

Onchocerca

(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 phasmodian 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 filarioidea (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 *Onchocerca* are transmitted by biting midges or black flies (in which L3 develop). Various species cause nodule formation in the connective tissues of domestic and wild animals, while *O. volvulus* causes severe disease in humans, involving the skin (cutaneous nodules, dermatitis, elephantiasis) and eyes (river blindness).

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: *Onchocerca* (parasitic in connective tissues of humans/cattle/horses)
Species: *O. volvulus* (causes skin lesions, nodules and river blindness 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 Chromadorea 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)]
<i>Incertae sedis</i> 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 spirurid 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 Diplotrienoidea (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 'filaroids' [Note: take care with terminology as the cognate family Filariidae (esp. genus *Filaria*) are known colloquially as 'filarids', 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	<i>Wolbachia</i> symbiotes
Family Onchocercidae						
<i>Onchocerca</i> (35 spp.)	primates, carnivores, ungulates, rodents	1.5-80 cm (subcutis, ligaments)	105-440 µm unsheathed (skin)	-	flies, midges	present
<i>Mansonella</i> (29 spp.)	primates, carnivores, ungulates, rodents	3-8 cm (subcutis, serosa)	170-300 µm unsheathed (blood/skin)	-	midges, flies, mosquitoes	present
<i>Dirofilaria</i> (34 spp.)	primates, carnivores, ungulates, rodents, lagomorphs, marsupials	4-31 cm (blood vessels)	180-385 µm unsheathed (blood)	-	mosquitoes, flies	present
<i>Dipetalonema, Acanthocheilonema</i> (57 spp.)	primates, carnivores, ungulates, rodents, cingulates, marsupials	1-7 cm (subcutis, serosa)	85-300 µm unsheathed (blood)	-	flies, fleas, lice, ticks	absent
<i>Wuchereria</i> (2 spp.)	primates	2.5-10 cm (lymphatics)	210-320 µm sheathed (blood)	nocturnal, subperiodic	mosquitoes	present
<i>Brugia</i> (10 spp.)	primates, carnivores, rodents	1-9 cm (lymphatics)	170-380 µm sheathed (blood)	nocturnal, subperiodic	mosquitoes	present
<i>Loa</i> (3 spp.)	primates, ungulates, rodents	2-7 cm (subcutis, eye)	250-300 µm sheathed (blood)	diurnal	flies	absent
Family Filariidae						
<i>Parafilaria</i> (4 spp.)	ungulates	2-7 cm (subcutis)	40-58 x 23-33 µm larvated eggs (skin)	diurnal	flies	absent
<i>Stephanofilaria</i> (7 spp.)	ungulates	0.2-1.4 cm (subcutis)	45-195 µm sheathed (skin)	-	flies	absent
Family Setariidae						
<i>Setaria</i> (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 Dirofilarinae (syn. Loainae) mostly in mammals but some in birds and reptiles, Waltonellinae and Icosiellinae in amphibians, Oswaldofilarinae in reptiles, Splendidofilarinae 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 Dirofilarinae 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. *Vestibulosestariam* *Finlaynema*), *Mansonella*,

Microfilaria, *Migonella*, *Molossinema*, *Monanema*, *Onchocerca* (syn. *Wehrdikmansia*, *Acanthospiculum*), *Paramadochotera*, *Paraochoterella*, *Paraprocta*, *Paulianfilaria*, *Pseudolitomosa*, *Rumenfilaria*, *Sandnema*, *Serofilaria*, *Skrjabinfilaria* (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* mansonielliasis in Africa); lymphatic filariasis (wuchereriasis in Africa and Asia, brugiasis in South Asia); and serous filariasis (*perstans* mansonielliasis in Africa, Central and South America, *ozzardi* mansonielliasis in Central and South America).

