Mansonella
(helminth: nematode)

Overview

Nematodes are triploblastic pseudocoelomate unsegmented worms that undergo protostomial embryonic cleavage and grow by cuticular moulting (ecdysis). Two groups identified by the presence/absence of sensory phasmids have partly been ratified by molecular studies recognising three subclasses: Enoplia and Dorylaimia (both without phasmids) and Chromadoria (most with phasmids). Many phasmidian parasites of vertebrates are grouped in the chromadorian order Rhabditida; including tylenchinids, rhabditinids and spirurinids. The latter contains the infraorder Spiruromorpha: an enigmatic clade linked by molecular characters, but all having indirect life-cycles involving one or more intermediate hosts, the first invariably being an arthropod. Most possess two trilobed lips (sometimes greatly reduced), a bipartite oesophagus (anterior muscular, posterior glandular) and non-bursate males with coiled tails and two dissimilar spicules. Several superfamilies are recognised: including filarioids (without lips) living in subcutaneous, intermuscular, vascular or lymphatic systems of mammals. Two main families include the oviparous filariids (lay eggs) and the ovoviviparous onchocercids (eggs hatch internally releasing pre-larvae called microfilariae). Infections by the onchocercid genus *Mansonella* are transmitted by sand flies and black flies and cause skin lesions in humans in Central America.

Classification:

Domain:	Eukaryota (membrane-bound nucleus)
Supergroup:	Amorphea (unikonts with single flagellum, or nonflagellated amoebae)
Kingdom:	Metazoa (multicellular eukaryotes, heterotrophs, notably animals)
Group:	Protostomia (triploblastic, spiral cleavage)
Subgroup:	Ecdysozoa (cuticle moulted = ecdysis)
Phylum:	Nematoda (unsegmented, pseudocoelomate roundworms, tubular digestive tract, dioecious)
Class:	Chromadorea (spiral amphids, three oesophageal glands, usually annulated bodies, free-living and parasitic)
Order:	Rhabditida (Secernentea, Phasmidea) (secretors, with phasmids, bipartite oesophagus, single testis)
Suborder:	Spirurina (mostly parasitic in vertebrate hosts)
Infraorder:	Spiruromorpha (enigmatic clade linked by molecular characters, indirect cycles with IHs)
Superfamily:	Filarioidea (tissue-dwelling filarial parasites, lack lips)
Family:	Onchocercidae (adults loose in tissues or in nodules, viviparous (live birth of microfilariae))
Genus:	*Mansonella* (parasitic in body cavities of humans)
Species:	various species cause skin lesions in humans

Parasite biodiversity and host range: Most Metazoa are multicellular triploblastic animals with differentiated tissues, many being bilaterally symmetrical with a body cavity. Most invertebrate animals are protostomes as their embryonic development involves spiral determinate cleavage. Those that moult their external cuticles during their life-cycles (process known as ecdysis) are grouped together in the unique clade Ecdysozoa, including the nematodes (roundworms), onychophorans (velvet worms), tardigrades (water bears) and arthropods (myriapods, chelicerates, crustaceans and hexapods, all with jointed limbs). Nematodes (roundworms) are unsegmented tubular worms with a fluid-filled body cavity (pseudocoelom) that acts as a hydrostatic skeleton. They have longitudinal muscles and typically exhibit a sideways thrashing motion. They have well developed digestive tracts with various partitions: the foregut comprising the mouth (often with lips and papillae), buccal capsule (sometimes with ridges, rods, plates, spears, stylets or teeth) and oesophagus (glandular, muscular or both); the midgut (nonmuscular absorptive section); and hindgut (rectum) emptying through a subterminal anus (cloaca in males). Most nematodes are dioecious and form separate sexes. Male worms have a single testis (sometimes 2), an elongate vas deferens often equipped with a seminal vesicle and ejaculatory duct (glandular and/or muscular), 1-2 copulatory spicules (sometimes with an accessory gubernaculum), and bursate species with elaborate posterior claspers. Female worms are usually didelphic (some monodelphic or polydelphic) with 2 ovaries, 2 oviducts usually with spermatheca, 2 uteri opening into a common vagina and a vulva often equipped with a muscular ovejector. Female worms are oviparous or viviparous and produce numerous eggs or larvae, respectively. Larval stages undergo several moults (L1-L4) before maturing into adult worms. Some nematodes have direct life-cycles where eggs or larvae infect definitive hosts (per os or per cutaneous), but many have indirect cycles where larvae first develop in invertebrate intermediate hosts before infecting definitive hosts (by ingestion, injection or deposition). Many nematode species are free-living in terrestrial and aquatic habitats, while some species from diverse groups have become plant or animal parasites. Two nematode groups identified by the presence/absence of sensory phasmids have partly been ratified by molecular studies recognising three subclasses: Enoplia and Dorylaimia (both without phasmids) and Chromadoria (most with phasmids). Most Enoplia are free-living marine organisms but some are found in freshwater, and on land as plant parasites. The Dorylaimia comprise numerous freshwater and terrestrial species, including major groups of plant and animal parasites. The Chromadoria is represented by many marine groups as well as a terrestrial group of plant and animal parasites. The taxonomic ranks of many nematode assemblages vary considerably depending on which classification system has been followed. Molecular phylogenetic studies, however, have supported the separate

classification of most groups, particularly at the level of superfamily. Collectively, species from at least 16 superfamilies are considered to pose serious threats to human and animal health as infectious diseases.

