identify specific demographic and environmental risk factors. Updated information will be important for making differential diagnoses in endemic and epidemic areas, promoting measures to control vectors in areas with significant burden from the disease, identifying the possible risks of co-infection with multiple filariases, and addressing the concerns of at-risk populations.

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