The genus *Onchocerca* comprises worms have simple mouths often lacking lips and almost no buccal capsule but with surrounding circlets of papillae. They have a flexible cuticle often with distinctive transverse striations and regular spiral thickenings (ridges or annulations) often interrupted in lateral fields, although some species have smooth cuticles. Female worms form nodules in subcutaneous tissues, ligaments and aponeuroses of large mammals and they produce vermiform embryos (microfilariae) which disperse and accumulate in dermal connective tissues, resulting in microfilariderma (while those of other filariae (e.g. *Wuchereria*, *Brugia*, *Dirofilaria*, *Acanthocheilonema*, *Setaria*) circulate in blood). *Onchocerca* spp. are transmitted by biting midges or black flies (in which infective L3 develop). There are some 36 *Onchocerca* species infecting humans and animals (predominantly ungulates) around the world. The species *O. volvulus* infects humans throughout central Africa, Central America and northern South America. It is thought to have originated in Africa and was taken to Central America by the slave trade. It is estimated that some 30 million people in Africa suffer from onchocerciasis, up to 1 million being blind. *O. volvulus* infections have also been recorded in higher primates, chimpanzees and gorillas. There appear to be two lineages of *Onchocerca* spp. in Africa: one more primitive lineage found in forested regions and another more derived lineage found in savannah regions. Onchocercal infections are common in cattle, horses, donkeys, camels, deer, antelopes and pigs, mainly in the tropics but also in temperate zones. Eight species have been described in cattle and four in horses. *Onchocerca* spp. are transmitted by dipteran vectors, predominantly black flies (*Simulium*, *Prosimulium*) but some species utilizing midges (*Culicoides*). Vector distribution, abundance and competence therefore influences the distribution of *Onchocerca* spp. infections. The primary vectors of *O. volvulus* are *S. damnosum*, *S. neavei* and *S. woodi* in Africa, *S. ochraceum*, *S. metallicum*, *S. callidum* in Mexico, *S. exiguum* in Colombia and Ecuador, *S. metallicum* and *S. exiguum* in Venezuela, and *S. guianense* and *S. oyapockense* in Brazil. Another 40 black fly species have been implicated in the transmission of *Onchocerca* spp. to domestic animals, and several *Culicoides* spp. have been found to transmit *O. reticulata*, *O. cervicalis* and *O. raillieti* to equids, *O. gibsoni*, *O. gutturosa* and *O. armillata* to cattle and sheep, *O. cebei* to buffalo, and *O. fasciata* to camels. Other filarial worms infect humans causing severe disease and disfigurement, most being restricted to tropical regions and involving mosquitoes or other flies as vectors.

<i>Onchocerca</i> spp.	Definitive Hosts (DH)	Location	Vectors/Intermediate Hosts (IH)	Distribution
<i>O. alcis</i>	Artiodactyla: cervid (moose)			North America
<i>O. armillata</i>	Artiodactyla: bovid (zebu, cattle, buffalo, goat, sheep, four-horned antelope), camelid (camel); Perissodactyla: equid (horse, donkey)	thoracic aorta	Diptera: ceratopogonid (<i>Culicoides</i>); simuliid (<i>Simulium</i>)	Africa, India, Middle East
<i>O. beaveri</i>	Artiodactyla: bovid (blue duiker)	ligaments		Africa
<i>O. boehmi</i> (now <i>Elaeophora</i>)	Perissodactyla: equid (horse)	metacarpal region		Europe
<i>O. caprae</i>	Artiodactyla: bovid (goat)			
<i>O. cebei</i> (syn. <i>O. sweetae</i>)	Artiodactyla: bovid (water buffalo, cattle)	abdomen, thorax, brisket	Diptera: ceratopogonid (<i>Culicoides</i>)	Far East, Australia
<i>O. cervicalis</i> (equine neck threadworms)	Perissodactyla: equid (horse, donkey); Primates: hominid (human)	ligamentum nuchae	Diptera: ceratopogonid (<i>Culicoides variipennis, victoriae, parotti, robersti, nubeculosus</i>); simuliid (<i>Simulium pictipes</i>)	Europe, North America, Australia
<i>O. cervipedis</i> (legworm)	Artiodactyla: cervid (mule deer, black-tailed deer, white-tailed deer, moose, caribou)	subcutaneous tissues, tibio-tarsal joint	Diptera: simuliid (<i>Prosimulium impostor, Simulium decorum, venustum</i>)	North America
<i>O. denkei</i>	Artiodactyla: bovid (cattle)	subcutaneous connective tissues		Africa
<i>O. dewittei</i> (incl. ssp. <i>dewittei</i> and <i>japonica</i>)	Artiodactyla: suid (boar, Japanese boar); Primates: hominid (human)	subcutaneous connective tissues	Diptera: simuliid (<i>Simulium bidentatum, bovis, damnosum, hargreavesi, vorax, aokii, arakawae, japonicum, quinquestriatum, rulibasis</i>)	Malaysia, Japan