CLASSIFICATION* OF SUPERFAMILIES OF PARASITIC NEMATODES
Class: Enoplea (Aphasmidea, Adenophorea) (gland-bearers, cylindrical oesophagus, no phasmids, setae, two testes)
Subclass: Dorylaimia (five or more oesophageal glands, buccal stylet (odontostyle), free-living or parasitic)[clade I(2)]
Order: Trichinellida (Trichocephalida, Trichurida) (single spicule, stichosome oesophagus, L1 with buccal stylet)
Superfamily: Trichinelloidea (oesophagus with short anterior muscular and long posterior glandular portions)
Class: Chromadorea (spiral amphids, 3 oesophageal glands, usually annulated bodies, free-living and parasitic)
Order: Rhabditida (Secernentea, Phasmidea) (secretors, phasmids present, amphids anterior, bulbous oesophagus)
Suborder: Rhabditina (free-living or parasitic in invertebrates/lower vertebrates)[clade V(9)]
Infraorder: Rhabditomorpha ('rod-shaped' buccal cavity)
Superfamily: Rhabditoidea (open tube stoma, excretory system with lateral canals)
Superfamily: Strongyloidea (bursate males, prominent buccal capsules, parasites of mammals, birds, reptiles)
Suborder: Spirurina (animal parasites, many use invertebrate intermediate hosts (IH))[clade III(8)]
Incertae sedis Superfamily: Dracunculoidea (elongate parasites of vertebrate tissues, freshwater crustacean IH)
Infraorder: Ascaridomorpha (large roundworms, three large lips, numerous caudal papillae)
Superfamily: Ascaridoidea (ascarids, eggs thick-shelled, larvae may undertake hepato-pulmonary migration)
Superfamily: Heterakoidea (preanal sucker anterior to cloaca in males, direct cycle, infection by egg ingestion)
Infraorder: Gnathostomatomorpha ('jaw-mouthed' due to unique bulbous armed heads)
Superfamily: Gnathostomatoidea (first IH copepod, often use paratenic hosts)
Infraorder: Oxyuridomorpha (pinworms, pointed tails, oesophagus with terminal bulb, males with single spicule)
Superfamily: Oxyuroidea (common in mammals, birds, reptiles, amphibians)
Infraorder: Spiruromorpha (enigmatic clade linked by molecular characters, indirect cycles with IHs)
Superfamily: Acuarioidea (small parasites mostly of birds, with cephalic cordons, ptilina or serrated shields)
Superfamily: Camallanoidea (conspicuous phasmids, L1 with dorsal tooth, ovoviviparous, L1-L3 in copepod)
Superfamily: Filarioidea (tissue-dwelling filarial parasites, lack lips, infect tissues/vessels, arthropod IH)
Superfamily: Habronematoidea (unique head structures with small pseudolabia and median lips)
Superfamily: Physalopteroidea (stomach worms in mammals, insect IH)
Superfamily: Spiruroidea (pseudolabia, bipartite oesophagus, infect birds (crop/gizzard), arthropod IHs
Superfamily: Thelazioidea (eye-worms of birds and mammals, transmitted by insects)
Suborder: Tylenchina (fungal, plant and animal parasites)[clade IV(10,11,12)]
Infraorder: Panagrolaimomorpha (free-living or parasitic (insects, reptiles, amphibians, mammals))
Superfamily: Strongyloidoidea (dauer stages, lip region without processes, striated cuticle)

*Contemporary genotypic classification schemes recognize strong monophyletic clades at the level of superfamily and infraorder, while previous phenotypic classification schemes had ranked many as separate orders.

Molecular phylogenetic studies have grouped a variety of superfamilies into the infraorder Spiruromorpha whose members are parasites of vertebrates with indirect life-cycles involving larval development within invertebrate intermediate hosts. Most members were previously classified within the order Spirurida: either within the suborder Camallanina (worms with conspicuous phasmids, uninucleate oesophageal glands, larvae without cephalic hooks, usually with copepodid intermediate hosts); or the suborder Spirurina (worms with inconspicuous phasmids, multinucleate oesophageal glands, larvae with cephalic hooks or spines, usually with non-copepodid intermediate hosts). Ten spirurinid superfamilies are recognised: Gnathostomatoidea and Physalopteroidea (buccal cavity weakly cuticularized, 2 large lateral pseudolabia); Habronematoidea and Acuarioidea (buccal cavity well cuticularized, 2 large lateral pseudolabia); Filarioidea, Rictularioidea, Aproctoidea and Diplotriaenoidea (buccal cavity well cuticularized, without pseudolabia); Thelazioidea (long cylindrical buccal cavity well cuticularized, body without caudal alae); and Spiruroidea (short buccal cavity well cuticularized, body with caudal alae).

