



Oncocercosis



Prof. Alfonso J. Rodríguez-Morales
Parasitología Grupos 4 y 5
Semestre I-2015

Introducción a las enfermedades parasitarias transmitidas por vectores

- Existen múltiples enfermedades causadas por parásitos helmintos y protozoarios que pueden ser transmitidas por vectores [biológicos]
- **Vector [biológico]:** aquel en el cual el parásito sufre transformación, evolución, parte de su ciclo evolutivo
- **Entre los helmintos transmitidos por vectores se encuentran las filarias.**

Table: Nematodes of Medical Importance

Family	Organism (genus and species)
<i>Ascaridae</i>	<i>Ascaris lumbricoides</i> <i>Toxocara canis</i> <i>Toxocara cati</i> <i>Lagochilascaris minor</i>
<i>Oxyuridae</i>	<i>Enterobius vermicularis</i>
<i>Trichinellidae</i>	<i>Trichuris trichiura</i> <i>Trichinella spiralis</i>
<i>Angiostrongylidae</i>	<i>Angiostrongylus costaricensis</i> <i>Angiostrongylus cantonensis</i>
<i>Ancylostomidae</i>	<i>Ancylostoma duodenale</i> <i>Ancylostoma caninum</i> <i>Ancylostoma braziliensis</i> <i>Necator americanus</i>
<i>Rhabditidae</i>	<i>Strongyloides stercoralis</i>
<i>Filaridae</i>	<i>Wuchereria bancrofti</i> <i>Onchocerca volvulus</i> <i>Mansonella sp.</i> <i>Gnathostoma sp.</i> <i>Brugia malayi</i> <i>Loa loa</i>
<i>Dracunculidae</i>	<i>Dracunculus medinensis</i>

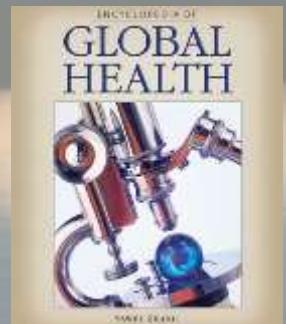
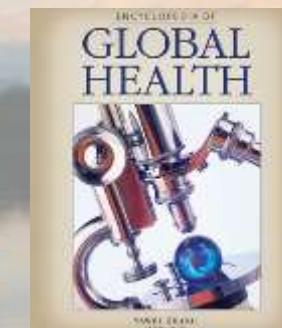


Table 1. Insects' Vectors of Medical Importance

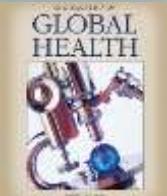
Vectors	Pathogens	Diseases
Anoplura (lice)	Bacteria	
<i>Pediculus humanus</i>	<i>Borrelia recurrentis</i>	epidemic relapsing fever
<i>Pediculus humanus</i>	<i>Rickettsia prowazekii</i>	louse-borne typhus
<i>Pediculus humanus</i>	<i>Rochalimaea quintana</i>	trench fever
Diptera (flies)	Viruses	
<i>Aedes</i> spp. particularly		
<i>A. aegypti</i>	DEN virus	dengue
<i>Aedes</i> spp. particularly		
<i>A. aegypti</i>	YF virus	yellow fever
<i>Aedes</i> spp. particularly		
<i>A. triseriatus</i>	LAC virus	LaCrosse encephalitis
<i>Culex</i> spp.	SLE virus	St. Louis encephalitis
<i>Culex</i> spp.	JBE virus	Japanese encephalitis
<i>Culex</i> and <i>Culiseta</i> spp.	WEE virus	western equine encephalitis
Various spp.	EEE virus	eastern equine encephalitis
Various spp.	VEE virus	Venezuelan equine encephalitis
Various spp.	RVF virus	Rift Valley fever
<i>Phlebotomus papatasi</i> (and other species)	sand fly fever virus	sand fly fever
	Protozoa	
<i>Anopheles</i> spp.	<i>Plasmodium falciparum</i> , <i>P. malariae</i> , <i>P. ovale</i> , <i>P. vivax</i>	malaria
<i>Glossina</i> spp.	<i>Trypanosoma brucei</i>	sleeping sickness
<i>Phlebotomus</i> spp. and <i>Lutzomyia</i> spp.	<i>Leishmania</i> spp.	Leishmaniasis, Kala-azar, dum-dum fever
	Nematodes	
<i>Aedes</i> , <i>Anopheles</i> , and <i>Mansonia</i> spp.	<i>Brugia malayi</i>	brugian filariasis
<i>Culex pipiens</i> , <i>Aedes</i> , and <i>Anopheles</i> spp.	<i>Wuchereria bancrofti</i>	Bancroftian filariasis
Various spp.	<i>Dirofilaria immitis</i>	dog heartworm
<i>Simulium</i> spp.	<i>Onchocerca volvulus</i>	onchocerciasis
<i>Chrysops</i> spp.	<i>Loa loa</i>	loiasis
	Protozoa	
<i>Triatominae</i> spp.	<i>Trypanosoma cruzi</i>	Chagas' disease



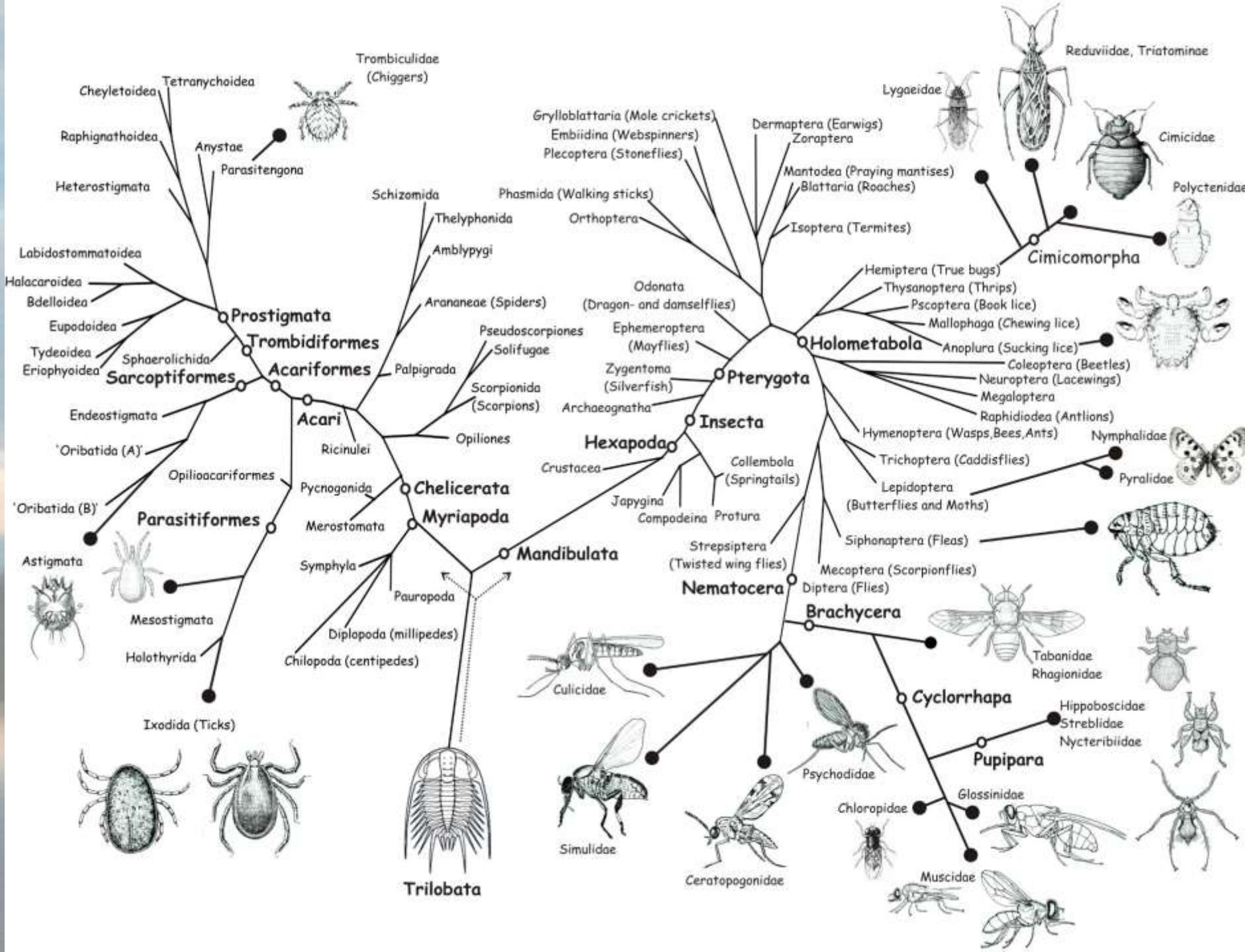
Rodriguez-Morales AJ, Franco-Paredes C. Medical Entomology. In: Zhang Y (Editor). Encyclopedia of Global Health. ISBN 9781412941860. SAGE Publications, California, USA, 2008: Volume 3: 1078-1081. Available at: <http://www.sage-ereference.com/abstract/globalhealth/n754.xml>

Table 2. Acari Vectors of Medical Importance

Vectors	Pathogens	Diseases
	Bacteria	
<i>Liponyssoides sanguineus</i>	<i>Rickettsia akari</i>	rickettsial pox
<i>Leptotrombidium</i> spp.	<i>Rickettsia tsutsugamushi</i>	scrub typhus
Various, particularly <i>Dermacentor</i> spp.	<i>Rickettsia rickettsii</i>	Rocky Mountain spotted fever
<i>Argas</i> spp.	<i>Borrelia anserina</i>	avian spirochetosis
<i>Ixodes scapularis</i> , <i>Ixodes pacificus</i>	<i>Borrelia burgdorferi</i>	Lyme disease
<i>Ornithodoros</i> spp.	<i>Borrelia recurrentis</i>	relapsing fever
Various spp.	<i>Francisella tularensis</i>	tularemia
	Virus	
<i>Dermacentor andersoni</i> (and other species)	CTF virus	Colorado tick fever
<i>Hyalomma marginatum</i>	CCHF virus	Crimean-Congo hemorrhagic fever
<i>Ixodes ricinus</i>	LI virus	louping ill
<i>Ixodes ricinus</i> (and other species)	TBE virus	tick-borne encephalitis

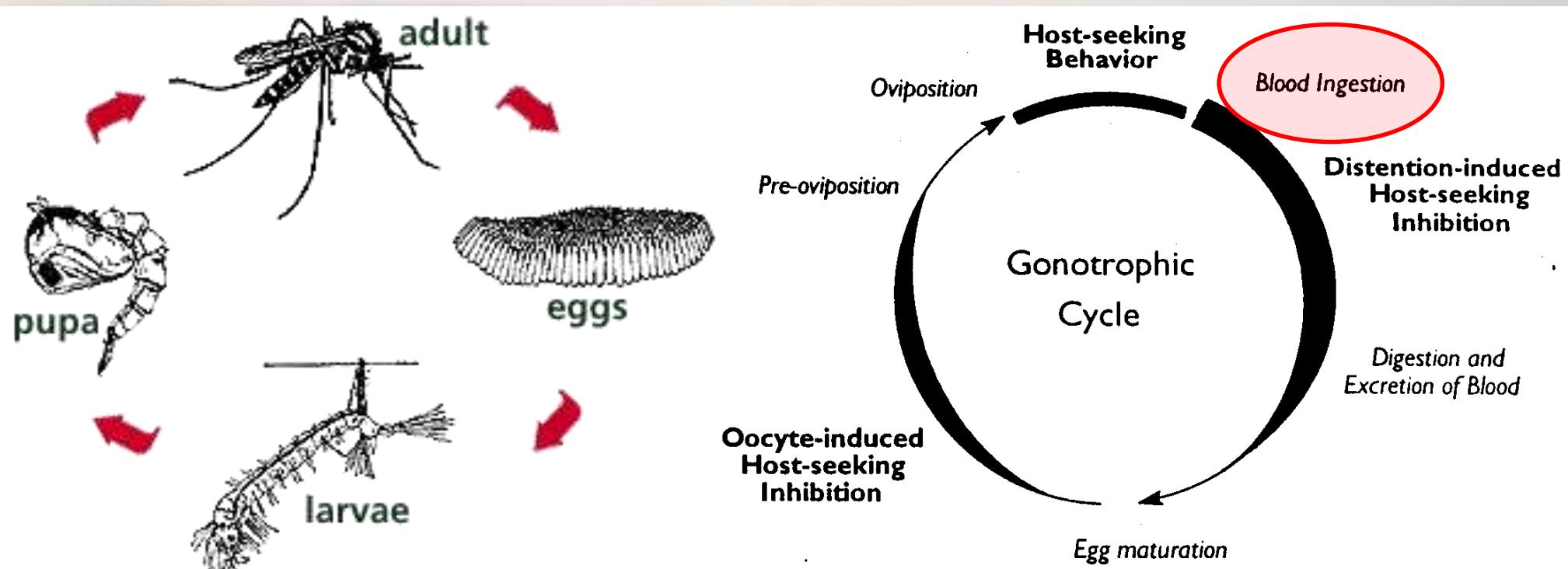


Rodriguez-Morales AJ, Franco-Paredes C. Medical Entomology. In: Zhang Y (Editor). Encyclopedia of Global Health. ISBN 9781412941860. SAGE Publications, California, USA, 2008: Volume 3: 1078-1081. Available at: <http://www.sage-ereference.com/abstract/globalhealth/n754.xml>