<i>O. dukei</i>	Artiodactyla: bovid (cattle)	intermuscular connective tissues	Diptera: simuliid (<i>Simulium bovis</i>)	Africa
<i>O. eberhardi</i>	Artiodactyla: cervid (sika deer)	carpal ligament		Japan
<i>O. fasciata</i>	Artiodactyla: camelid (camel, dromedary)	connective tissues, ligamentum nuchae	Diptera: ceratopogonid (<i>Culicoides</i>)	Arabia, Australia, Asia
<i>O. flexuosa</i>	Artiodactyla: cervid (roe deer, fallow deer, red deer), bovid (goat)	subcutaneous tissues	Diptera: simuliid (<i>Simulium ornatum, argyreatum, Prosimulium nigripes, Boophthora erythrocephala, Wilhelmsia equina</i>)	Europe
<i>O. garmsi</i>	Artiodactyla: cervid (red deer)	subcutaneous tissues	Diptera: simuliid (<i>Simulium</i>)	Europe
<i>O. gibsoni</i>	Artiodactyla: bovid (cattle, zebu, buffalo, sheep), camelid (camel)	connective tissues, esp. brisket	Diptera: ceratopogonid (<i>Culicoides buckleyi, marksi, orientalis, oxystoma, pungens, shortii, Forcipomyia townsvillensis</i>), simuliid (<i>Simulium</i>)	Africa, Asia, Australasia
<i>O. gutturosa</i> (syn. <i>O. lienalis</i>)	Artiodactyla: bovid (cattle, European bison, American bison, buffalo, sheep), camelid (camel); Perissodactyla: equid (horse, donkey); Carnivora: canid (dog); Primates: hominid (human)	connective tissue, ligamentum nuchae, femurotibial ligaments, gastro-splenic ligament	Diptera: simuliid (<i>Simulium arakawae, bidentatum, daisense, decorum, erythrocephalum, galeratum, jenningsi, kyushuense, ornatum, pictipes, reptans, tuberosum, variegata, vittatum, Boophthora sericata</i>), ceratopogonid (<i>Culicoides variipennis, nubeculosus</i>)	Europe, Africa, Americas, Australia, Asia
<i>O. hamoni</i>	Artiodactyla: bovid (kob, reedbok)	subcutaneous nodules		Africa
<i>O. indica</i>	Artiodactyla: bovid (cattle, buffalo)			
<i>O. jakutensis</i> (syn. <i>O. tubingensis</i>)	Artiodactyla: cervid (red deer); Macroscelidea: macroscelidid (four-toed elephant shrew); Primates: hominid (human)	subcutaneous tissues	Diptera: simuliid (<i>Simulium</i>)	Europe
<i>O. katangensis</i> (syn. <i>Katanga?</i>)	Macroscelidea: macroscelidid (four-toed elephant shrew)			Africa
<i>O. lerouxi</i>	Artiodactyla: bovid (black-fronted duiker)	intermuscular connective tissue		Africa
<i>O. lupi</i>	Carnivora: canid (dog, wolf, steppe wolf), felid (cat); Primates: hominid (human)	sclera of eyes	Diptera: simuliid (<i>Simulium tribulatum</i>)	Europe, Middle-East, North America
<i>O. ochengi</i> (syn. <i>O. dermatata</i>)	Artiodactyla: bovid (cattle, zebu)	connective tissue, scrotum, udder	Diptera: simuliid (<i>Simulium damnosum, hargreavesi, ornatum, sanctipauli, sirbanum, squamosum, wellmanni</i>)	West and Central Africa
<i>O. pandei</i>	Artiodactyla: bovid (buffalo)			
<i>O. raillieti</i>	Perissodactyla: equid (horse, donkey)	cervical ligament, intermuscular connective tissue	Diptera: ceratopogonid (<i>Culicoides kingi?</i>)	Africa
<i>O. ramachandrini</i>	Artiodactyla: suid (warthog)	subcutaneous tissue (feet), tibia-tarsal ligaments	Diptera: simuliid (<i>Simulium damnosum, squamosum</i>)	West Africa
<i>O. reticulata</i> (Kasen summer mange, equine dhobie itch)	Perissodactyla: equid (horse, donkey, mule)	connective tissues, flexor tendons, suspensory ligaments of fetlock	Diptera: ceratopogonid (<i>Culicoides nubeculosus, obsoletus</i>)	worldwide
<i>O. schulzkeyi</i>	Artiodactyla: bovid (roan antelope)	dermal nodules		Africa
<i>O. skrjabini</i> (syn <i>O. tarsicola</i>)	Artiodactyla: cervid (roe deer, Japanese serow, red	subcutaneous tissue,	Diptera: simuliid (<i>Simulium arakawae, bidentatum, daisense, japonicum,</i>	Western Europe,