The superfamily Filarioidea contains long thread-like nematodes which are predominantly tissue-dwelling parasites infecting the body cavities, subcutis, intermuscular tissues, blood vessels or lymphatic systems of terrestrial hosts. These worms are known colloquially as 'filariae', 'filarids' or 'filarioids' [Note: take care with terminology as the cognate family Filariidae (esp. genus *Filaria*) are known colloquially as 'filariids', and the unrelated metastrongyle (lungworm) family Filaroididae (genus *Filaroides*) are known colloquially as 'filaroids']. Adult filariae have a cylindroid pharynx with an anterior muscular portion and a posterior glandular portion. Males often have spirally-coiled tails, well-developed alae and dissimilar spicules. Females of most species are ovoviviparous (eggs hatch within body of parent) releasing pre-larval stages known as microfilariae (sometimes sheathed). Filariae have indirect life-cycles whereby microfilariae are taken up by blood-sucking or tissue-feeding invertebrates (arthropods, esp. mosquitoes) which act as intermediate hosts for the development of infective L3 larvae. Ten families are recognised: Filariidae and Onchocercidae infecting mammals, birds, reptiles and amphibians; Setariidae infecting mammals; Aproctidae infecting birds; and Creagrocercidae, Drilonematidae, Homungellidae, Mesidionematidae, Scolecophilidae and Ungellidae infecting terrestrial annelids. Examples of filarioid genera covered in this resource are compared in the following table.

Genus	Definitive hosts	Adults (location)	Microfilariae (location)	Periodicity	Vectors	*Wolbachia* symbiotes
Family Onchocercidae						
Mansonella (29 spp.)	primates, carnivores, ungulates, rodents	3-8 cm (subcutis, serosa)	170-300 µm unsheathed (blood/skin)	-	midges, flies, mosquitoes	present
Onchocerca (35 spp.)	primates, carnivores, ungulates, rodents	1.5-80 cm (subcutis, ligaments)	105-440 µm unsheathed (skin)	-	flies, midges	present
Dirofilaria (34 spp.)	primates, carnivores, ungulates, rodents, lagomorphs, marsupials	4-31 cm (blood vessels)	180-385 µm unsheathed (blood)	-	mosquitoes, flies	present
Dipetalonema, Acanthocheilonema (57 spp.)	primates, carnivores, ungulates, rodents, cingulates, marsupials	1-7 cm (subcutis, serosa)	85-300 µm unsheathed (blood)	-	flies, fleas, lice, ticks	absent
Wuchereria (2 spp.)	primates	2.5-10 cm (lymphatics)	210-320 µm sheathed (blood)	nocturnal, subperiodic	mosquitoes	present
Brugia (10 spp.)	primates, carnivores, rodents	1-9 cm (lymphatics)	170-380 µm sheathed (blood)	nocturnal, subperiodic	mosquitoes	present
Loa (3 spp.)	primates, ungulates, rodents	2-7 cm (subcutis, eye)	250-300 µm sheathed (blood)	diurnal	flies	absent
Family Filariidae						
Parafilaria (4 spp.)	ungulates	2-7 cm (subcutis)	40-58 x 23-33 µm larvated eggs (skin)	diurnal	flies	absent
Stephanofilaria (7 spp.)	ungulates	0.2-1.4 cm (subcutis)	45-195 µm sheathed (skin)	-	flies	absent
Family Setariidae						
Setaria (42 spp.)	primates, ungulates, rodents, lagomorphs	4-19 cm (body cavities)	140-310 µm sheathed (blood)	-	mosquitoes	absent

Members of the family Onchocercidae form adult worms that live loose in body cavities or in tissue nodules. Female worms release microfilariae which disperse into the blood or dermal connective tissues (unlike filariids which live in the skin close to where they deposit eggs or larvae). Some 88 onchocercid genera are divided into 7 subfamilies: Onchocercinae and Dirofilariinae (syn. Loainae) mostly in mammals but some in birds and reptiles, Waltonellinae and Icosiellinae in amphibians, Oswaldofilariinae in reptiles, Splendidofilariinae and Lemdaninae in birds, reptiles and mammals (former subfamily Setariinae in large mammals recently elevated to family status as Setariidae). Members of the subfamily Onchocercinae are characterised as forming males with markedly dissimilar spicules and long tails lacking caudal alae (while members of the subfamily Dirofilariinae form males with highly developed caudal alae). Some 43 genera occur in the subfamily Onchocercinae: namely, *Acanthocheilonema, Ackertia*, *Agamofilaria*, *Andersonfilaria*, *Bisbalia*, *Breinlia* (incl. *Johnstonema*), *Brugia*, *Cercopithifilaria*, *Chabfilaria*, *Cherylia*, *Courduriella*, *Cruorifilaria*, *Cystofilaria*, *Deraiophoronema*, *Dessetfilaria*, *Dipetalonema*, *Elaeophora* (syn. *Cordophilus*, *Alcefilaria*), *Filarissima*, *Fuscicorpa*, *Josefilaria*, *Litomosa*, *Litomosoides* (syn. *Vestibulosetariam Finlaynema*), *Mansonella*, *Microfilaria*, *Migonella*, *Molossinema*, *Monanema*, *Onchocerca* (syn. *Wehrdikmansia*, *Acanthospiculum*), *Paramadochotera*, *Paraochoterenella*, *Paraprocta*, *Paulianfilaria*, *Pseudolitomosa*, *Rumenfilaria*, *Sandnema, Serofilaria*, *Skrjabinofilaria* (syn. *Cortiamosoides*), *Sprattia, Strianema*, *Wuchereria* and *Yatesia* in mammals, *Struthiofilaria* in birds, and *Macdonaldius* (syn.