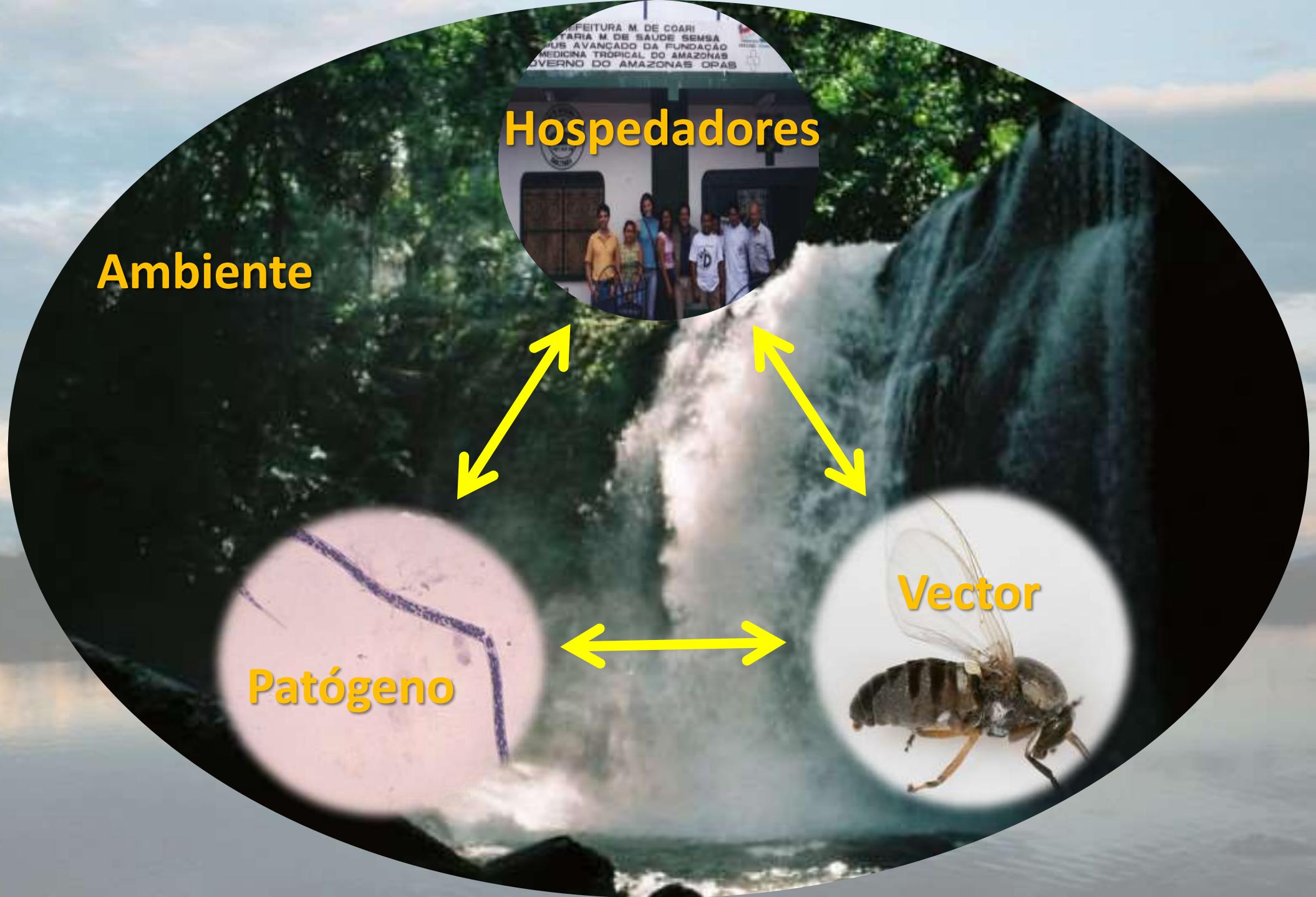
Ciclo de vida de los vectores

- La razón por la cual estos insectos son vectores es una característica de su ciclo y su necesidad biológica-energética de *reproducción*: la **hematofagia/hematofilia**



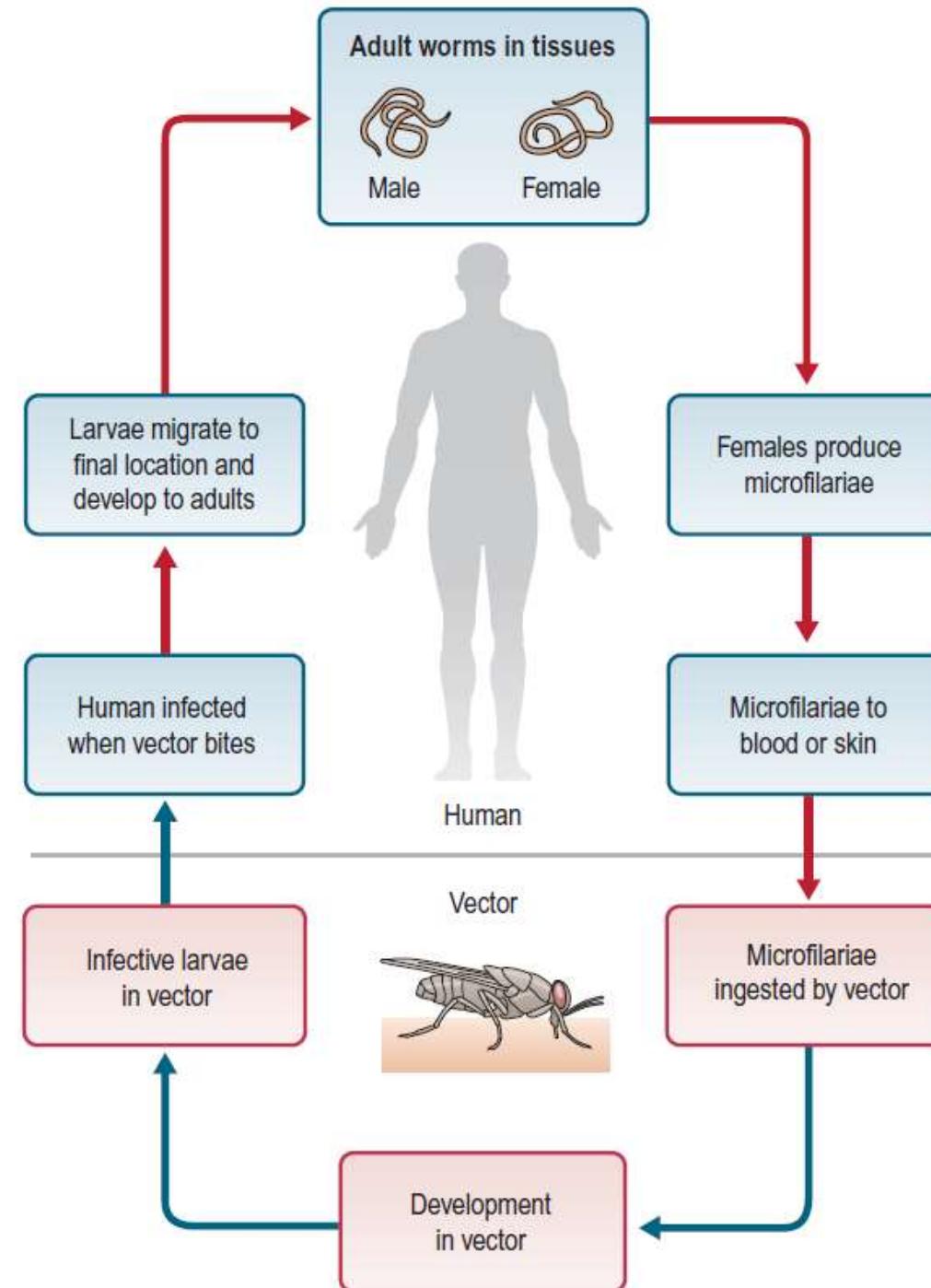
¿Qué es un buen vector?

- **Alta antropofagia/zoofagia:** alta afinidad por sangre humana y de otros vertebrados.
 - Antropofagia exclusiva: determina enfermedades antroponóticas (e.j. dengue y malaria)
 - Zoofagia exclusiva: determina enfermedades exclusivamente en animales (e.j. dirofilariasis)
 - Anfifagia: zoonosis, el vector se alimenta tanto de sangre humana como animal
- **Alta longevidad:** alta sobrevivencia de insectos infectados
- **Alta capacidad de dispersión:** mayor propagación y transmisión
- **Alta susceptibilidad a la infección con el parásito:** alta competencia vectorial



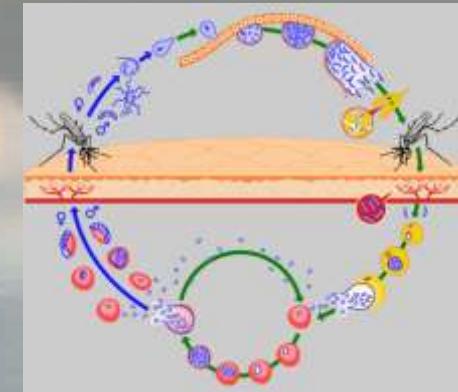
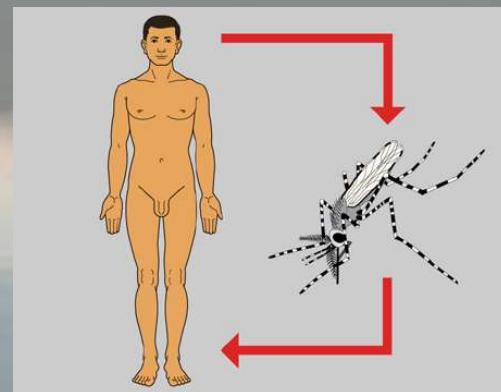
MUNICÍPIO DE COARI
SECRETARIA M. DE SAÚDE SEMSA
CENTRO AVANÇADO DA FUNDAÇÃO
MEDICINA TROPICAL DO AMAPÁ
GOVERNO DO AMAZONAS - DPAS

General life cycle of filariae



Capacidad vectorial

- C: “Número de nuevas infecciones originadas por un insecto vector a partir de un caso (persona infectada) por día”,
- Suposición: *que todas las hembras del insecto se infecten y que la población humana a ser picada sea susceptible a la infección por el parásito.*



CAPACIDAD VECTORIAL: C:

$$C = \frac{ma^2 P^n}{-\log_e P}$$

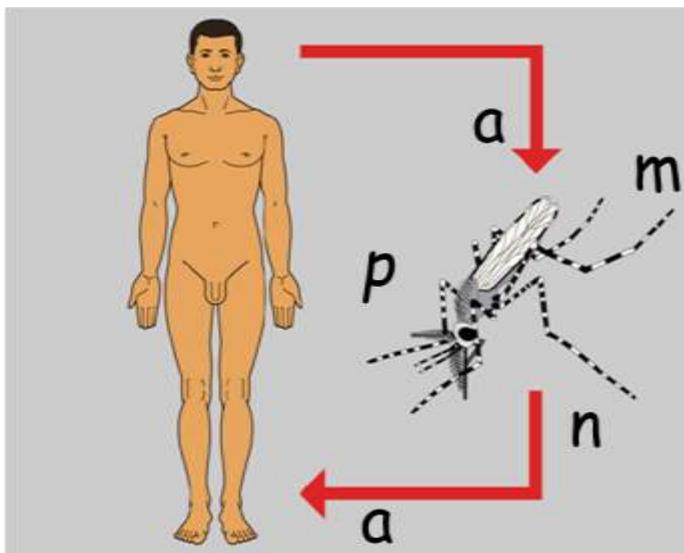
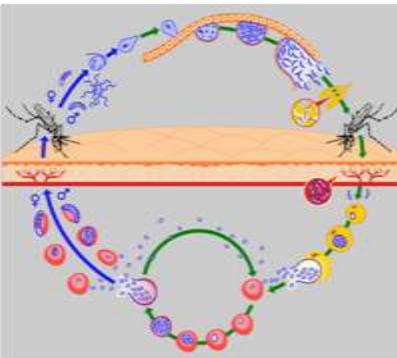
ma = the man biting rate in bites/man/night.

$mabs$ = EIR, the entomological inoculation rate in infective bites/man/night where s is the sporozoite rate and b is defined in Equation 1. In practice, the separation of b and s is difficult and b usually is deleted.

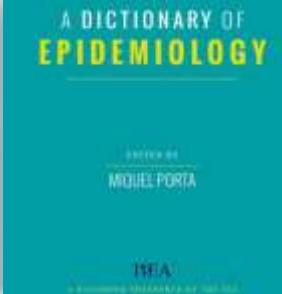
a = AI/GC where AI is the proportion of females feeding on man and GC is the duration of gonotrophic cycle in days. a is multiplied by ma in Equation 2, since refeeding is necessary for transmission

P = probability of daily survival, estimated vertically from the population age structure if the duration of the gonotrophic cycle is known or horizontally from the daily loss rate of identified cohorts over time. Thus, vector life expectancy = $1/(-\log_e P)$.

n = time from infection to infectivity in days and is usually estimated from the ambient temperature using a degree day relationship. Thus, P^n = probability of a mosquito surviving to become infective and the duration of infective life in days = $P^n/-\log_e P$.



$$C = \frac{ma^2 V P^n}{-\log_e P}$$



Entomological inoculation rate (EIR):
An indicator related to the number of infectious bites from a malaria mosquito an individual is exposed to in a given time period. It allows a direct estimation of transmission which is easy to understand and to compare, and is theoretically one of the best ways to define malaria endemicity.

Rodriguez-Morales AJ. Entomological inoculation rate (EIR). In: Porta M (ed). A Dictionary of Epidemiology. ISBN: 9780199976737. Pág: 92-93. 6th Ed. New York: Oxford University Press, 2014.

Competencia vectorial

- Representa una síntesis de aquellos factores que afectan a la habilidad innata del insecto vector para servir de hospedador biológico al patógeno.
- Variables que afectan:
 - Entrada al vector: la ingesta del patógeno
 - Evolución en el vector: multiplicación y desarrollo
 - Salida del vector: de estados infectivos (transmisión)
 - (condicionado a la sobrevivencia del insecto)
- Todas estas variables son necesarias para hablar de competencia de un vector

Ceguera de los ríos



Grillet et al (2003)

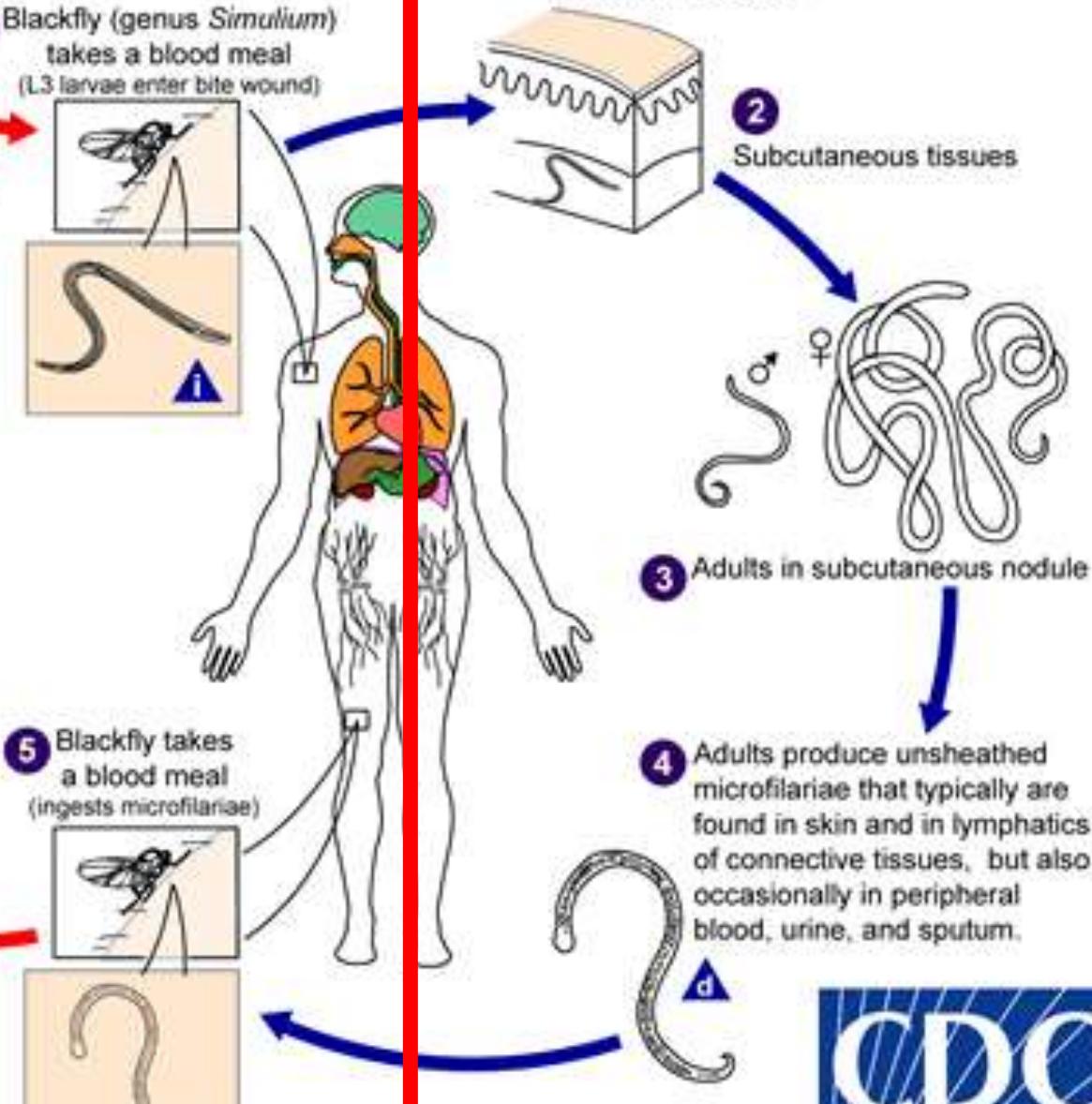
Onchocerca volvulus

Blackfly Stages

- 1 Blackfly (genus *Simulium*) takes a blood meal (L3 larvae enter bite wound)
- 2 Subcutaneous tissues
- 3 Adults in subcutaneous nodule
- 4 Adults produce unsheathed microfilariae that typically are found in skin and in lymphatics of connective tissues, but also occasionally in peripheral blood, urine, and sputum.
- 5 Blackfly takes a blood meal (ingests microfilariae)
- 6 Microfilariae penetrate blackfly's midgut and migrate to thoracic muscles
- 7 L1 larvae
- 8 L3 larvae
- 9 Migrate to head and blackfly's proboscis