	deer, sika deer, reindeer)	tarsal/carpal joints	<i>oitanum, ornatum, aokii, Prosimulium nigripes, tomosvaryi, Odagmia ornato, Twinnia japonensis</i>)	Japan
<i>O. sonini</i>	Artiodactyla: bovid (black-fronted duiker)	tendon		Africa
<i>O. stilesi</i>	Artiodactyla: bovid (cattle)	connective tissues stifle joints		North America
<i>O. suzukii</i>	Artiodactyla: bovid (cattle), cervid (Japanese serow)	subcutaneous tissues	Diptera: simuliid (<i>Simulium bidentatum, japonicum, Prosimulium</i> sp.)	Japan
<i>O. synceri</i>	Artiodactyla: bovid (African buffalo)	subcutaneous tissue		Africa
<i>O. takaokai</i>	Artiodactyla: suid (Japanese wild boar)	skin		Japan
<i>O. volvulus</i> (river blindness, 'craw craw')	Primates: atelid (Geoffroy's spider monkey), cercopithecid (sooty mangabey), hominid (human, gorilla, chimpanzee, bonobo); Artiodactyla: bovid (cattle), camelid (dromedary); Rodentia: murid (mouse)	subcutaneous tissues, skin nodules, dermatitis, pachyderma, ocular complications	Diptera: simuliid (<i>S. albivirgulatum, amazonicum-sanguineum</i> complex, <i>callidum, damnosum, dieguerense, ethiopiense, exiguum, gonzalezi, guianense, haematopotum, hargreavesi, horacioi, incrustatum, kilibanum, konkourense, leonense, limbatum, mengense, metallicum, neavei, ochraceum, oyapockense, pinto, quadrivittatum, rasyani, sanctipauli, sirbanum, soubrense, squamosum, thyolense, veracruzatum, woodi, yahense, yarzabali</i>)	Africa, Central and South America

Parasite morphology: Filarial worms form adults (sometimes called macrofilariae) and pre-larvae (microfilariae) in vertebrates, while three larval developmental stages occur in the arthropod vectors. Adult worms are long and slender and have simple mouths with two surrounding circles of four papillae (they lack lips and buccal capsules). They are filariform with a long oesophagus not divided conspicuously. They have a flexible cuticle with distinctive transversal (cross) striations and regularly-spaced spiral thickenings (ridges or annulations) which are often interrupted in lateral fields. Differences in cuticular characters have been used to identify three groups of *Onchocerca* spp.: one group comprising species with ridges ~25 µm apart and 2-3 intervening striations (e.g. *O. volvulus*, *O. reticulata*, *O. gibsoni*, *O. ochengi*); a second group with ridges ~50 µm apart and 4-5 intervening striations (e.g. *O. cervicalis*, *O. gutturosa*); and a third group with smooth cuticles (e.g. *O. raillieti*, *O. cervipedis*, *O. jakutensis*). The size of mature worms varies according to species, but all exhibit marked sexual dimorphism with female worms being much larger (250-800 x 0.2-0.6 mm) than males (15-270 x 0.1-0.3 mm). In females, the vulva is located at the anterior end of the worm but posterior to the nerve ring. In males, the tail is curved ventrally, bears caudal papillae arranged in several groups (4-6 pairs precloacal/pericloacal/adanal, 6-8 pairs postcloacal/postanal/terminal), two unequal and dissimilar spicules and some species have small caudal alae. Differences in the dispositions of caudal papillae have been noted between (and sometimes within) several *Onchocerca* spp., with variations from a basic (primitive) plan (of 4+6) exhibited by *O. raillieti* including precloacal papillae grouping towards the cloaca (*O. volvulus*), and terminal papillae grouping towards the cloaca (*O. reticulata*, *O. armillata*), being modified into cuticular points (*O. gutturosa*, *O. ochengi*, *O. dukei*, *O. skrjabini*) or being reduced in number (*O. jakutensis*). Gravid females are ovoviviparous and produce eggs which hatch internally releasing motile pre-larvae known as microfilariae (sometimes reported as first-stage (L1) larvae although they are not as developed as those of other nematodes). Microfilariae are elongate, measuring from 105-440 µm long by 5-9 µm wide depending on the species, and have rounded heads (some species with ventral cephalic hooks), a thread-like oesophagus, nerve ring, excretory vesicle, median sac-like inner body (Innenkorper) and a series of posterior nuclei forming the genital primordia. The microfilariae of various filarial worms can be differentiated on the basis of their morphology, those of *Onchocerca* being unsheathed with pointed attenuated tails possessing nuclei which do not extend to the posterior tip (compared to those of *Wuchereria*, *Brugia* and *Loa* which are ensheathed retaining their thin flexible 'egg-shell' membrane). In the invertebrate vectors, microfilariae ingested during feeding undergo further development to become infective third-stage (L3) larvae which vary in size depending on the species (ranging from 380-1,030 µm in length). The infective larvae generally have trapezoidal heads, short buccal capsules and a long glandular oesophagus.