Saurofilaria) in reptiles. Three groups of human filariasis are distinguished on the basis of their tissue tropism: cutaneous dermal filariasis (onchocerciasis in Africa, Asia, Central and South America, loiasis in Africa, *streptocerca* mansonelliasis in Africa); lymphatic filariasis (wuchereriasis in Africa and Asia, brugiasis in South Asia); and serous filariasis (*perstans* mansonelliasis in Africa, Central and South America, *ozzardi* mansonelliasis in Central and South America).

Members of the genus *Mansonella* form worms in subcutaneous tissues and sometimes the body cavities of mammals (mainly primates, but also including carnivores, insectivores, rodents and ungulates). Worms have a small pore-like mouth with almost no buccal capsule and a slender thread-like oesophagus. Females have 4 caudal lappets and are ovoviviparous releasing unsheathed microfilariae into the blood or skin where they are taken up by dipteran intermediate hosts (midges, black flies or mosquitoes). Around 30 *Mansonella* spp. are recognised in 7 subgenera: *M.* (*Mansonella*) (with non-striated cuticle, annular swellings, vulva anterior to oesophageal-intestinal junction, short vagina, male tail without lappets, right spicule with heel, microfilariae without terminal nuclei, parasitic in rodents, carnivores and primates); *M.* (*Cutifilaria*) (with non-striated cuticle, without annular swellings, area rugosa with transverse bands of pointed rugosities, vulva posterior to oesophageal-intestinal junction, short vagina, male tail without lappets, right spicule with distal spoon-like portion, microfilariae with terminal nuclei, parasitic in cervids); *M.* (*Esslingeria*) (with non-striated cuticle, some with annular swellings, vulva anterior to oesophageal-intestinal junction, long vagina, male tail without lappets, right spicule without heel, microfilariae with terminal nuclei, parasites in rodents and primates); *M.* (*Filyamagutia*) (with non-striated cuticle, annular swellings, vulva anterior to oesophageal-intestinal junction, long tubular vagina, microfilariae without terminal nuclei, parasitic in carnivores); *M.* (*Pseudolitomosa*) (with non-striated cuticle, without annular swellings, vulva level to oesophageal-intestinal junction, long vagina, male tail with lappets, right spicule with heel, parasitic in rodents); *M.* (*Tetrapetalonema*) (with striated cuticle, some with annular swellings, vulva anterior to oesophageal-intestinal junction, globular vagina, male tail with lappets, right spicule without heel, microfilariae with terminal nuclei, parasitic in primates); and *M.* (*Tupainema*) (with non-striated cuticle, with annular swellings, vulva at level of oesophageal-intestinal junction, globular vagina, male tail with lappets, right spicule without heel, microfilariae without terminal nuclei, parasitic in tree shrews). Another subgenus (viz. *M.* (*Sandnema*) containing 2 species) has recently been elevated to generic status. Infections by *Mansonella* spp. occur primarily in tropical regions where warm climatic conditions are conducive to the survival of the invertebrate intermediate hosts. Nonetheless, most species differ in their geographical distribution and tissue tropism. Infections in humans usually involve 3 species: *M.* (*E.*) *perstans* and *M.* (*E.*) *streptocerca* in Africa (the former translocated to the Americas during the slave trade era) and *M.* (*M.*) *ozzardi* in the New World (South and Central America). It is currently conservatively estimated that over 114 million people are infected.

***Mansonella* species**	**Definitive Hosts (DH)**	**Location**	**Vectors/Intermediate Hosts (IH)**	**Distribution**
Subgenus: *Mansonella*				
M. interstitium (syn. *Dipetalonema, Tetrapetalonema*)	Rodentia: sciurid (eastern gray squirrel)	subcutaneous tissues		North America
M. llewellyni (syn. *Dipetalonema, Tetrapetalonema*)	Carnivora: procyonid (raccoon)	subcutaneous tissues and fascia, microfilariae in blood	Diptera: ceratopogonid (*Culicoides hollensis*)	North America
M. ozzardi (syn. *Dipetalonema, Filaria, F. demarquayi, F. juncea, F. tucumana*)	Primates: cercopithecid (patas monkey), hominid (human)	subcutaneous tissues, peritoneal cavity, visceral adipose tissue, microfilariae in blood (unsheathed, nonperiodic)	Diptera: ceratopogonid (*Culicoides barbosai, furens, paraensis, phlebotomus, Leptoconops becquaerti*), simuliid (*Simulium amazonicum, argentiscutum, exiguum, oyapockense, sanguineum*)	Central and South America, Caribbean
Subgenus: *Cutifilaria*				
M. perforata	Artiodactyla: cervid (sika deer)			Japan
M. wenki (syn. *Cutifilaria*)	Artiodactyla: cervid (red deer)			Europe
Subgenus: *Esslingeria*				
M. gorillae (syn. *Dipetalonema, Microfilaria*)	Primates: hominid (gorilla)			Africa
M. leopoldi (syn. *Dipetalonema, Microfilaria, Tetrapetalonema*)	Primates: hominid (gorilla)			Africa