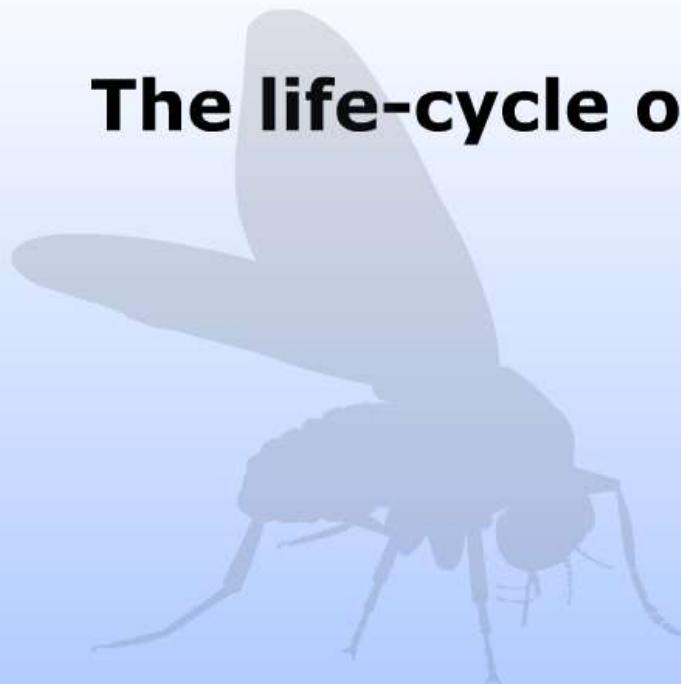
▲ = Infective Stage
▼ = Diagnostic Stage

Human Stages



CDC
SAFER • HEALTHIER • PEOPLE™

The life-cycle of onchocerciasis in humans



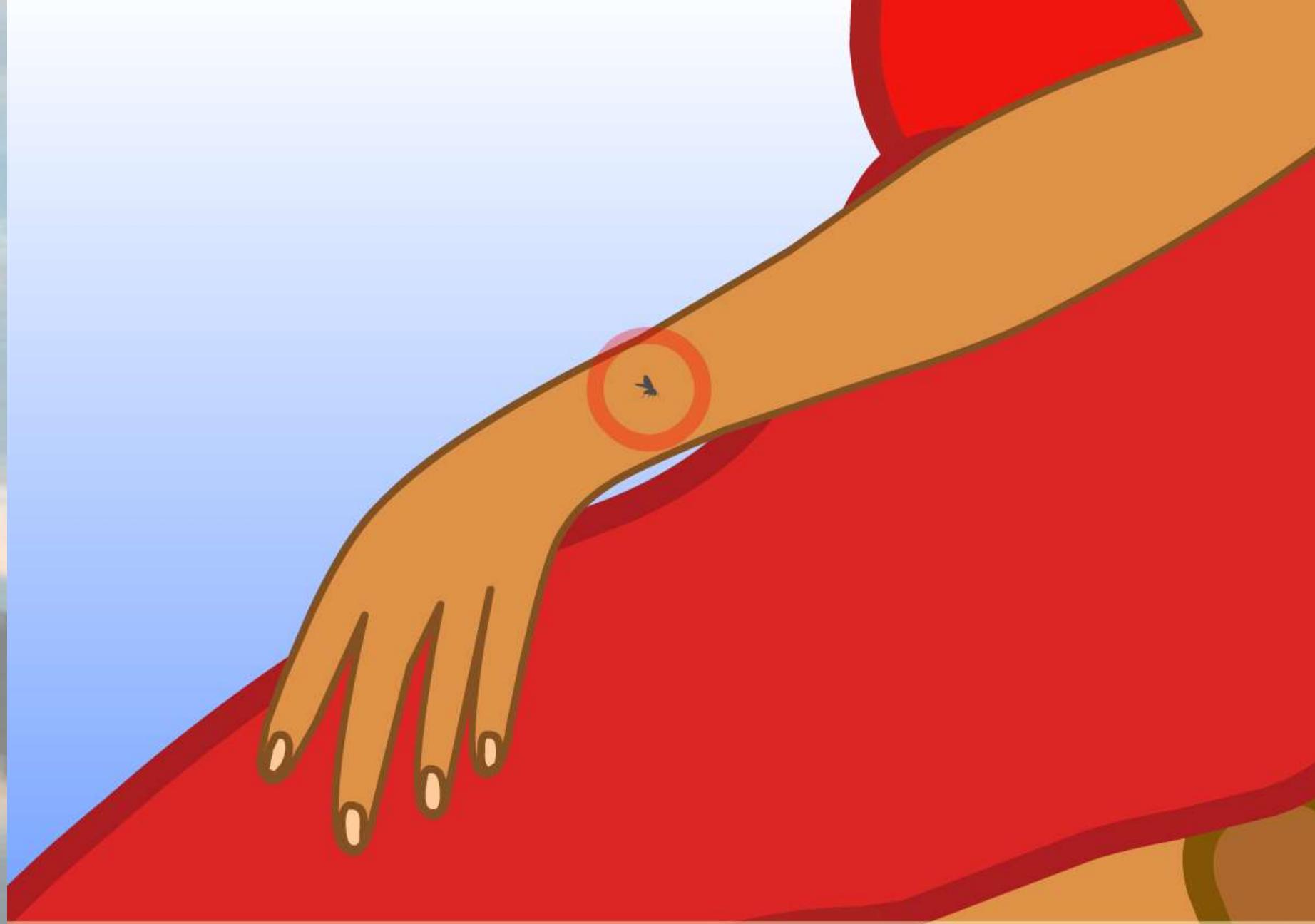
click to play ◀ 1 ▶



Onchocerciasis is associated with fast flowing rivers where
Simulium blackfly vectors breed

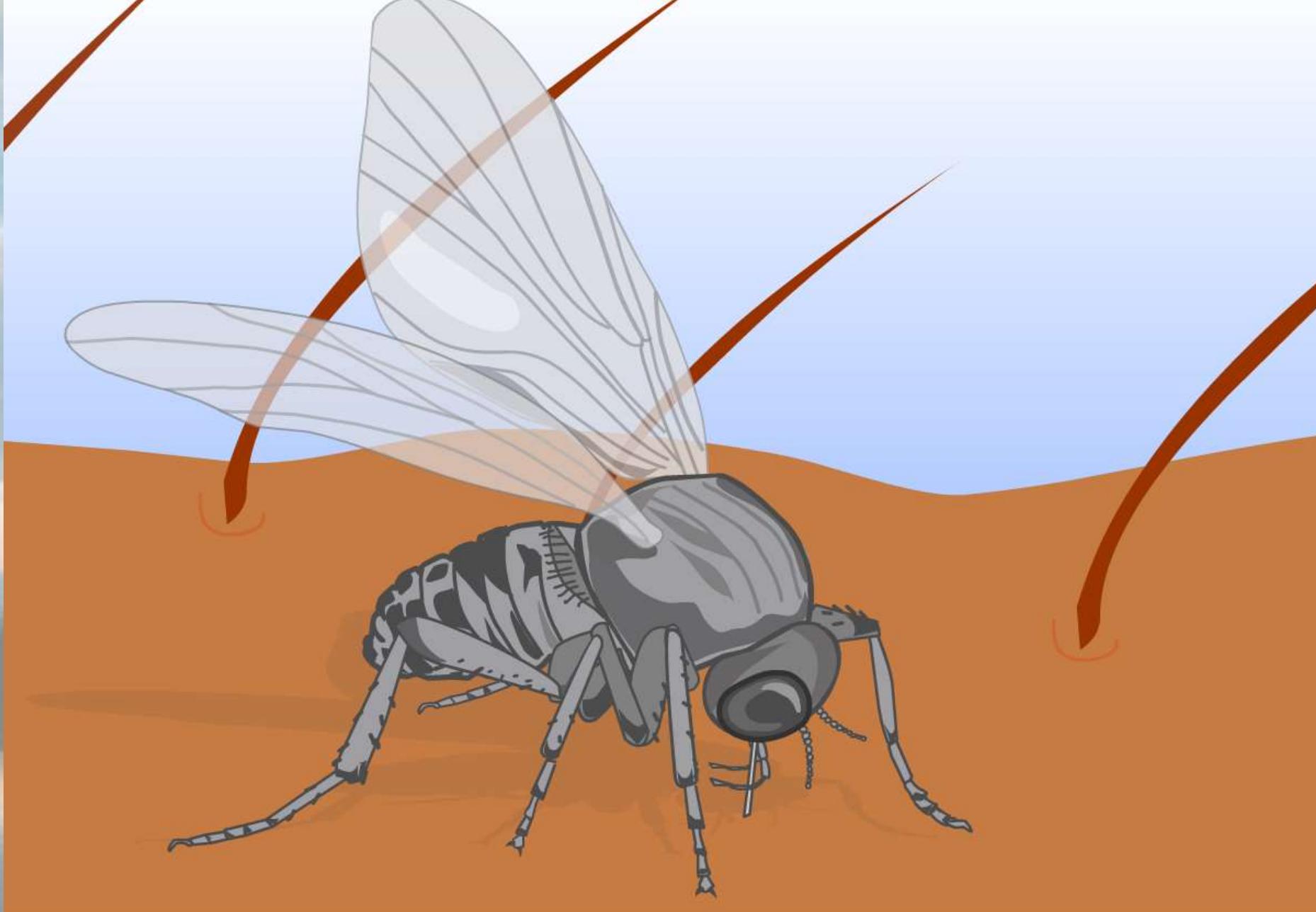


②



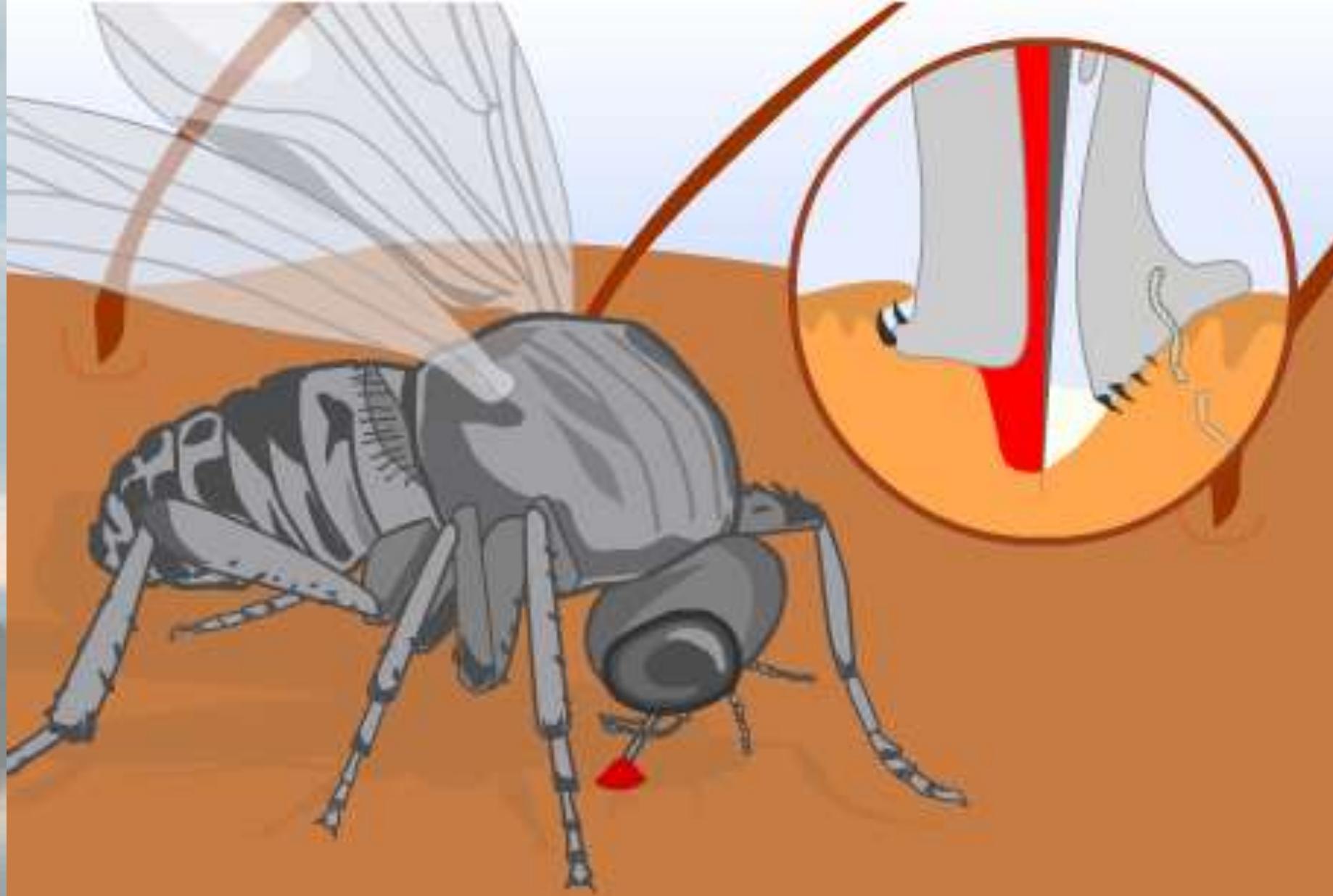
A parasitized female blackfly takes a blood-meal from a host