Site of infection: Adult worms live in the connective tissues and/or ligaments in their definitive (vertebrate) hosts, where they become encapsulated forming distinctive nodules containing tangled pairs or groups of worms. Differences in the anatomical locations of the worms have been used to identify five groups of *Onchocerca* spp.: one comprising species that induce encapsulation of adults within fibrous nodules (e.g. *O. volvulus*, *O. fasciata*, *O. gibsoni*, *O. dukei*, *O. cervipedis*, *O. flexuosa*); one whose adults live in the connective tissues of the gastro-splenic and cervical ligaments (*O. gutturosa*, *O. cervicalis*); one in the subcutaneous connective tissues (*O. reticulata*, *O. raillieti*, *O. tarsicola*, *O. dewittei*); one intradermal (*O. ochengi*, *O. cebei*); and one in the aorta

(*O. armillata*). Live microfilariae are released directly into adjacent host tissues (or blood for other filarial worms). In the intermediate (invertebrate) hosts, infective larvae have been recovered from the head, thorax and/or abdomen of the dipteran vectors.

Pathogenesis: *Onchocerca* causes the disease onchocerciasis which has four principal manifestations: subcutaneous nodule formation, dermatitis, lymphadenopathy and blindness. Adult worms coil up and become surrounded by fibrous nodules (onchocercomas) often containing a single female and a single male worm. They become embedded in intensely eosinophilic material (proteins, immune complexes, inflammatory debris, etc.) consistent with Splendore-Hoeppli reactions surrounding other micro-organisms (including fungi, bacteria and parasites). In humans, *O. volvulus* nodules usually develop over bony prominences (especially the pelvis in Africa and the head in Mexico). The most pathogenic effects, however, are caused by the death and degeneration of numerous microfilariae into host tissues (live microfilariae elicit little inflammation). Early-stage infections are often associated with intense pruritus (itching) progressing to papular rashes (known as crawl-crawl in Africa). Over time (months to years), inflammatory responses manifest as chronic papular dermatitis characterised by large papules and hyper-pigmented thickened skin. Affected skin may also exhibit asymmetric lichenization ('sowda' in Africa), spotty depigmentation ('leopard' skin), thickened wrinkled pachyderma ('crocodile' or 'elephant' skin) or purplish depigmentation ('mal morado' in Mexico). The World Health Organization has adopted a staged classification scheme for recording acute papular onchodermatitis (APOD), chronic papular onchodermatitis (CPOD), lichenified onchodermatitis (LOD), atrophy (ATR) and depigmentation (DPM). In addition to dermatitis, infections by microfilariae cause intradermal oedema with enlargement and inflammation of draining lymph nodes (lymphadenopathy), particularly in the groin or axilla, with progressive loss of elastic fibres causing hernias or hanging groin. Infections have also been associated occasionally with an unusual form of epilepsy (Nodding disease) in young children in Africa. Ocular infections by microfilariae may result in compromised sight (reduced vision to total blindness) due to anterior (corneal) lesions causing punctate opacities and sclerosing keratitis, or posterior (retinal) lesions resulting in marked sclerosis (hardening) of choroidal vessels, retinochoroiditis and atrophy of the optic nerve. Infections have also been associated with increased intraocular pressure leading to secondary cataracts and glaucoma. People are afflicted more in savannah than forest regions, and the common name 'river blindness' actually indicates an association between the distribution of infections and suitable habitats for the insect vector. Immunological studies have indicated that host resistance to infection and disease wanes when cellular responses are impaired or down-regulated leading to persistent chronic conditions. Infections in animals by other *Onchocerca* spp. usually do not result in severe diseases; infections in cattle may lead to blemished hides and devaluation of carcasses due to nodules, and infections in horses have been associated with fistulous withers (verminous granulomatous nodules in ligaments), cutaneous lesions (hypersensitivity reactions (scaliness, pruritus, alopecia) of ventral body, head and neck), periodic ophthalmia (with corneal vascularization) and lameness (due to parasitic suspensory desmitis, flexor tendonitis or navicular syndrome).