M. longicapita	Rodentia: caviid (capybara)			South America
M. lopeensis	Primates: hominid (gorilla)			Africa
M. perstans (syn. *Dipetalonema, D. semiclarum, Filaria, Acanthocheilonema, Tetrapetalonema*)	Primates: hominid (human, gorilla, chimpanzee)	pleural and abdominal cavities, pericardial, perirenal and retroperitoneal tissues, skin lesions, serous cavity filariasis, microfilariae in blood (unsheathed)	Diptera: ceratopogonid (*Culicoides austeni, grahami*?, *inornatipennis*)	sub-Saharan Africa, Central and South America, Caribbean
M. rodhaini (syn. *Dipetalonema, Microfilaria, Monnigofilaria, Tetrapetalonema*)	Primates: hominid (human, bonobo, chimpanzee)			Africa
M. rotundicapita	Rodentia: caviid (capybara)	dermal and subcutaneous tissues		South America
M. streptocerca (syn. *Agamofilaria, Dipetalonema, Acanthocheilonema, Moennigofilaria, Tetrapetalonema*)	Primates: hominid (human, bonobo, gorilla, chimpanzee)	subcutaneous tissues, microfilariae in skin/blood (unsheathed, nonperiodic)	Diptera: ceratopogonid: (*Culicoides austeni, grahami, milnei*)	Central Africa
M. vanhoofi (syn. *Dipetalonema, Acanthocheilonema, Tetrapetalonema*)	Primates: hominid (bonobo, gorilla), cercopithecid (baboon)	subcutaneous tissue		Africa
Subgenus: *Filyamagutia*				
M. akitensis (syn. *Tetrapetalonema*)	Carnivora: ursid (Japanese black bear)	adipose tissue, mesentery, serous membrane		Japan
Subgenus: *Pseudolitomosa*				
M. musasabi (syn. *Pseudolitomosa*)	Rodentia: sciurid (Japanese giant flying squirrel)	abdominal cavity		Japan
Subgenus: *Tetrapetalonema*				
M. atelensis (syn. *Tetrapetalonema*) (incl. subspp. *atelensis*, *amazonae*)	Primates: atelid (Geoffroy's spider monkey, Columbian black spider monkey), cebid (wedge-capped capuchin)	subcapsular region		South America
M. barbascalensis (syn. *Dipetalonema, Tetrapetalonema*)	Primates: aotid (three-striped night monkey, Spix's night monkey)			South America
M. colombiensis (syn. *Tetrapetalonema*)	Primates: cebid (common squirrel monkey, tufted capuchin)	ns	Diptera: culicid (*Aedes aegypti*)	South America
M. mariae	Primates: cebid (common squirrel monkey)		Diptera: culicid (*Aedes aegypti*)	South America
M. marmosetae (syn. *Dipetalonema, Tetrapetalonema*)	Primates: callitrichid (Geoffroy's tamarin, cotton-top tamarin, brown-mantled tamarin), cebid (Central American squirrel monkey, black-capped squirrel monkey, common squirrel monkey, Columbian white-faced capuchin), atelid (red-faced spider monkey, howler monkey, Columbian black spider monkey, Geoffroy's spider monkey), aotid (three-striped night monkey,	intermuscular connective tissue, microfilariae in blood	Diptera: ceratopogonid: (*Culicoides furens, hollensis*)	South and Central America

	Panamanian night monkey)			
M. mystaxi (syn. *Tetrapetalonema*)	Primates: callitrichid (moustached tamarin)			South America
M. obtusa (syn. *Microfilaria, Dipetalonema, Tetrapetalonema*)	Primates: cebid (Colombian white-faced capuchin, Humboldt's white-fronted capuchin, Central American squirrel monkey)			South and Central America
M. panamensis (syn. *Microfilaria, Tetrapetalonema*)	Primates: cebid (Colombian white-faced capuchin, red-backed squirrel monkey, tufted capuchin), aotid (Panamanian night monkey, three-striped night monkey, Nancy Ma's night monkey)	subcutaneous tissue		South America
M. parvum (syn. *Tetrapetalonema*)	Primates: cebid (Colombian white-faced capuchin, black-crowned Central American squirrel monkey)			South and Central America
M. peruviana	Primates: cebid (common squirrel monkey)			South America
M. saimiri (syn. *Tetrapetalonema*)	Primates: cebid (common squirrel monkey)			South America
M. tamarinae (syn. *Dipetalonema, Tetrapetalonema*)	Primates: callitrichid (black-mantled tamarin)			South America
M. zakii sp. inq. (syn. *Parlitomosa, Dipetalonema, Tetrapetalonema*)	Primates: callitrichid (golden lion tamarin)			Egypt (ex. Brazil)
Subgenus: *Tupainema*				
M. dunni (syn. *Dipetalonema, Tetrapetalonema*)	Scandentia: tupaiid (common treeshrew, large treeshrew)	subcutaneous tissue		Malaysia

Another subgenus, *Mansonella* (*Sandnema*), has recently been promoted to generic status on the basis of morphotypic differences; in that worms possess a tubular buccal capsule, the vulva is at the level of the oesophageal-intestinal junction, the vagina is long and surrounded by muscle fibres, the area rugosa has transverse bands of short longitudinal cuticular crests, the 2 spicules are unequal but both are divided into handle and lamina regions, and the microfilariae have nuclei in the tip of the tail.