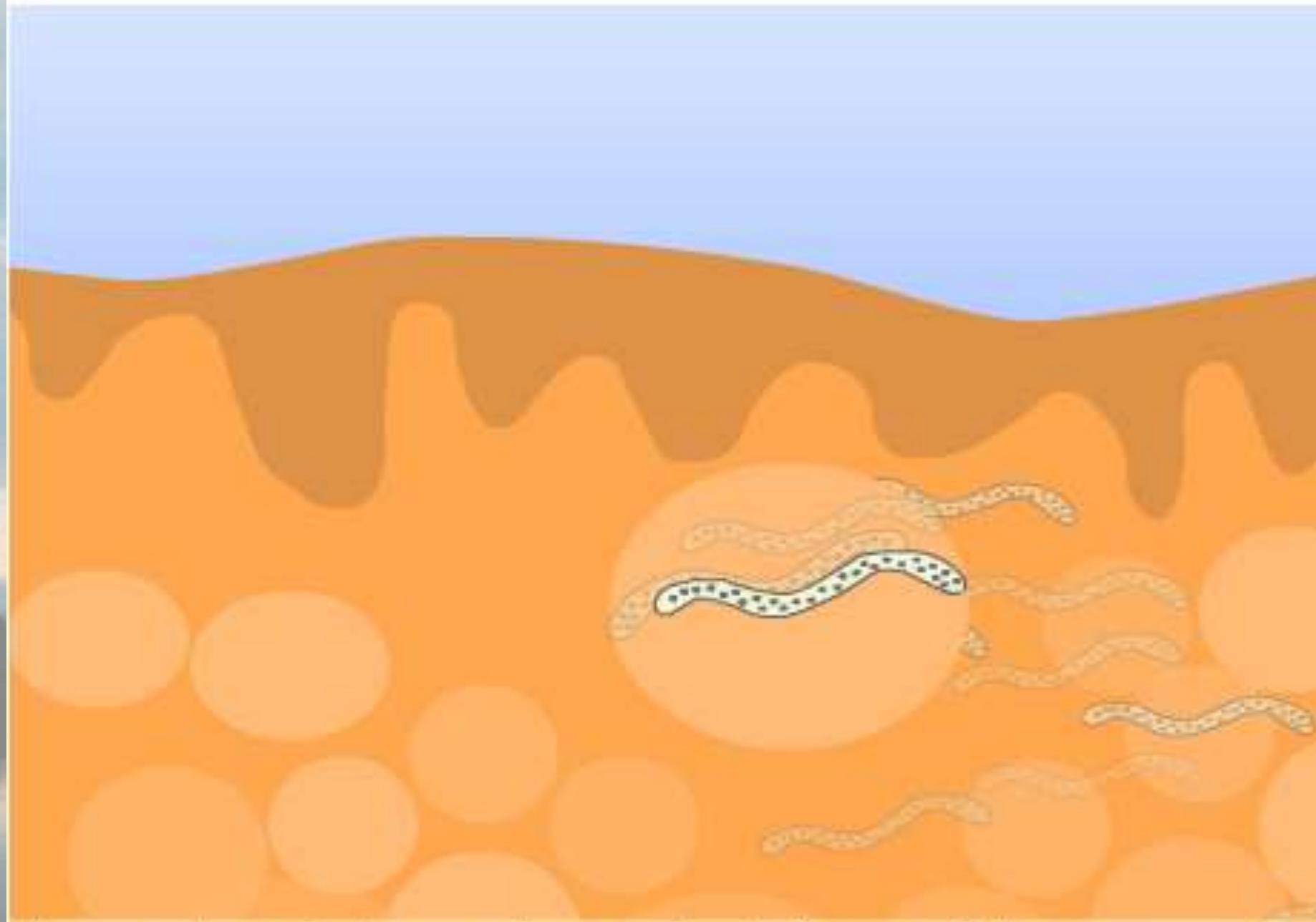
The host's skin is stretched by the fly's apical teeth and sliced by its mandibles





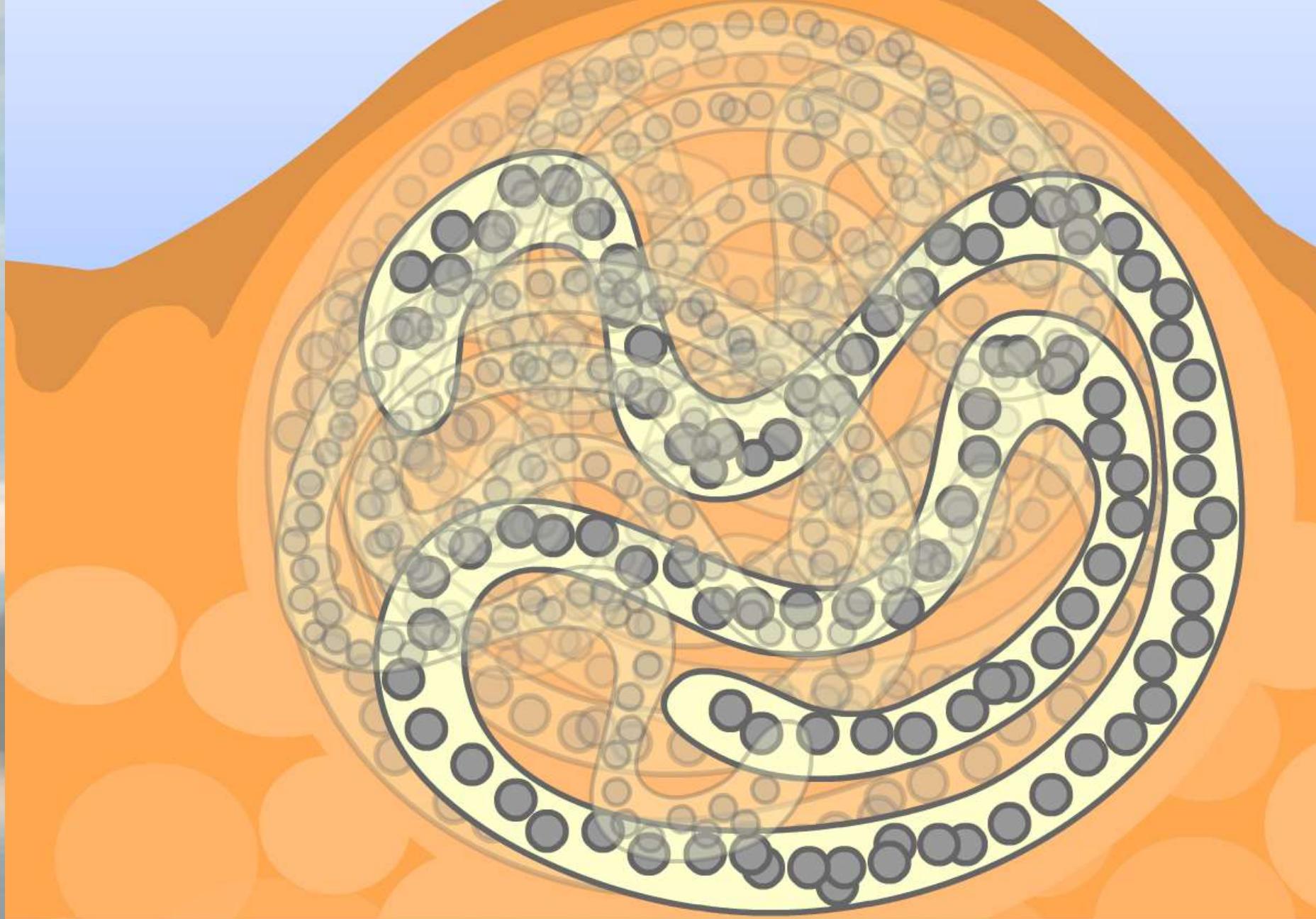
Infective filarial larvae pass from the blackfly into the host's skin



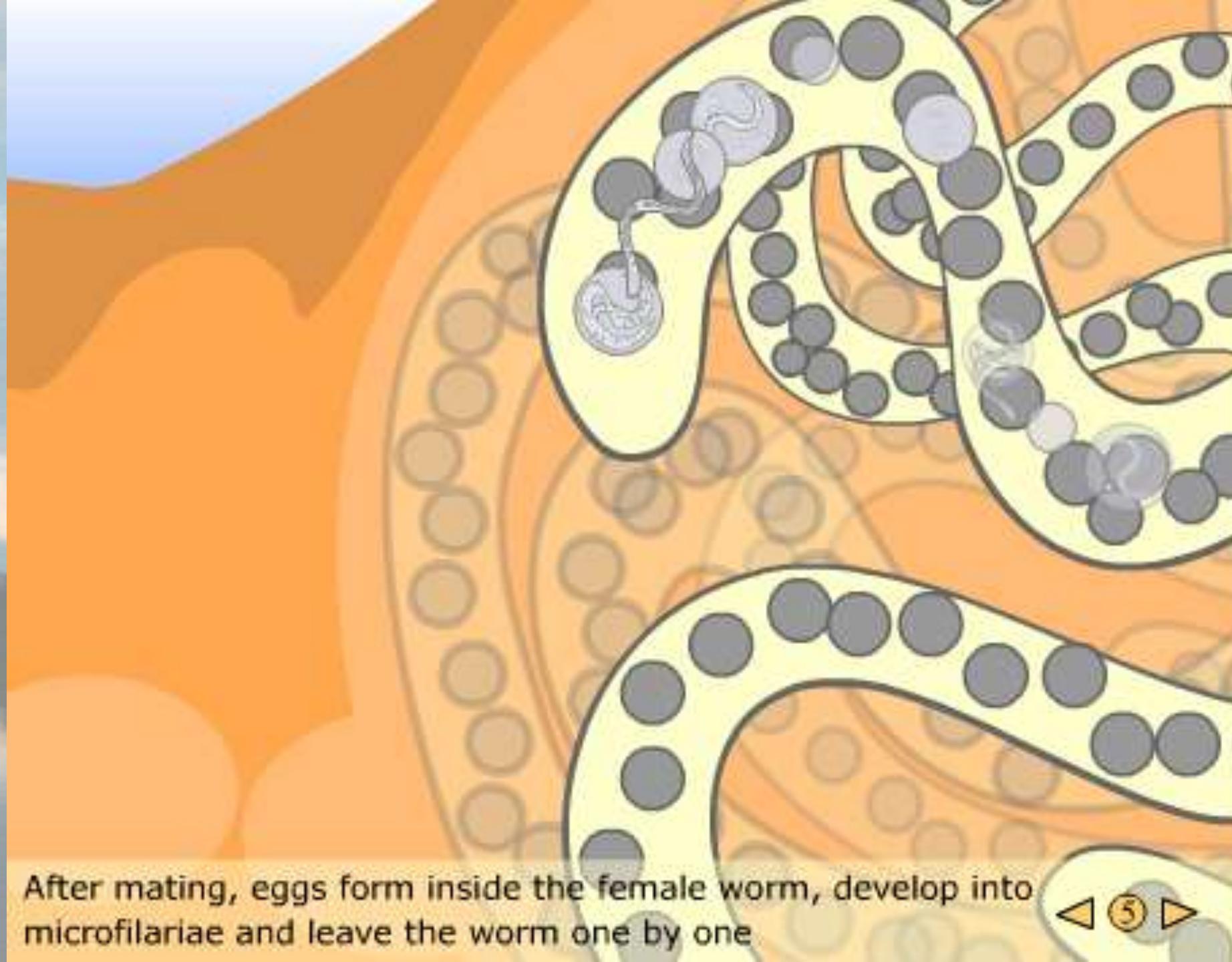


Larvae enter subcutaneous tissue, migrate, form and lodge in nodules, and slowly mature into adult worms