The recent discovery of unique endosymbiotic rickettsial α -proteobacteria (*Wolbachia* supergroups C, D and F) in many filarial nematodes, including most *Onchocerca* spp. except *O. flexuosa*, has interesting implications for both worm biology and pathogenicity. The bacteria are present in all worm developmental stages; they occur in syncytial hypodermal cord cells and also undergo transovarian transmission to developing embryos. They are considered to be essential for the normal development and longevity of many filarial worms, with various biochemical benefits shown for each of the symbiotic partners (mutualism). This dependency has been exploited by using antibiotics to eliminate the bacteria, with subsequent detrimental effects on worm vitality. On the down-side, while microfilariae are well known to induce intense inflammatory reactions, especially upon their death, there is now evidence to suggest that the consequential release of endosymbiotic bacteria may exacerbate that inflammation (bacterial surface proteins have been shown to trigger innate immune responses and Th1 pro-inflammatory responses).

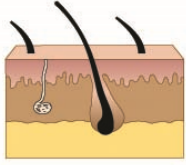
Developmental cycle and mode of transmission: All filarial worms have indirect life-cycles, involving vector-borne transmission using dipteran (simuliid or ceratopogonid) intermediate hosts. *O. volvulus* infections are transmitted by small black flies (sometimes called buffalo gnats) of the genus *Simulium*. Larval black flies only live in clear fast-running streams and adult flies live in adjacent areas with high humidity and abundant streamside vegetation. The adult flies are pool-feeders with coarse mouthparts that rasp and tear host tissues. They feed on a variety of mammals and birds, and their painful bites cause considerable annoyance. Microfilariae ingested during feeding enter the gut and migrate to the thoracic flight muscles of the fly progressing to first-stage (L1) larvae. The larvae moult to second-stage (L2) larvae which migrate to the proboscis and moult into infective third-stage (L3) larvae. Larval development in flies takes around 7-12 days depending mostly on prevailing temperatures. Infective larvae are not injected into definitive hosts when flies feed, but break out of the proboscis when it is bent during feeding and are deposited on the skin where they wriggle and invade the puncture wound. They move to subcutaneous tissues and moult twice developing into mature worms over 1-3 months before mating. Immature adults may be attracted to existing nodules and settle on their surface as satellite nodules, or juvenile female worms may provoke encapsulation and form new separate nodules. The large females remain within nodules their entire lives, but the small males may move from nodule to nodule (re-insemination appears necessary to maintain annual cyclic phases of reproduction, each phase lasting 2.0-4.5 months). The prepatent period (time from infection to first microfilariae release) may be as long as 16 months for some species and the patent period (duration of microfilariae release) may vary considerably with intermittent production occurring over years. Adult worms may live up to 9-16 years and produce billions of microfilariae, with estimates of peak numbers released over 3-4 weeks ranging from 700-1,500 per day. The microfilariae migrate to the skin and eyes and may remain viable for up to 6-24 months. Many studies have demonstrated differences in the temporal and spatial distribution of microfilariae; many species exhibit a daily periodicity or tissue tropism which is attuned to the feeding habits of the vector

species; e.g. microfilariae of *Onchocerca* in Africa normally concentrate in the lower body to maximize transmission to low-biting *Simulium damnosum* but infections in Guatemala concentrate in the upper body where the vector is the high-biting *Simulium ochraceum*. In animals, microfilariae accumulate in different regions of the body (e.g. dorsal midline for *O. gutturosa*, ventral midline and legs for *O. gibsoni*, ventral abdomen for *O. cervicalis*, etc.) which are predilection biting sites for their specific black fly or midge vectors.

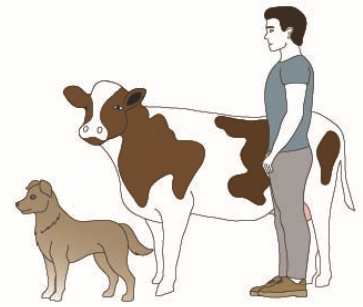
Differential diagnosis: The diagnosis of early-stage infections on the basis of the appearance of a pruritic rash is not distinctive enough as other conditions may cause similar conditions. Infections are generally diagnosed after they have become patent and worms have formed characteristic palpable nodules under the skin. Portions of worms can be obtained by biopsy to confirm diagnosis. Infections can also be detected by examining skin-snip biopsies for active microfilariae after incubation in saline for 30 mins. In heavy infections, microfilariae can occasionally be found in blood and urine. The morphological characteristics of microfilariae are distinctive enough to differentiate all human filarial worms, but it is recommended that multiple samples be collected from different body sites at different times of the day to account for any species-specific differences in tissue tropism and periodicity. *Onchocerca* microfilariae are rarely found in blood whereas those of other filarial worms are commonly found in peripheral blood samples (from which they can be concentrated using Knott's technique to lyse erythrocytes or by filtration using 3-5 µm pore-sized polycarbonate filters). A variety of immunoserological tests (enzyme immunoassays, immunoblots, immunoprecipitation assays) have been developed in attempts to detect specific host antibodies or parasite antigens, especially during early-stage infections, but most tests have lacked sensitivity and specificity. Various molecular biological techniques are currently under development to detect parasite DNA in skin biopsies, blood samples and vector pools using polymerase chain reactions (PCR) to amplify specific sequences (tandemly repeated DNA units (O-150 family), major sperm protein (msp) genes and internal transcribed spacer (ITS) regions of ribosomal DNA).