***Sandnema* species**	**Definitive Hosts (DH)**	**Location**	**Vectors/Intermediate Hosts (IH)**	**Distribution**
S. digitatum (syn. *Mansonella, Dirofilaria, Tetrapetalonema, Dipetalonema, Moennigofilaria*)	Artiodactyla: bovid (cattle); Primates: hylobatid (hoolock gibbon, Lar gibbon, northern white-cheeked gibbon), cercopithecid (dusky leaf monkey, stump-tailed macaque)	abdominal cavity		Asia
S. sunci (syn. *Mansonella, Dipetalonema, Tetrapetalonema, Moennigofilaria*)	Eulipotyphla: soricid (Asian house shrew)	subcutaneous tissue		Asia

Parasite morphology: *Mansonella* species form 3 different morphological stages in their developmental cycles: adult worms, pre-larvae (microfilariae) and 4 sequential larval stages (designated L1-4). Gravid female worms produce elongate sinuous microfilariae generally ranging in size from 170-240 x 4-7 µm. Microfilariae of some species may contract and expand significantly, ranging up to 300 µm long (e.g. *M. marmosetae*), but they are usually smaller than microfilariae produced by other filarial worms (such as *Wuchereria* or *Loa*). All *Mansonella* microfilariae are unsheathed and have curled attenuated tails with a blunt, pointed or knob-like tip with or without terminal nuclei (*M. ozzardi* has a pointed button-hook tail without terminal nuclei, *M. streptocerca* has a curved shepherd's crook tail with a single row of terminal nuclei, and *M. perstans* has a rounded tail with a nuclear column terminating in a single large nucleus). Microfilariae develop into sausage-shaped first-stage larvae (L1) measuring around 230 x 23 µm, which moult to elongate second-stage larvae (L2) measuring up to 370 x 23 µm, and then to longer third-stage larvae (L3) measuring around 570 x 19 µm. L3 grow to infective stages measuring up to 600-900 µm in length characteristically with a long glandular oesophagus and a broad posterior with a long tail ending in 4 small terminal papilla-like swellings. They moult twice to form long thin thread-like adult worms measuring 30-80 mm long by 45-120 µm wide. Adults are covered with a tough white cuticle, some species having cuticular striations and some having annular cuticular swelling. They have small pore-like mouths without buccal capsules, and a long thread-like oesophagus and intestinal tract separated from the body wall by a fluid-filled pseudocoelom. Most worms have hair-like setae (mechanoreceptors), rostral amphids and caudal phasmids (chemoreceptors). Mature adults exhibit sexual dimorphism, with female worms being larger than males (50-80 mm x 80-120 µm cf. 30-55 mm by 45-60 µm). Males have a gubernaculum, 2 unequal spicules (the right spicule sometimes bearing a distal heel) and the tail is often coiled (e.g. *M perstans*) or bent like a shepherd's crook (e.g. *M. streptocerca*), often bearing 4 caudal lappets. The female tail is short, half -coiled curving ventrad, and bears 4 caudal lappets (2 lateral and a bifurcated axial point). Gravid females are ovoviviparous and produce embryonated eggs in the uterus which hatch internally releasing live microfilariae which pass out through the anterior vulva (located posterior to the nerve ring but near the oesophageal-intestinal junction).

Site of infection: Adult *Mansonella* worms live in the dermis, subcutaneous tissues or serous body cavities (peritoneal, pleural and pericardial) of their mammalian definitive hosts. Different parasite species exhibit tissue tropism for particular predilection sites of infection: *M. streptocerca* infecting the dermis, *M. ozzardi* forming nodules in subcutaneous tissues, and *M. perstans* developing in deep connective tissues in the mesenteries in serous body cavities. Microfilariae are found in the peripheral blood (*M. perstans, M. ozzardi*) or in dermal tissues (*M. streptocerca*). Adults and/or microfilariae have also occasionally been detected in pleural effusions, ascitic fluid, cerebrospinal fluid, bone marrow and other body organs. Larval stages develop mainly in the thoracic (flight) muscles of their dipteran vectors (intermediate hosts).

Pathogenesis: Studies on *Mansonella* infections are often confounded by high rates of co-infections with other filarial parasites, especially *Onchocerca* spp., and other microbial diseases, including malaria, tuberculosis and human immunodeficiency virus (HIV). Although it has been suggested that *Mansonella* infections may interfere with homeostatic mechanisms and immune function, they are usually asymptomatic or produce a benign self-limiting illness. Infections may produce a variety of nonspecific clinical symptoms that become evident on the death of adult worms and microfilariae; including transient angioedematous swellings of the arms, face or other body parts (not unlike the Calabar swellings of loiasis), upper abdominal pain, arthralgias, urticaria, pruritus, eosinophilia, fever, headache, extreme exhaustion, and neurologic or psychologic symptoms. Infections have occasionally been associated with pericarditis, hepatitis and hepatomegaly, pulmonary symptoms, lymphadenopathy, skin lesions and elephantitis. In Africa, *M. perstans* may invade the conjunctiva of the eye resulting in periorbital oedema (known as Kampala or Ugandan eye worm), but rarely progressing to blindness. *M. perstans* is considered mildly pathogenic in man and apes, with subcutaneous lesions, angioedema, and periorbital oedema generally more common in Africa, and arthralgia more prevalent in South America. *M. streptocerca* infections in Africa commonly cause chronic pruritic dermatitis, hypopigmented macules and skin thickening over the thorax and shoulders, occasionally with abscess or granuloma formation. *M. ozzardi* is generally considered asymptomatic, but chronic infections have been associated with skin nodules, lymphadenopathy, arthralgia, fever and eosinophilia in humans in the New World and West Indies. Infections occur more frequently and heavily in males than in females, and the incidence increases with age with little evidence of host resistance or protective immunity.