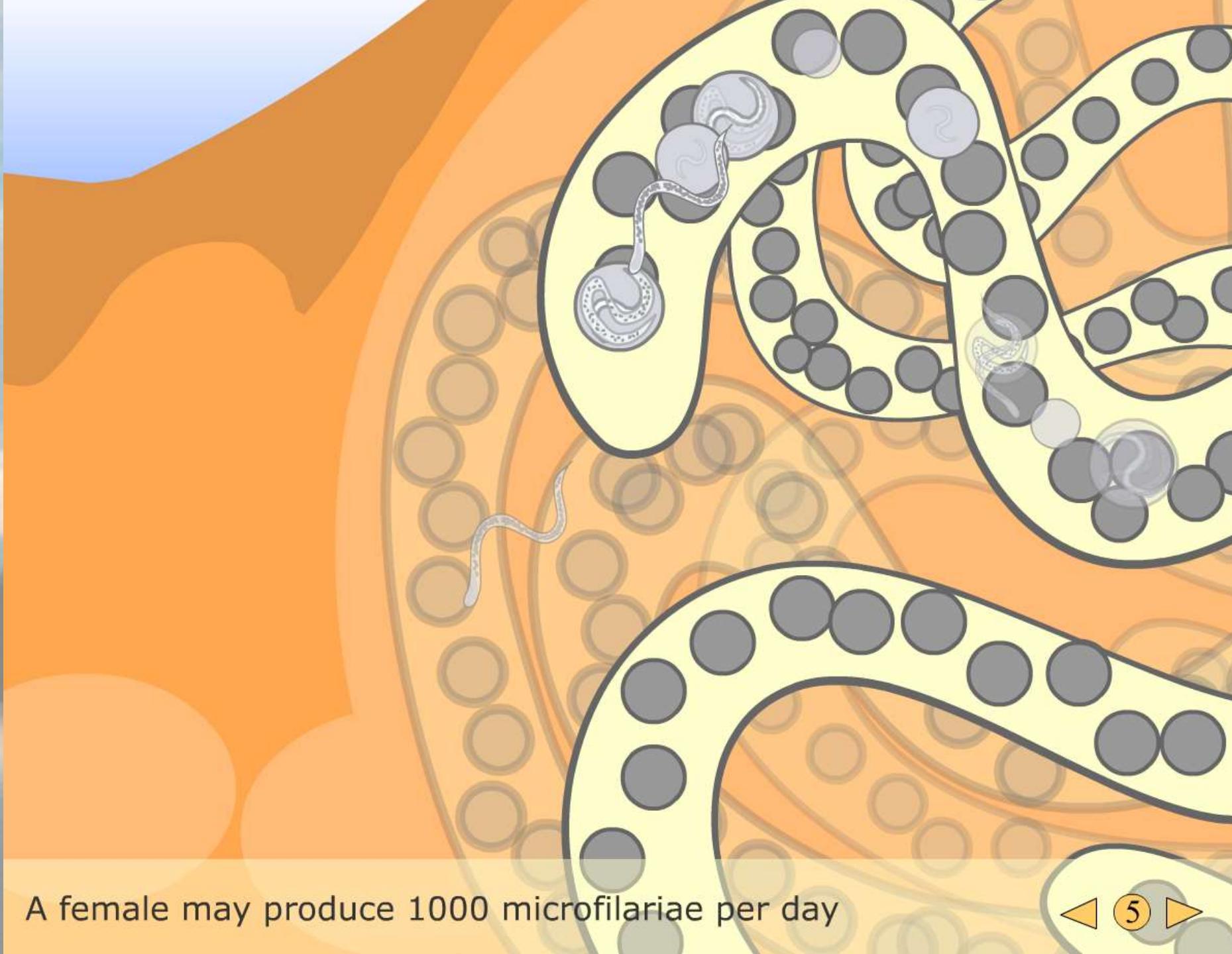


New worms form new nodules or find existing nodules and cluster together



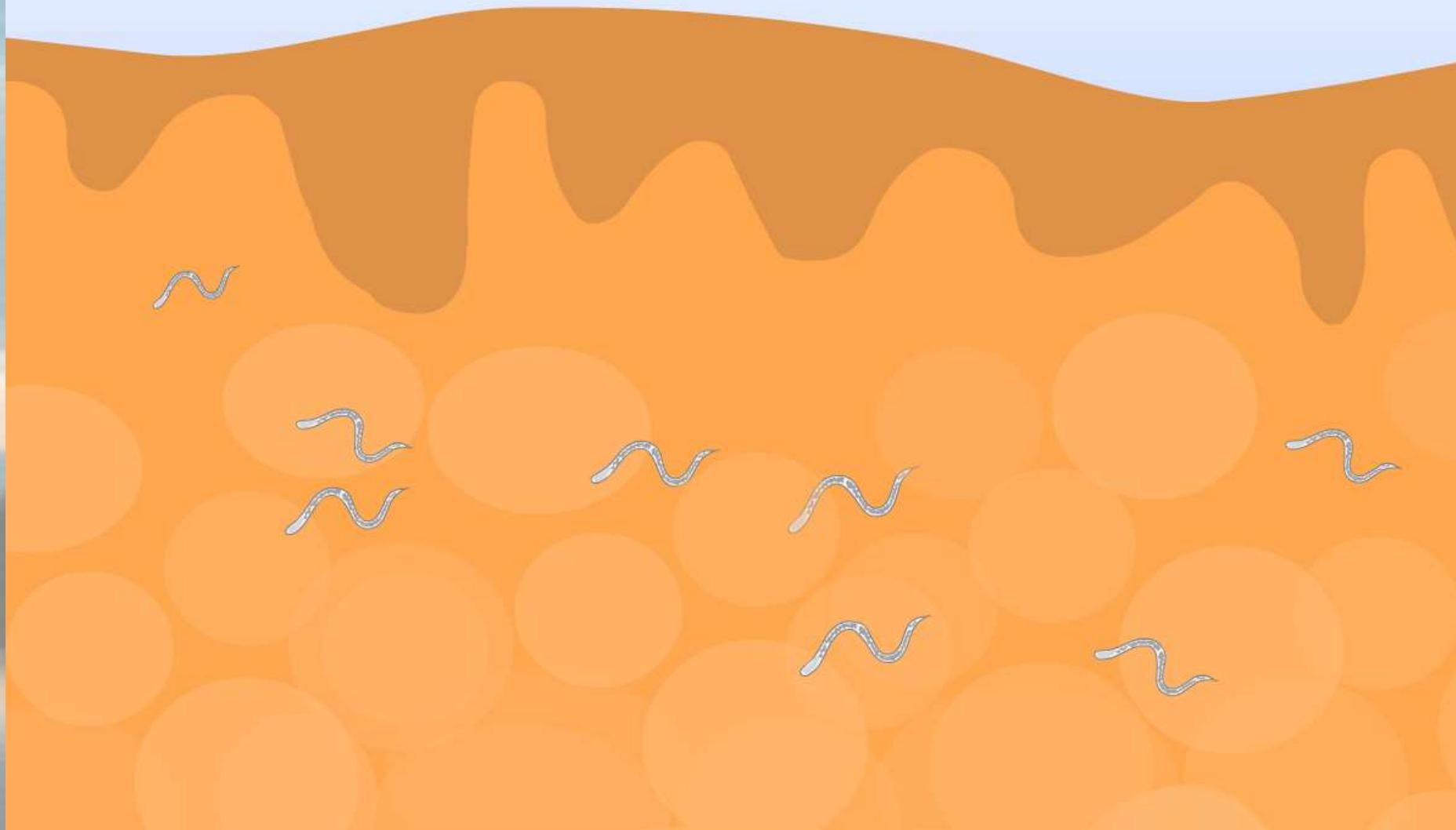
After mating, eggs form inside the female worm, develop into microfilariae and leave the worm one by one





A female may produce 1000 microfilariae per day

◀ 5 ▶



Many thousands of microfilariae migrate in the subcutaneous tissue

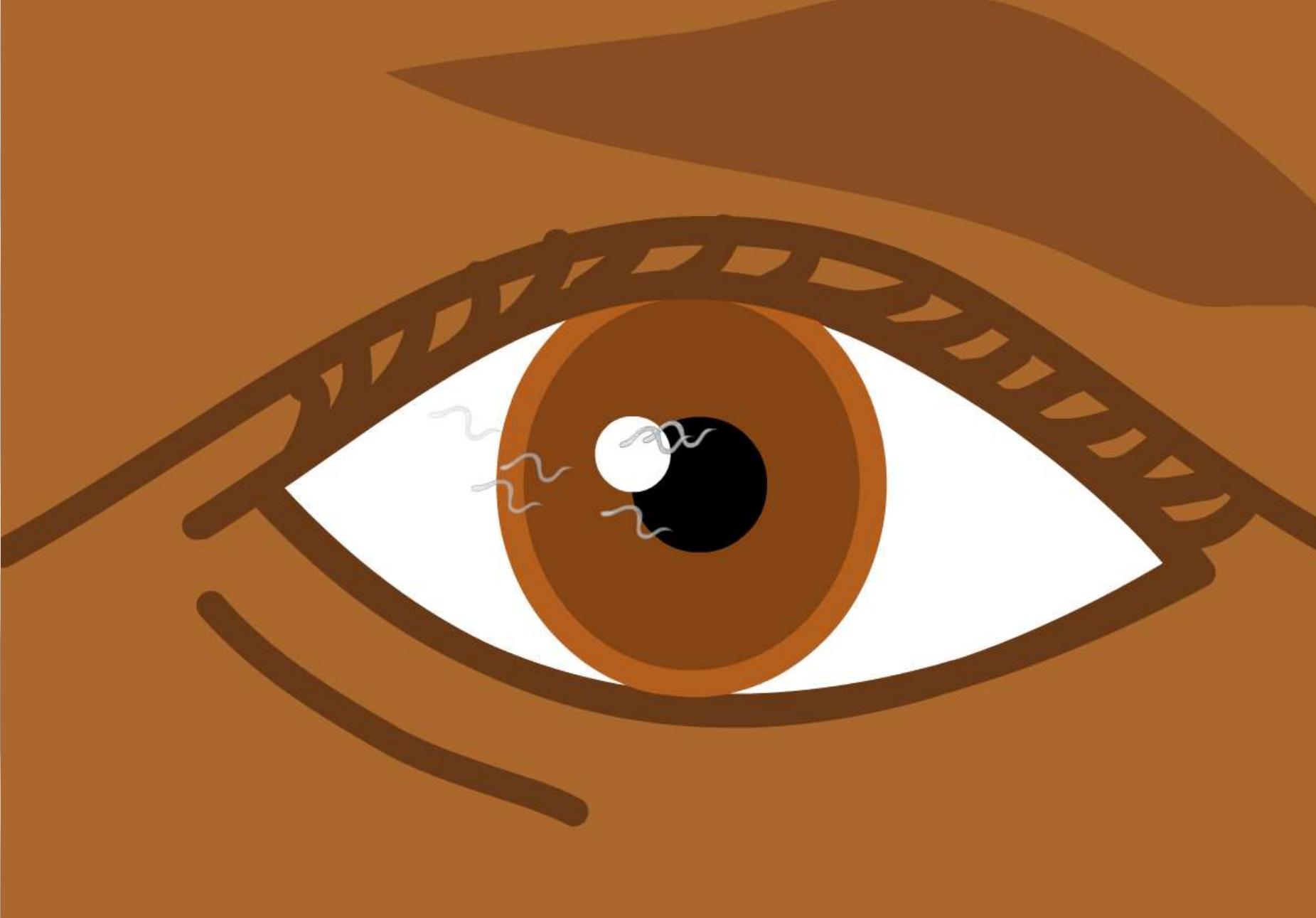


Microfilariae die and cause skin rashes, lesions, intense itching and skin depigmentation

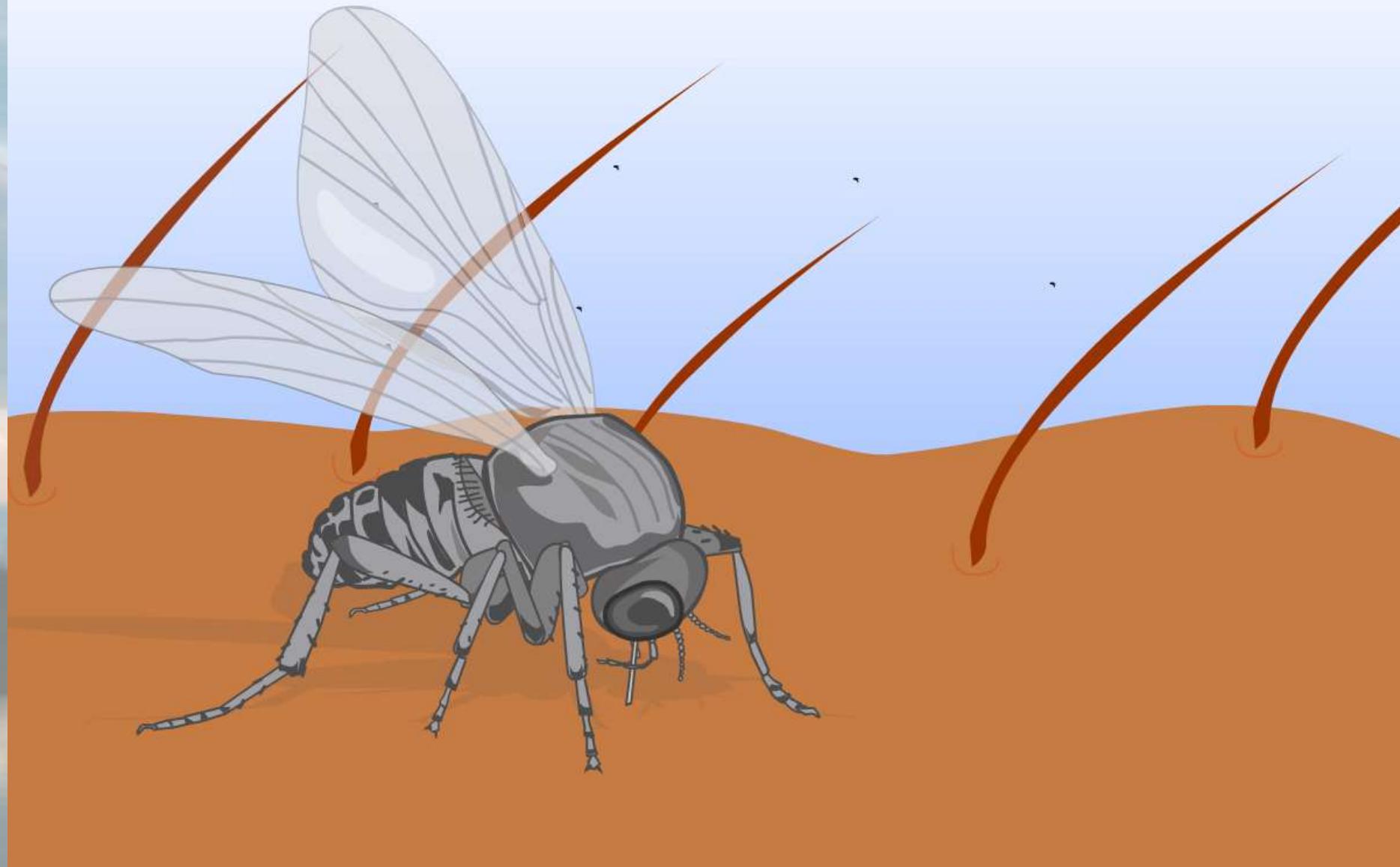


Microfilariae also migrate to the eye and can cause blindness

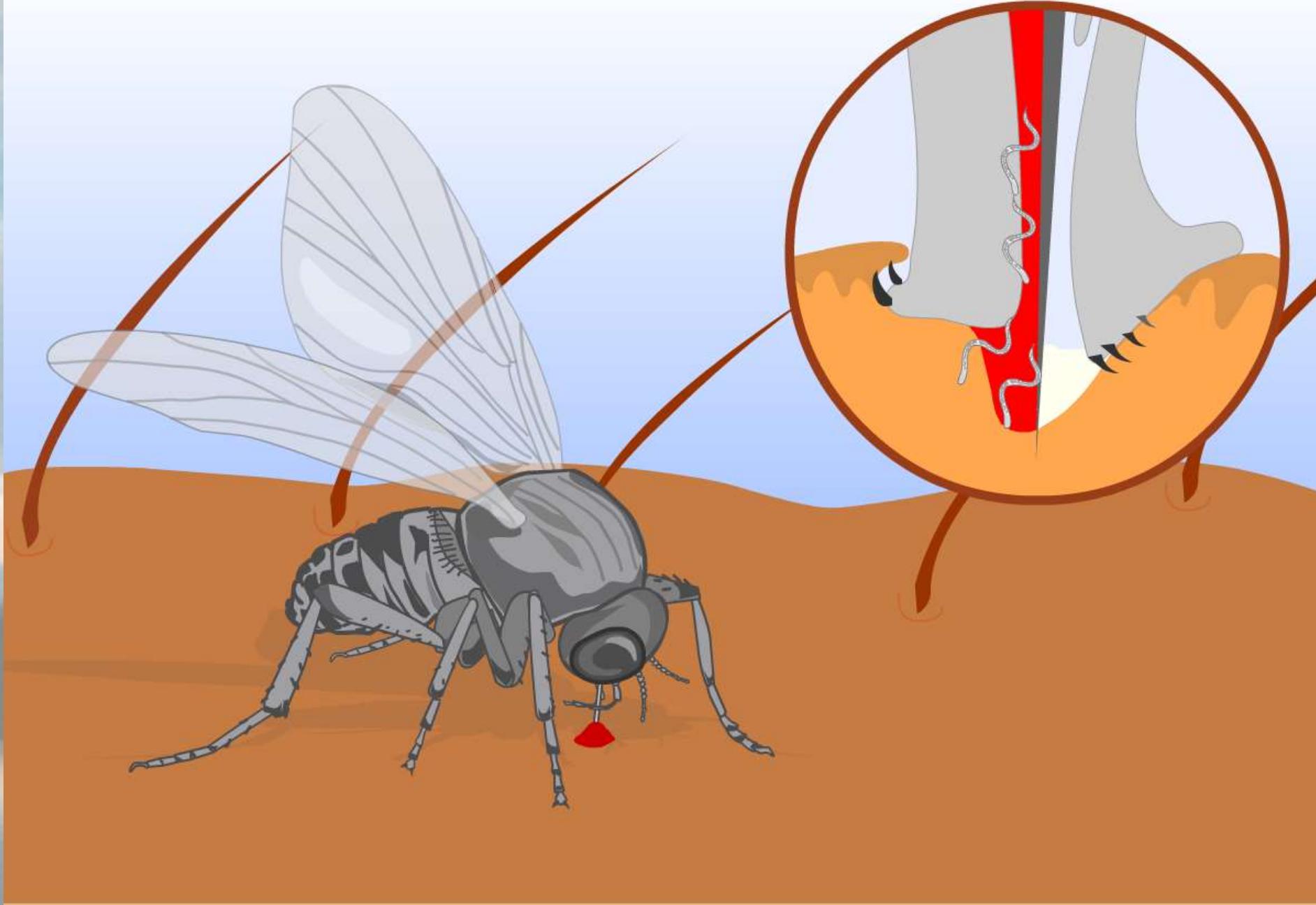




Microfilariae also migrate to the eye and can cause blindness



The infected host is bitten by another female fly



Microfilariae are transferred from the host to the blackfly
where they develop into infective larvae



370



371

370 y 371. Fases acuáticas de los vectores

Las filarias se transmiten por la picadura de las moscas del género *Simulium*. Las larvas (370, izquierda) y las pupas (371, derecha) de *Simulium* se adhieren a objetos sumergidos en agua que corre rápidamente, a partir de los cuales obtienen el oxígeno mediante los filamentos de la cabeza. (x 5) (V. también 374.)