Treatment and control: A common therapeutic practice in endemic regions is that of nodulectomy, that is, the surgical removal of detectable nodules from superficial aspects to stop microfilariae production and curb attendant pathology. Some nodules, however, may be non-palpable or the adults may be freely migrating. Chemotherapy is therefore warranted, and a major advance was made with the development of ivermectin which is well tolerated in humans and animals. Single doses were found to eliminate microfilariae from the skin, and to suppress their release from adults for over a year. Multiple doses were also found to slowly kill adults. Ivermectin treatment, however, is contraindicated in patients infected with *Loa loa*, as severe reactions may occur. Other microfilaricidal drugs include diethylcarbamazine (DEC), mebendazole, flubendazole and benzimidazole derivatives, but they have little or no effect on adult *Onchocerca* worms. DEC treatment may also precipitate serious dermal, systemic or ocular complications caused by dying microfilariae, although such side-effects can be ameliorated by the use of anti-inflammatory drugs. Skin-patch tests can also be used to monitor for possible Mazzotti reactions before DEC treatment. Suramin does have an effect on adult worms, but it must be administered systemically and it is nephrotoxic. More recently, the antibiotic doxycycline has been used to treat filariae-infected individuals to eliminate *Wolbachia* endosymbiotic bacteria with resultant reductions in adult worm fecundity and survival. Preventive measures involve vector control and avoiding black fly bites. Residual insecticides can be used around dwellings to reduce adult fly numbers, but better results are obtained using larvicides to treat rivers and streams where black flies breed. Unfortunately, there are recurring problems with the development of insecticide resistance in black fly populations.

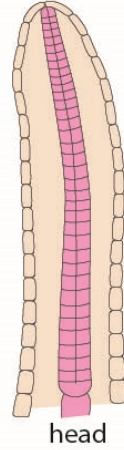
Onchocerca



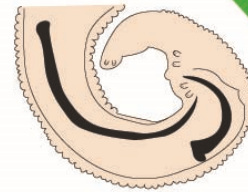
subcutis, ligaments
(nodules, dermatitis,
elephantiasis, blindness)



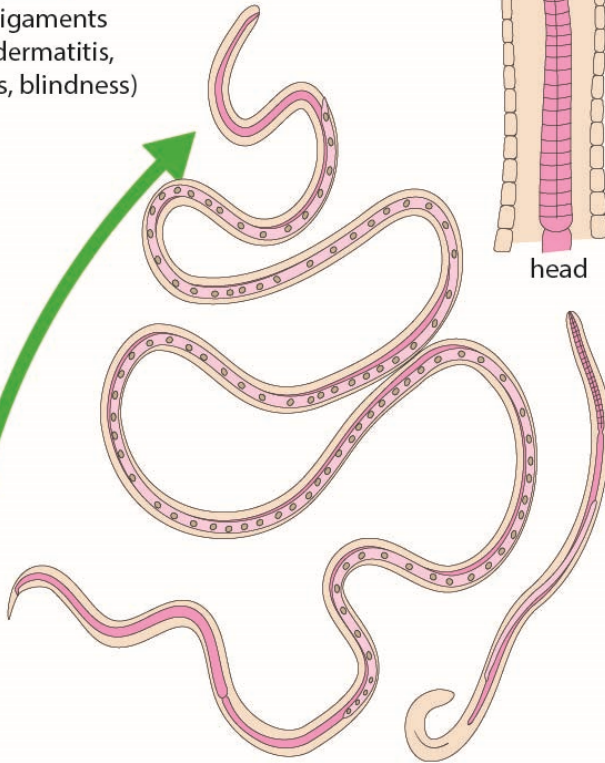
Definitive Hosts
(primates, carnivores,
ungulates, rodents)



head

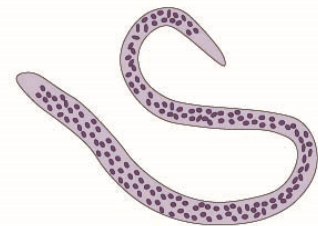


male tail (lateral)



adult female
(~ 600 mm)

adult male
(~ 100 mm)