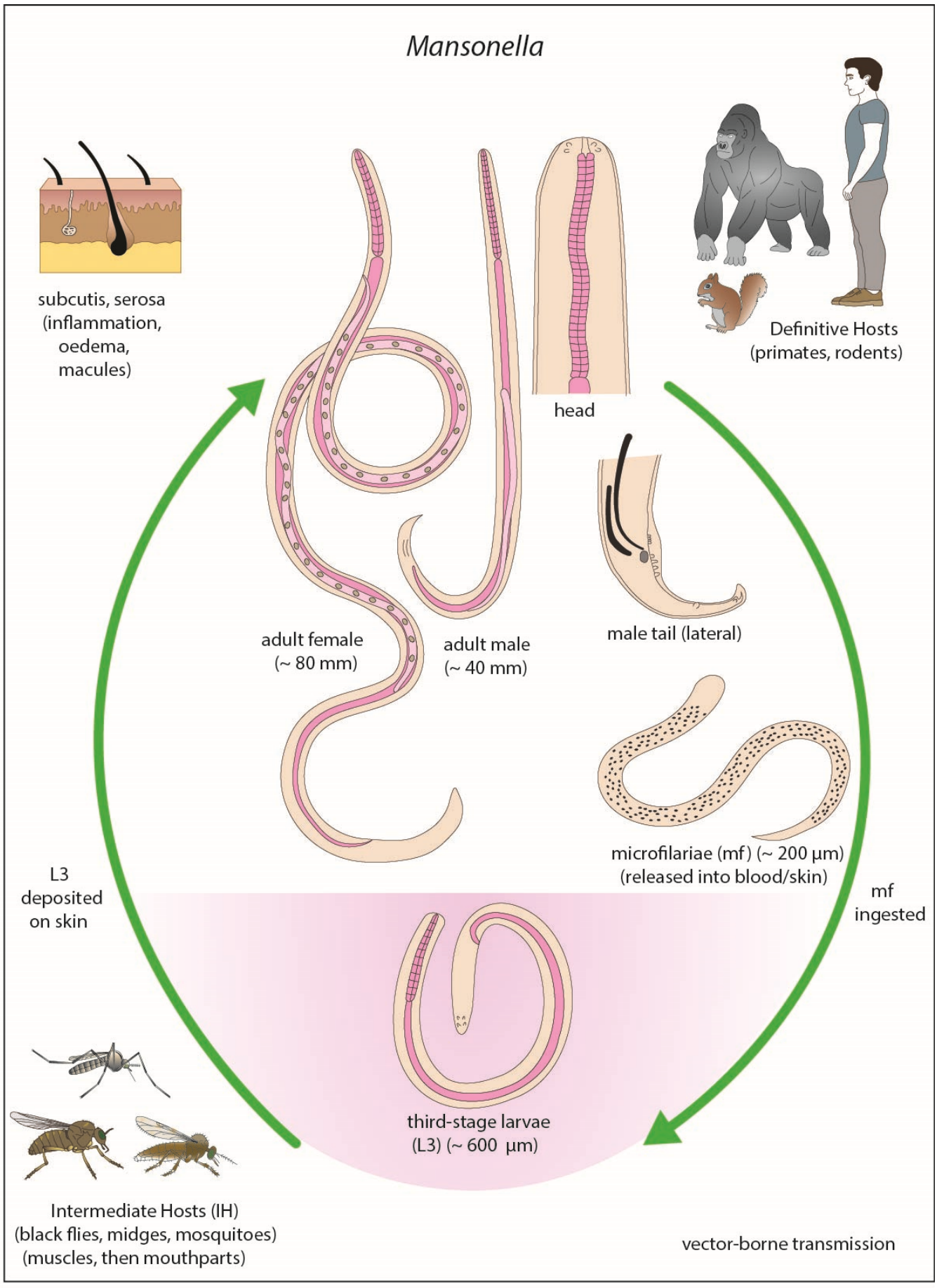
The occurrence of endosymbiotic bacteria (*Wolbachia*) within worms has contradictory implications for disease development and management. The bacteria are considered to be mutualistic symbionts crucial for worm survival and reproduction. However, surface proteins from freed bacteria provoke strong innate immune responses in humans, thus contributing to the chronic inflammatory disease produced by material released from dead and dying worms. Treating patients with antibiotics to kill the bacteria may therefore reduce worm burdens and fecundity, but it may also exacerbate host inflammation.