372. Ejemplar adulto de *Simulium damnosum*

Dada su postura con la espalda encorvada, en algunas zonas estos insectos se denominan «moscas búfalo». Actualmente se acepta que *Simulium damnosum* constituye un gran complejo de especies similares con al menos diez vectores demostrados en diferentes partes de África. En África oriental, el complejo *Simulium neavei* ha sido un factor importante en algunas áreas de altitud. *Simulium ochraceum* y *Simulium metallicum* son vectores importantes en América Central y en América del Sur. (x 10)



373. Localización característica de *Simulium* en África occidental

El agua altamente oxigenada y que se mueve con rapidez en los arroyos, los ríos, las cascadas, etc., proporciona el ambiente ecológico esencial. La figura muestra uno de los pequeños afluentes de la zona alta del río Volta. En aldeas hiperendémicas del África occidental, la tercera parte de todos los adultos puede presentar ceguera por oncocercosis.

El patógeno y el vector

- Phylum: *Nematoda*
 - Clase: *Chromadorea*
 - Orden: *Spirurida*
 - Superfamilia: *Filarioidea*
 - Familia: *Onchocercidæ*
 - Género: *Onchocerca volvulus*
- 

- Phylum: *Arthropoda*
 - Clase: *Insecta*
 - Orden: *Diptera*
 - Suborden: *Nematocera*
 - Superfamilia: *Chironomoidea*
 - Familia: *Simuliidæ*
 - Género: *Simulium metallicum*
- 
- 

Una bacteria que el parásito requiere para desarrollarse y reproducirse (endosimbionte)

- Súper Reino: *Bacteria*
- Phylum: *Proteobacteria*
- Clase: *Alphaproteobacteria*
- Orden: *Rickettsiales*
- Familia: *Anaplasmataceæ*
- Género: *Wolbachia*

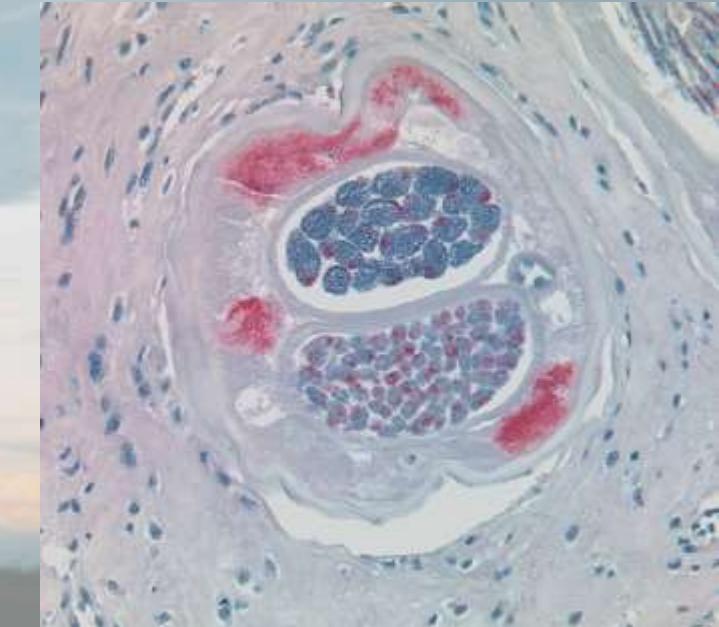
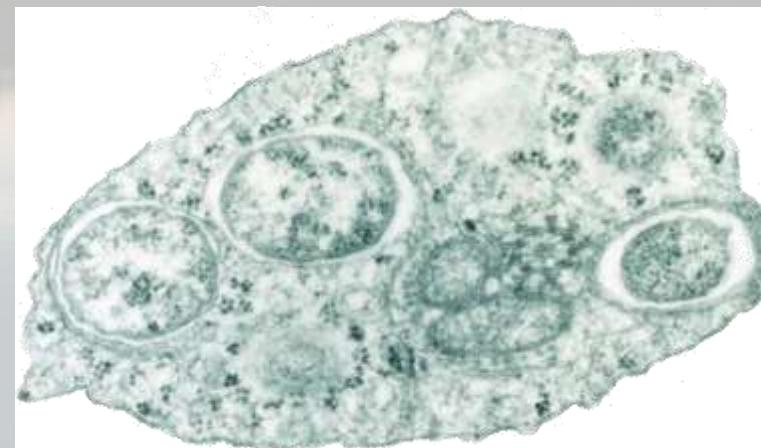


Figure 54.21 Cross-section of an adult female *O. volvulus* worm showing *Wolbachia* endobacteria stained in red.

TABLE I. Prominent filarial species of human and veterinary interest

Clin Microbiol Infect 2013; 19: 131–140

Species	Vectors Genus (family)	Vertebrate hosts	Main tissue localization of adult worms	Localization of microfilariae	Main pathologies	Wolbachia supergroup	References
Onchocercinae							
<i>Acanthocheilonema draunculoides</i> (Cobbold, 1870)	<i>Hippobosca</i> (Hippoboscidae)	Canids	Coelomic cavity and subcutaneous tissue	Blood	Usually asymptomatic	NA	[1,2]
<i>Acanthocheilonema reconditum</i> (Grassi, 1889)	<i>Heterodoxus</i> (Boopiidae)	Canids	Subcutaneous tissue	Blood	Usually asymptomatic	Absent	[1,3]
<i>Acanthocheilonema viteae*</i> (Krepkogorskaya, 1933)	<i>Ctenocephalides</i> (Pulicidae)	Canids	Subcutaneous tissue	Blood	Usually asymptomatic	Absent	[1,4,5]
<i>Brugia malayi</i> (Brug, 1927)	<i>Pulex</i> (Pulicidae)	Rodents	Subcutaneous tissue	Blood	Usually asymptomatic	D	[1,6,7]
	<i>Heterodoxus</i> (Boopiidae)	Humans, ^a	LS, LN, testes	Blood	Adenopathy		
	<i>Ornithodoros</i> (Argasidae)				Lymphoedema		
<i>Brugia pahangi</i> (Buckley & Edeson, 1956)	<i>Mansonia</i> (Culicidae)	Dogs, felids, ^{b, c}	LS, LN, testes	Blood	Lymphoedema	D	[1,6,7]
<i>Brugia timori</i> (Partono et al., 1977)	<i>Anopheles</i> (Culicidae)	Humans	LS, LN, testes	Blood	Lymphoedema	D	[1,7,8]
	<i>Aedes</i> (Culicidae)						
<i>Cercopithifilaria grassii</i> (Noè, 1907)	<i>Rhipicephalus</i> (Ixodidae)	Dogs	Subcutaneous tissue	Skin	Usually asymptomatic	NA	[1,9,10]
<i>Litomosoides sigmodontis*</i> (Chandler, 1931)	<i>Ornithonyssus</i> (Macronyssidae)	Rodents	Coelomic cavity	Blood	Usually asymptomatic	D	[1,11]
<i>Mansonella (Mansonella) ozzardi</i> (Manson, 1897)	<i>Culicoides</i> (Ceratopogonidae)	Humans	Coelomic cavity	Blood	Usually asymptomatic	F	[1,12]
	<i>Simulium</i> (Simuliidae)						
<i>Mansonella (Esslingeria) perstans</i> (Manson, 1891)	<i>Culicoides</i> (Ceratopogonidae)	Humans and monkeys	Coelomic cavity	Blood	Usually asymptomatic	F	[1,13]
<i>Mansonella (Esslingeria) streptocerca</i> (Macfie & Corson, 1922)	<i>Culicoides</i> (Ceratopogonidae)	Humans and monkeys	Intradermal	Skin	Dermatitis	NA	[1,14]
<i>Onchocerca cervicalis</i> (Railliet & Henry, 1910)	<i>Culicoides</i> (Ceratopogonidae)	Equids	Nuchal ligament	Skin	Dermatitis		[1,15]
<i>Onchocerca gutturosa</i> (Neumann, 1910)	<i>Simulium</i> (Simuliidae)	Bovids	Nuchal ligament	Skin	Ocular trauma		[1,16]
<i>Onchocerca lupi</i> (Rodonaja, 1967)	<i>Culicoides</i> (Ceratopogonidae)	Canids		Skin	Dermatitis		[1,17]
<i>Onchocerca ochengi</i> (Bwangamoi, 1969)	Unknown				Ocular trauma		
<i>Onchocerca volvulus</i> (Leuckart, 1893)	<i>Simulium</i> (Simuliidae)	Bovids	Intradermal	Skin	Nodules	C	[1,11,18,19]
	<i>Simulium</i> (Simuliidae)	Humans	Subcutaneous tissue	Skin	Dermatitis	C	[1,20]
<i>Wuchereria bancrofti</i> (Cobbold, 1877)	<i>Culex</i> (Culicidae)	Humans	LS, LN, testes	Blood	Ocular trauma	D	[1,7,21]
	<i>Anopheles</i> (Culicidae)						
	<i>Aedes</i> (Culicidae)						
Dirofiliariinae							
<i>Dirofilaria immitis</i> (Leidy, 1856)	<i>Aedes</i> (Culicidae)	Canids, felids, ^d	Right ventricle Pulmonary artery Vena cava	Blood	Heart worm disease	C	[1,22,23]
<i>Dirofilaria repens</i> (Railliet et Henry, 1911)	<i>Aedes</i> (Culicidae)	Canids, felids, ^e	Subcutaneous tissue	Blood	Subcutaneous tissue nodules	C	[1,24]
<i>Loa loa</i> (Cobbold, 1864)	<i>Culex</i> (Culicidae)	Humans	Connective tissue	Blood	Calabar swelling	Absent	[1,25]
	<i>Chrysops</i> (Tabanidae)		Subcutaneous tissue		Ocular trauma		
			Connective tissue				
Setariinae							
<i>Setaria equina</i> (Abildgaard, 1789)	<i>Aedes</i> (Culicidae)	Horses	Coelomic cavity	Blood	Usually asymptomatic	Absent	[1,26,27]

LN, lymph nodes; LS, lymphatic system; NA, data not available. Extra hosts are indicated by ^{a–e}: ^a—monkeys, cats, dogs, viverrids, pangolins; ^b—cebids, erinaceids, lorisids, sciurids, manids, viverrids; ^c—transmissible to humans; ^d—ferrets, raccoons, sea lions; ^e—raccoons, sea lions.*Rodent filariae commonly used as experimental models of filariasis.

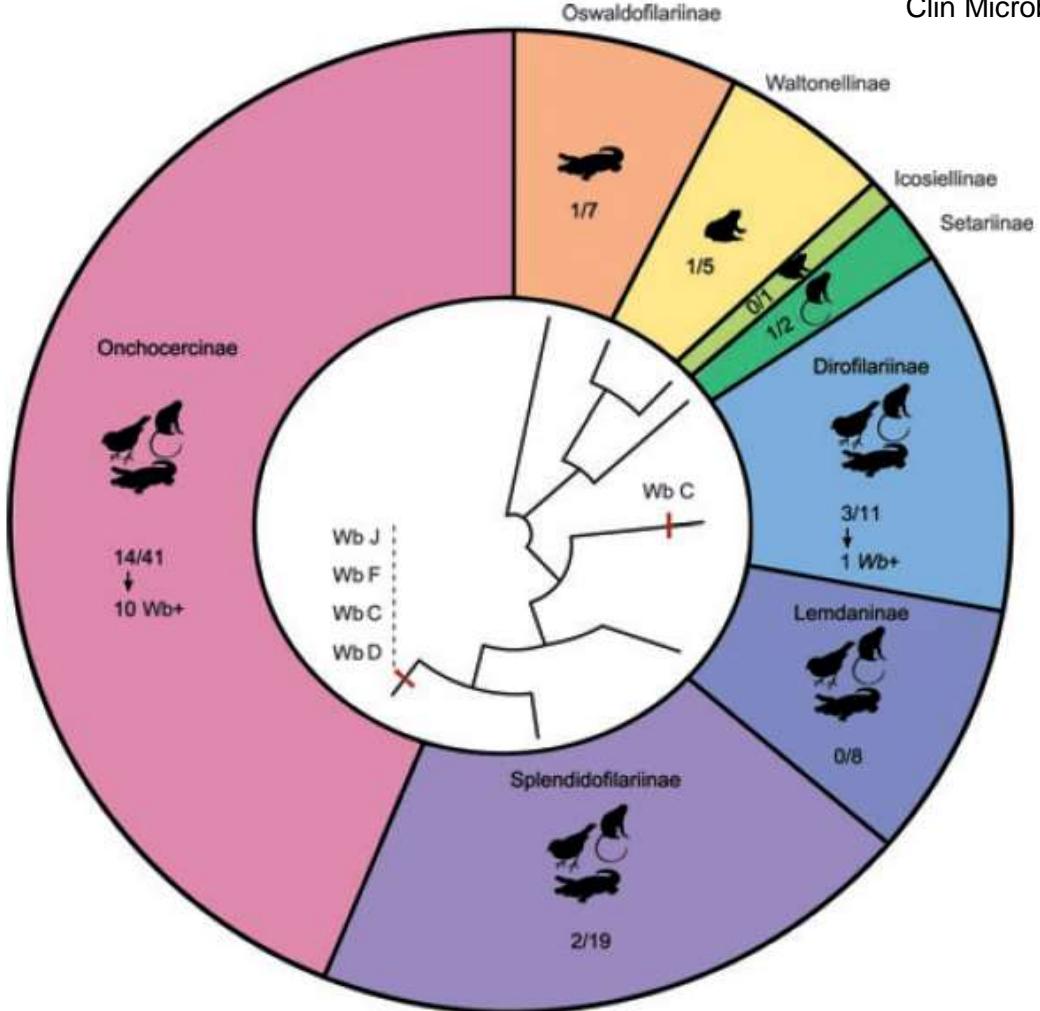


FIG. 1. The presence of *Wolbachia* infection mapped on the hypothetical evolution and distribution of Onchocercidae. The eight subfamilies of Onchocercidae are represented on the 'pie chart'; the sector size of each subfamily is based on the number of onchocercid genera present per subfamily. The host range is shown by a symbol: the crocodile represents clade Reptilia, the frog represents class Amphibia, the bird represents class Aves, and the monkey represents class Mammalia. For each subfamily, X/Y represents the number of genera in which the presence of *Wolbachia* was analysed/the total number of genera in the subfamily. Underneath X/Y and below the black arrow, the number of genera that harbour *Wolbachia* (Wb+) is specified. The dendrogram in the centre of the diagram represents the hypothetical evolutionary history of Onchocercidae, based on morphological criteria. *Wolbachia* was absent from the lineages leading to Oswaldo filariinae, Waltonellinae, Setariinae, and Splendidofilarinae. *Wolbachia* of supergroup C was acquired on the lineage leading to the Dirofilariinae. *Wolbachia* was acquired on the lineage leading to the Onchocerinae, diverging into supergroups C, D, J, and F.