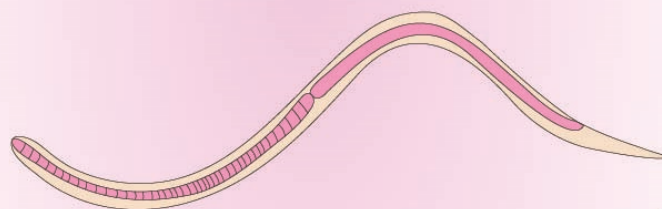
microfilariae (mf) (~ 250 μ m)
(released into subcutis)

L3
deposited
on skin

mf
ingested



Intermediate Hosts (IH)
(black flies, biting midges)
(haemocoel, then mouthparts)

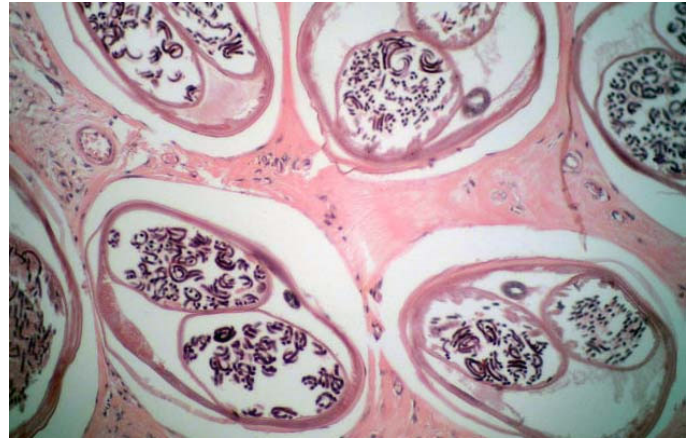


third-stage larvae
(L3) (~ 1 mm)

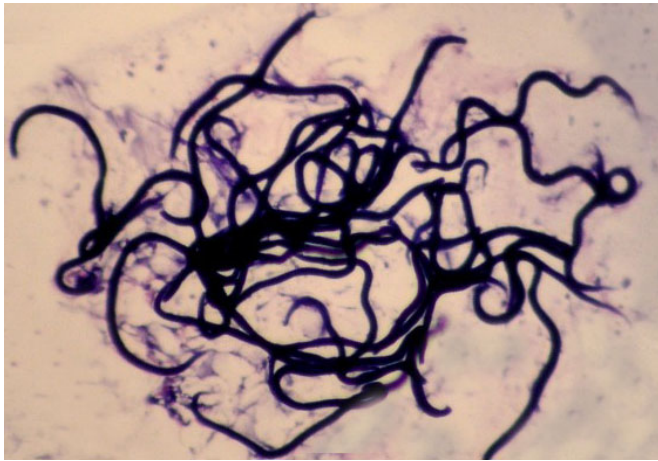
vector-borne transmission



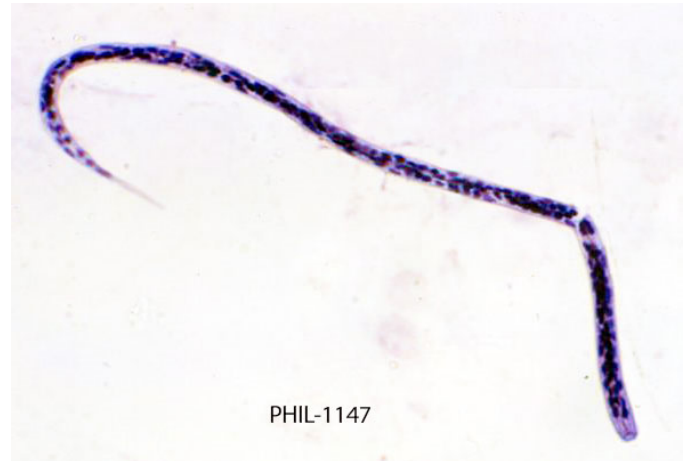
Onchocerca nodule



Onchocerca nodule



Onchocerca microfilariae



Onchocerca microfilaria