Developmental cycle and mode of transmission: *Mansonella* spp. have indirect heteroxenous life-cycles with adult worms forming in vertebrate definitive hosts (mammals) and larval stages developing in invertebrate intermediate hosts (dipteran vectors). Female worms release live young (microfilariae) into the tissues of their mammalian hosts which make their way to the bloodstream or accumulate in dermal tissues. Most *Mansonella* spp. do not exhibit any periodicity in microfilaraemia, although some studies suggest that *M. perstans* may sometimes be nocturnally subperiodic (microfilariae always present but peak in concentration at night). All species utilize blood-sucking or tissue-feeding dipteran insects as intermediate hosts, notably ceratopogonids (biting

midges) in the Americas and Africa, simuliids (black flies) and culicids (mosquitoes) in South America. Female insects require blood meals for egg maturation, and they often bite around dawn and dusk. They breed in organically-enriched sites such as stream, swamps, and sometimes dung. They often have flight ranges limited to a few hundred metres, but can move further in windy conditions. Ingested microfilariae migrate from the midgut through the haemocoel to the thoracic flight muscles where they undergo a series of moults (first moult in 3-7 days, second moult in 6-9 days) to form L3 larvae that move to the insect mouthparts in 10-14 days. These infective larvae are transmitted to mammalian hosts when the midges, mosquitoes or blackflies feed on blood or tissues. Transmission is contaminative rather than inoculative as the larvae escape the insect proboscis by stretching and bursting the terminal membrane of the labrum and are deposited on mammalian skin. The larvae penetrate the skin, usually though bites sites or adjacent wounds, and then moult twice while migrating to their predilection sites of infection where they mature into adult worms and mate. Gravid females are ovoviviparous and birth live microfilariae which accumulate in dermal tissues or make their way to the bloodstream. The incubation or prepatent period (time from infection to first microfilarial release) ranges from 5-8 months, but can extend up to 2 years in some individuals.

Differential diagnosis: While most infections remain asymptomatic, some may be suspected on the basis of transient swellings and allergic reactions, but these symptoms are nonspecific and may be caused by other conditions. Infections are conventionally diagnosed by the microscopic detection of characteristic microfilariae (small, unsheathed, bent tails with or without terminal nuclei) in blood samples (thick or thin smears, filtrates, sediments or lysates) or in skin tissues (skin snips or punch biopsies incubated in saline or media). Microfilariae may be stained with Giemsa, haematoxylin, cresyl blue or methylene blue. A small range of immunological tests have been developed to detect host antibodies against parasite antigens, including complement fixation, bentonite flocculation, haemagglutination and intradermal tests, but there have been problems with poor sensitivity and cross-reactions with other filarial worms. More recently, an enzyme immunoassay has been used to detect filarial antigens in blood samples. Molecular biological techniques have also been used to detect parasite DNA in clinical samples following single, nested or multiplex polymerase chain reaction (PCR) amplification of nuclear gene sequences (5S and 28S ribosomal RNA, internal transcribed spacer regions 1 and 2, and major sperm protein (MSP)).

Treatment and control: *Mansonella* infections have proven difficult to treat and while various anthelmintic drugs have been shown to reduce worm growth and fecundity (decreased microfilarial counts), they have not cured infections. An extended course of treatment with the benzimidazole-methylcarbamates mebendazole or albendazole were most effective in the treatment of symptomatic infections, while treatment with the diethylenediamine diethylcarbamazine (DEC) or the macrocyclic lactone ivermectin were less effective. Combination therapies using DEC with mebendazole or ivermectin with albendazole were found to significantly reduce microfilaraemia, but they sometimes produced undesirable side-effects, including abdominal pain, headache, nausea and vomiting. The tetracycline antibiotic doxycycline was recently found to be partially effective in the treatment of *M. perstans* infections, by targeting the endosymbiotic *Wolbachia* bacteria regarded to be vital for worm growth and development. It has been noted that patients undergoing chemotherapy should be carefully monitored for allergic responses arising from the death of too many worms and/or bacteria suddenly releasing potent inflammatory immunogens. In cases where worm nodules are superficial or localized in accessible areas, recourse may be made to their surgical excision. The prevention of infections is based around vector control, better sanitation, protective barriers and public education. Insecticides may be used against adult midges, mosquitoes and blackflies, especially those chemicals with long-lasting residual activity around homes and workplaces. Larvicides may also be used to target aquatic developmental stages, but this approach is confined to small accessible water bodies in semi-rural situations rather than wilderness areas. Careful monitoring of insecticidal efficacy should also be conducted to address mounting concerns about the emergence and spread of resistance in insects. Where possible, environmental interventions may be made to eliminate insect breeding sites, such as draining temporary standing waters, puddles and ditches, using non-flooding irrigation practices, covering tanks and ponds, and improving sewerage systems and waste management. An alternative approach to vector population control is to minimise contact with vectors, by using chemical repellents (sprays, lotions), physical barriers (bed nets, protective clothing), or changing behaviour patterns (avoid waterways, limit outdoor activities at dusk and dawn). Many infections occur in poor rural areas so proactive public education campaigns should aim to inform residents of risks as well as to provide treatment opportunities.


Mansonella
subcutis, serosa
(inflammation,
oedema,
macules)
Definitive Hosts
(primates, rodents)
head
adult female
(~ 80 mm)
adult male
(~ 40 mm)
male tail (lateral)
microfilariae (mf) (~ 200 µm)
(released into blood/skin)
L3
deposited
on skin
mf
ingested
third-stage larvae
(L3) (~ 600 µm)
Intermediate Hosts (IH)
(black flies, midges, mosquitoes)
(muscles, then mouthparts)
vector-borne transmission

Mansonella microfilaria