TABLE 2. Old and new therapies against *Wolbachia*

Clin Microbiol Infect 2013; 19: 131–140

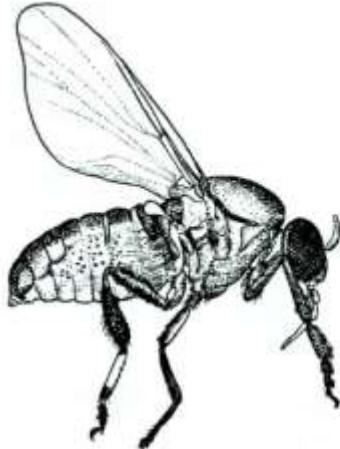
Drugs	Target	Mechanisms	Effects on filariae	References
Current antibiotic treatment				
Doxycycline/ tetracycline	30S ribosomal subunit (+50S ribosomal subunit)	1. Blockade of protein synthesis by preventing the binding of aminoacyl-tRNA to the ribosome 2. Activation of apoptosis of germline and somatic cells of embryos and microfilariae 3. Nitric oxide production	(a) Decrease in filaria growth. (b) <i>In vitro</i> female sterilization; (c) Disappearance of Mfs (d) Blockage of first and third moults. (d) Death of adult worms	[8,48,49,58,73,84,85,95,97–102,104,122]
New anti-Wb approaches				
Berberin	FtsZ	Blockade of bacterial cytokinesis	<i>In vitro</i> sterilization of <i>Brugia malayi</i> female	[116]
Corallopyronin A	RNA polymerase	Blockade of RNA synthesis	<i>In vitro</i> decrease in Wb growth in <i>B. malayi</i> <i>In vivo</i> sterilization of <i>Litomosoides sigmodontis</i> female	[117]
Succinyl acetone Rapamycin	ALAD bTOR	Blockade of haem pathway Inhibition of bTOR, which controls autophagy	Decrease in <i>Litomosoides sigmodontis</i> growth (a) Reduction in motility. (b) Sterility <i>In vitro</i> decrease in Wb growth in <i>B. malayi</i>	[54] [119]
Globomycin	LspA	Accumulation of pro-lipoprotein in the cytoplasmic membrane	<i>In vitro</i> decrease of Wb growth in <i>B. malayi</i>	[120]
Rifampicin		Inhibition of RNA polymerase	<i>In vitro</i> reduction in motility of <i>B. malayi</i> (a) Abnormal and decreased embryogenesis (b) Reduction of the L3 to L4 moult (C) Decrease in worm growth	[94,105,110]

ALAD, 5'-aminolevulinic acid dehydratase; bTOR, *B. malayi* target of rapamycin; FtsZ, filamentous temperature-sensitive protein Z; LspA, lipoprotein signal peptidase II; Wb, *Wolbachia*.

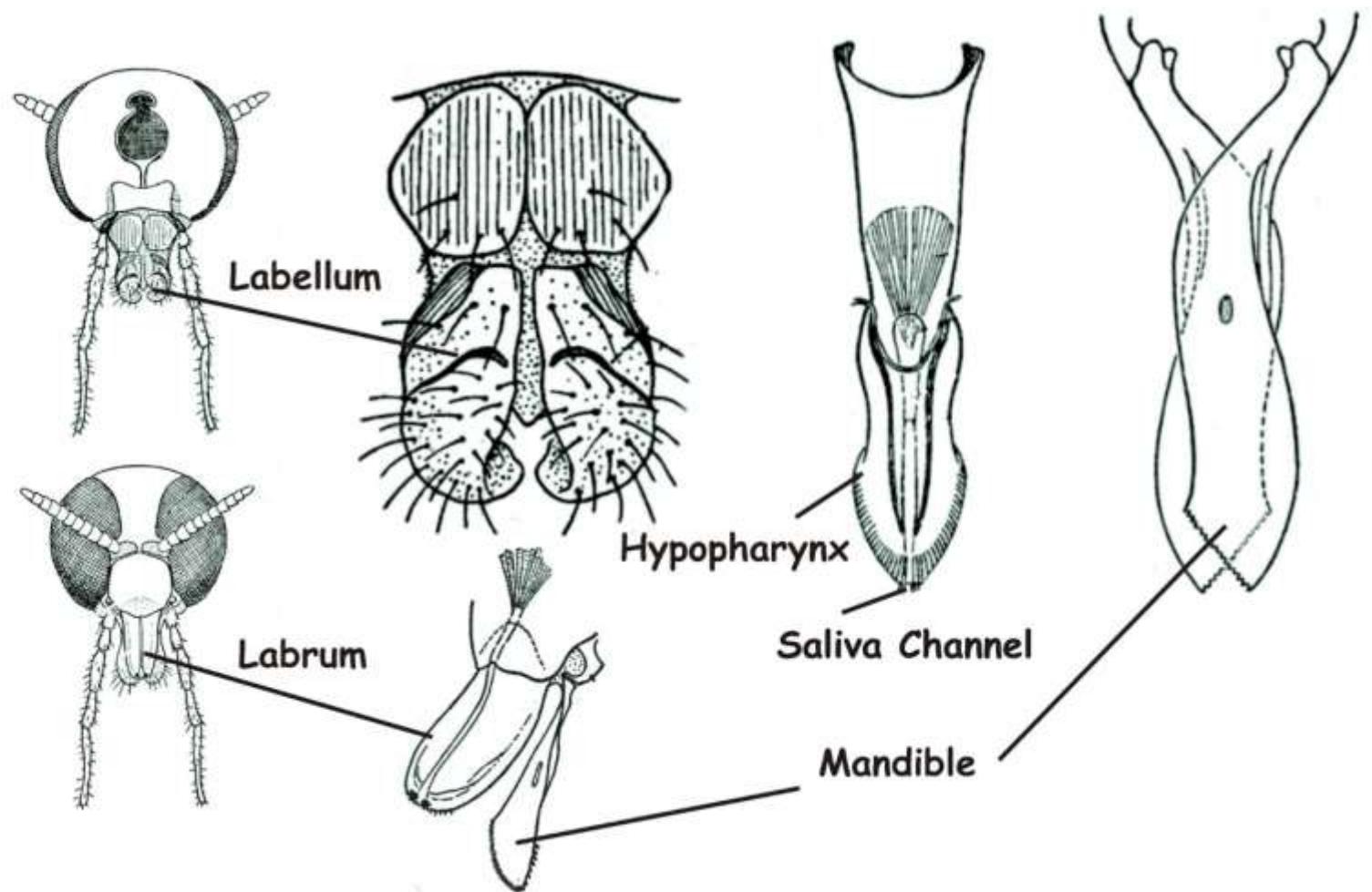
The target of doxycycline is mainly the bacterial 30S ribosomal subunit and, to a lesser extent, the 50S subunit.

En adición al manejo con Ivermectina (Mectizan®).

La picadura ideal



Anticoagulants - Simulidin
Vasodilators - SVEP
Immunomodulator- Simulidin
Anesthetic ?



La saliva del vector: un complejo conjunto de proteínas



Pergamon

0022-1910(95)00039-9

J. Insect Physiol., Vol. 41, No. 11, pp. 1001–1006, 1995
Copyright © 1995 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0022-1910/95 \$9.50 + 0.00

Simulidin: a Black Fly (*Simulium vittatum*) Salivary Gland Protein with Anti-thrombin Activity

M. ABEBE,* M. S. CUPP,† D. CHAMPAGNE,† E. W. CUPP*†‡

Received 19 December 1994; revised 3 March 1995

A protein purified from the salivary gland lysate of female *Simulium vittatum* was found to inhibit bovine α -thrombin. This protein is stable to heat, has a mass of 11,334 Da and is rich in threonine. Based on N-terminal sequencing for the first 35 amino acids, no significant sequence similarity with other proteins was detected, indicating that this salivary component may be unique in structure. Because of its source and its anti-hemostatic properties, this protein has been named simulidin.

Simulium vittatum Black flies Salivary glands Thrombin Bloodfeeding

OPEN ACCESS Freely available online

PLOS one

Simukunin from the Salivary Glands of the Black Fly *Simulium vittatum* Inhibits Enzymes That Regulate Clotting and Inflammatory Responses

Hitoshi Tsujimoto^{1,2*}, Michail Kotsyfakis³, Ivo M. B. Francischetti⁴, Jai Hoon Eum¹, Michael R. Strand^{1,2}, Donald E. Champagne^{1,2*}

¹ Department of Entomology, The University of Georgia, Athens, Georgia, United States of America, ² Center for Tropical and Emerging Global Diseases, The University of Georgia, Athens, Georgia, United States of America, ³ Laboratory of Genomics and Proteomics of Disease Vectors, Institute of Parasitology, Biology Center of the Academy of Sciences of Czech Republic, České Budějovice, Czech Republic, ⁴ Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, Maryland, United States of America

Abstract

Background: Black flies (Diptera: Simuliidae) feed on blood, and are important vectors of *Onchocerca volvulus*, the etiologic agent of River Blindness. Blood feeding depends on pharmacological properties of saliva, including anticoagulation, but the molecules responsible for this activity have not been well characterized.

Methodology/Principal Findings: Two Kunitz family proteins, SV-66 and SV-170, were identified in the sialome of the black fly *Simulium vittatum*. As Kunitz proteins are inhibitors of serine proteases, we hypothesized that SV-66 and/or –170 were involved in the anticoagulant activity of black fly saliva. Our results indicated that recombinant (r) SV-66 but not rSV-170 inhibited plasma coagulation. Mutational analysis suggested that SV-66 is a canonical BPTI-like inhibitor. Functional assays indicated that rSV-66 reduced the activity of ten serine proteases, including several involved in mammalian coagulation. rSV-66 most strongly inhibited the activity of Factor Xa, elastase, and cathepsin G, exhibited lesser inhibitory activity against Factor IXa, Factor XIa, and plasmin, and exhibited no activity against Factor XIIa and thrombin. Surface plasmon resonance studies indicated that rSV-66 bound with highest affinity to elastase ($K_D = 0.4$ nM) and to the active site of FXa ($K_D = 3.07$ nM). We propose the name "Simukunin" for this novel protein.

Conclusions: We conclude that Simukunin preferentially inhibits Factor Xa. The inhibition of elastase and cathepsin G further suggests this protein may modulate inflammation, which could potentially affect pathogen transmission.

A**SV-66**

TGAATTGGATCGAAMNSATATTCCATAGTCTTCTCTGTTATCTGGCATTTTGGCCA
 M H I L P I S A F F L L Y L G H S L A Q
 -19 -10 1
 GAGAACGTTGCAATCTCCGGTGGACGAGGTGTATGTAGAGCGTTATTCAGCGTTTACTACGAAACCGCA
 E N V C M L P V D E G V C R A L F K R F Y Y E P A
 10 20 30 40 50
 ACCGATAGTTGCAAMGAGTTCTACTATGGAGGTGTAGGGAAATGGAACAGGTTCAAAGTAAAAAGGAATGCT
 T D S C K E F Y Y G G C E G H G N R F K S K K E C
 30 40 50
 ATTCTCAGTGTCAGRGRATAAACAGCTCATAAAAACAGNARACGCAACAAAAGAACACCACACCCCCG
 I L K C Q K N K Q L I K T R K R K P K K T T K P P
 60 70 80
 ATACAAATTAATTGTTGGACAAAGGACTCAATAGTATAGACAATTTCAATA
 I P I I S L D -
 80
 TGAAAAATAAAATCGAACTGTGAAAAATTAAATTGACCAGAAAAA
 AAAAAA

SV-170

GCATTAATCATTAGTACACCTGAGAGAATTTGAACATCTCGGACAT
 M L K T I I L G T I
 -22
 GCCATACTGATATGATGGCAAAATTCAGCAGTCAGTCGACTCATGGAT
 A I L I C M A H N S E A R K S A D I C R L P M D K G
 -10 1 10
 ATTGCACTCCAACAGAATTGCGTTATTTGACGCAAJAGTOTTATGTTCGGGAT
 I C T P T E W R Y H F D P A K N K C F M F P W G C
 20 30
 CTGGGAATGCCACRAATTCAACCARAGTGTAGCAGCACGGA
 L G N A A N H F K T R Q E C K A K K C M -
 40 50
 TAAAAATGATTGACCGATTGTTATTAATAAGGCATAAACAATTGATAGCAATGAAAAA
 AAAAAA

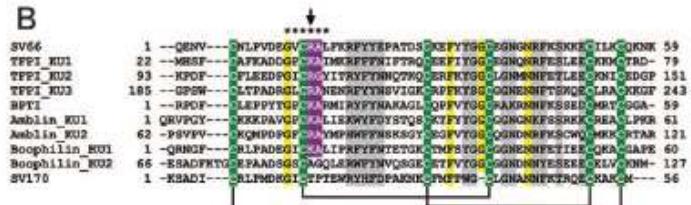
B

Figure 1. SV-66 and SV-170 belong to the Kunitz family of protease inhibitors. (A) Nucleotide and translated polypeptide sequences of SV-66 and SV-170. Start and stop codons are in white with black shading. Numbers below the amino acid residues are designated based on the putative mature protein. Signal sequences predicted by SignalP are underlined. Top: SV-66 encodes a 102 amino-acid polypeptide (Simukunin), which includes a 19 amino-acid N-terminal signal sequence. Mature Simukunin is predicted to consist of 83 amino-acid residues, with a theoretical mass of 9627.22 Da and pI of 9.93. SV-66 also contains a putative O-glycosylation site at position 81 (Ser). Bottom: SV-170 encodes a 78 amino-acid polypeptide, which includes an N-terminal 22 amino-acid signal sequence. Mature SV-170 is predicted to consist of 56 amino-acid residues, and theoretical mass and pI are 6526.66 Da and 8.87, respectively. (B) Alignment of representative Kunitz domain sequences with SV-66 and SV-170. Each Kunitz domain was separated from the original sequences for alignment. (Numbers denote amino-acid positions in the original mature peptides). All reference sequences were retrieved from GenBank. Accession numbers are: TFPI (human; 3 Kunitz domains), P10646; BPTI (*Bos taurus*; 1 Kunitz domain), AAI49369; Amblin (*Amblyomma hebraicum*; 2 Kunitz domains), AAR97367; Boophilin (*Rhipicephalus microplus*; 2 Kunitz domains), CAC82583. Strictly conserved cysteine residues are white with green shading, and predicted conserved disulfide bonds are shown in solid lines. The reactive site loop (RSL) P₁-P₂' residues, conserved in canonical binding inhibitors, are indicated by asterisks (*). The P₁ residue is indicated with an arrow. Highly conserved P₁-P₁' (Arg/Lys-Ala/Gly) residues are shown in white with purple shading. Other identical residues across the domain are shaded with yellow and conserved or semi-conserved residues are shaded with grey.
 doi:10.1371/journal.pone.0029964.g001



Contents lists available at ScienceDirect

Insect Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/ibmb



Review

An insight into the sialome of blood-feeding Nematocera

José M.C. Ribeiro ^{a,*}, Ben J. Mans ^{b,c}, Bruno Arcà ^d

^a Section of Vector Biology, Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, 12735 Twinbrook Parkway, Room 2E32D, Rockville MD 20852, USA

^b Parasites, Vectors and Vector-Borne Diseases, Onderstepoort Veterinary Institute, Pretoria, South Africa

^c Department of Veterinary Tropical Diseases, University of Pretoria, Pretoria, South Africa

^d Department of Structural and Functional Biology, University Federico II, Naples, Italy

Table 1

Salivary transcriptomes and transcripts from Nematocera compiled in this review.

Family	Species	Reference
Culicidae	<i>Aedes aegypti</i>	(Ribeiro et al., 2007; Valenzuela et al., 2002b)
	<i>Aedes albopictus</i>	(Arca et al., 2007)
	<i>Ochlerotatus triseriatus</i>	(Calvo et al., 2010b)
	<i>Culex quinquefasciatus</i>	(Ribeiro et al., 2004)
	<i>Culex tarsalis</i>	(Calvo et al., 2010a)
	<i>Anopheles gambiae</i>	(Arca et al., 1999; Arca et al., 2005; Calvo et al., 2006b; Francischetti et al., 2002)
	<i>Anopheles funestus</i>	(Calvo et al., 2007a)
	<i>Anopheles dirus</i>	(Jariyapan et al., 2006)
	<i>Anopheles albimanus</i>	(Cazares-Raga et al., 2007; Montero-Solis et al., 2004)
	<i>Anopheles darlingi</i>	(Calvo et al., 2004; Calvo et al., 2009b)
	<i>Anopheles stephensi</i>	(Valenzuela et al., 2003)
	<i>Toxorhynchites amboinensis</i>	(Calvo et al., 2008)
Simuliidae	<i>Simulium vittatum</i>	(Andersen et al., 2009)
Ceratopogonidae	<i>Simulium nigrikanum</i>	(Ribeiro et al., 2010)
	<i>Culicoides sonorensis</i>	(Campbell et al., 2005)
Psychodidae	<i>Culicoides nubeculosus</i>	(Russell et al., 2009; Wilson et al., 2008)
	<i>Lutzomyia longipalpis</i>	(Charlab et al., 1999; Valenzuela et al., 2004)
	<i>Phlebotomus papatasii</i>	(Valenzuela et al., 2001a)
	<i>Phlebotomus ariasi</i>	(Oliveira et al., 2006)
	<i>Phlebotomus arabicus</i>	(Hostomska et al., 2009)
	<i>Phlebotomus duboscqi</i>	(Kato et al., 2006)

Table 2

Summary classification of the protein families possibly associated with a salivary function in blood sucking Nematocera.

Class	Total proteins	Total families
I – Ubiquitous protein families existing outside Diptera, function known or presumed		
Enzymes	170	23
Ubiquitous protease inhibitor domains	52	6
Immunity-related proteins	75	12
Mucins	106	12
OBP superfamily	186	14
Other ubiquitous families	22	5
II – Ubiquitous protein families existing outside Insects, function unknown	40	1
III – Ubiquitous insect protein families existing outside Nematocera, function unknown	31	6
IV – Protein families exclusive of blood sucking Nematocera	56	2
V – Protein families specific of mosquitoes		
Found in both culicines and anophelines	83	12
Uniquely found in culicines	40	7
Uniquely found in anophelines	63	10
Uniquely found in <i>Aedes</i>	21	3
Uniquely found in <i>Culex</i>	33	1
VI – Protein families specific of black flies	123	24
VII – Protein families specific of sand flies	32	9
VIII – Protein families specific of Culicoides	41	8
IX – Salivary-orphan proteins of conserved secreted families	43	43
X – Orphan proteins of unique standing	63	63
Total	1280	261

Table 3
Classification and functional status of protein families putatively assigned a salivary function in blood-feeding Nematocera.

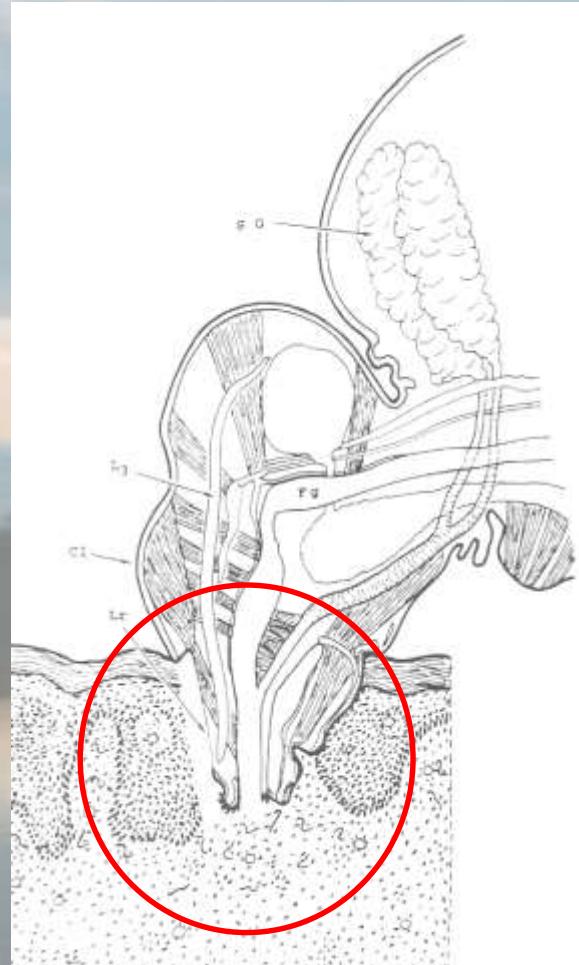
Class	Number	Function known?	Reference
Subclass			
Name			
I – Ubiquitous protein families existing outside Diptera, function known or presumed			
Enzymes			
Phlebotomine Cimex-type apyrase	11	Y	(Valenzuela et al., 2001b)
5'-nucleotidase/Apyrase family	17	Y	(Champagne et al., 1995; Sun et al., 2006)
Adenosine deaminase family	7	Y	(Ribeiro et al., 2001)
Purine hydrolase	3	Y	(Ribeiro and Valenzuela, 2003)
Pyrophosphatase/Phosphodiesterase - Phlebotomine specific	3		
Endonuclease	11	Y	(Calvo and Ribeiro, 2006)
Hyaluronidase	5	Y	(Cema et al., 2002; Ribeiro et al., 2010)
Ribonucleases	3		
Alkaline phosphatase	2		
Serine proteases	48		
Metalloprotease – may be housekeeping	1		
Dipeptidyl peptidase	1		
Cathepsins – may be housekeeping	2		
Glutamate carboxypeptidase – may be housekeeping	1		
Phlebotomus phospholipase A2	3		
Mosquito lipase	2		
Triacylglycerol lipase	1		
Carboxylesterase	1		
Destabilase family	3		
Anopheline peroxidases	4	Y	(Ribeiro and Valenzuela, 1999)
Peroxiredoxin	3		
Glycosidases	34	Y	(James et al., 1989; Marinotti et al., 1996; Marinotti et al., 1990; Marinotti and James, 1990)
Chitinase	4		
Ubiquitous protease inhibitor domains			
Serpin family	10	Y	(Stark and James, 1998)
Simulium Kunitz proteins	6		
Culicoides Kunitz proteins	15		
Cystatins – may be housekeeping	2		
TIL domain family found in mosquitoes	8		
Kazal-domain containing peptides	11		
Immunity-related proteins			
Lysozyme	13	Y	(Moreira-Ferro et al., 1998; Rossignol and Lueders, 1986)
Defensin	9		
Diptericin	1		
Gambicin	4	Y	(Vizioli et al., 2001)
Cecropins	7		
GGY peptide	3		
Fred/Ficolin domain containing proteins	7		
Gram-negative binding protein	7		
Peptidoglycan recognition protein	2		
Leucine rich protein	2		
Galectin – maybe housekeeping	2		
C-type lectins	18		
Mucins			
Widespread mucin family	3		
Virus induced mucin	6		
Mucin I mosquito family	29		
gSGS mucin protein family	5		
SG3 mucin family	11		
Aedes-specific mucin	4		
Simulium mucin	5		
30 kDa Phlebotomine mucin family	13		
Culicoides 10 kDa mucin	3		
Other mucins	12		
Peritrophin/chitin binding	6		
OBP superfamily			
Long D7 mosquito family	23	Y	(Calvo et al., 2006a; Calvo et al., 2009a; Mans et al., 2007)
Anopheline short D7 family	27	Y	(Calvo et al., 2006a; Isawa et al., 2002)
Culicine short D7 proteins	15		
Salivary mosquito OBP	6		
Phlebotomine long D7 family	22		
Phlebotomine SP-15 family	33		
Lutzomyia short D7	3		
Simulium specific long D7 family with 2 OBP domains	3		
Simulium nigrimanum long D7 with only 1 OBP domain	1		

(continued on next page)

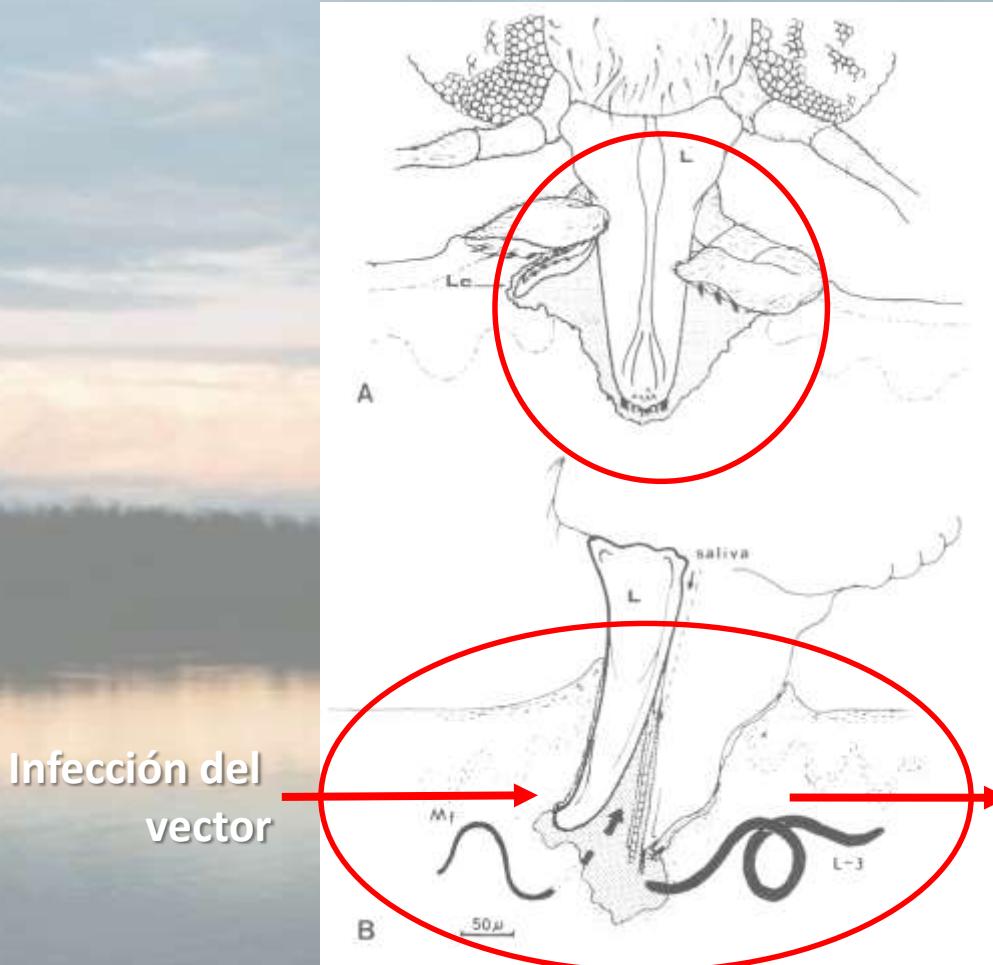
Table 3 (continued)

Class	Number	Function known?	Reference
Subclass			
Name			
Simulium OBP			
Simulium nigrimanum OBP	3		
Simulium short D7 family	28	Y	(Cupp and Cupp, 2000)
Culicoides OBP family	12		
Culicoides OBP family II	7		
Other ubiquitous families			
Aedes sialokinin – neuropeptide family	2	Y	(Beernstsen et al., 1999; Champagne and Ribeiro, 1994; Zeidner et al., 1999)
Selenoprotein	1		
Phosphatidylethanolamine-binding protein	3		
Aedes Phosphatidylethanolamine-binding protein	2		
Yellow phlebotomine family	14		
II – Ubiquitous protein families existing outside Nematocera, function unknown			
Antigen-5 family	40		
III – Ubiquitous insect protein families existing outside Nematocera, function unknown			
15–17 kDa Insect family	7		
Simulium/Culicoides insect conserved secreted protein family	9		
12–14 kDa mosquito family	8		
Hypothetical conserved secreted protein	3		
Culex/Drosophila WAP subfamily	3		
Aedes hypothetical secreted conserved protein	1		
IV – Protein families exclusive of blood sucking Nematocera			
30 kDa/Aegyptin family	55	Y	(Boppana et al., 2009; Calvo et al., 2007b; Calvo et al., 2010; Yoshida et al., 2008)
41 kDa family	18		
V – Protein families specific of mosquitoes			
Found in both culicines and anophelines			
56 kDa mosquito family	7		
37.7 kDa mosquito family	3		
Basic tail mosquito family	13		
4.3 kDa mosquito peptide	3		
HHH peptide family	10		
Glycine-rich mosquito family	3		
Salivary protein 16 family	2		
Aedes/darlingi 14–15 family	2		
gSG8 family	3		
Hyp62 family	5		
SG1/62 kDa superfamily			
Anopheline SG1 family	27		
Aedes 62 kDa family	5		
Uniquely found in Culicines			
9.7 kDa	8		
hyp8.2 culicine family	5		
30.5 kDa protein	12		
23.5 kDa culicine family	4		
KKK circle family	2		
GQ-rich culicine family	7		
Culex/Toxorhynchites family	2		
Uniquely found in anophelines			
cES/Anophelin family	7	Y	(Francischetti et al., 1999; Valenzuela et al., 1999)
gSG7 family/Anophensins	9	Y	(Isawa et al., 2007)
gSG6 family	3		
Hyp8.2 family	6		
hyp15–17 family	7		
SG2 family	8		
hyp10/hyp12 family	7		
4.2 kDa family	4		
Anopheline acidic protein	7		
An. darlingi GGGC peptide family	5		
Uniquely found in Aedes			
Aedes 6.5–8.5 protein family	4		
Aedes W-rich peptides	8		
34 kDa Aedes family	9		
Uniquely found in Culex			
Culex WRP/16 kDa family	33		

Simulidos son alimentadores de “pozos” (pool-feeders): laceración (telmofagia)



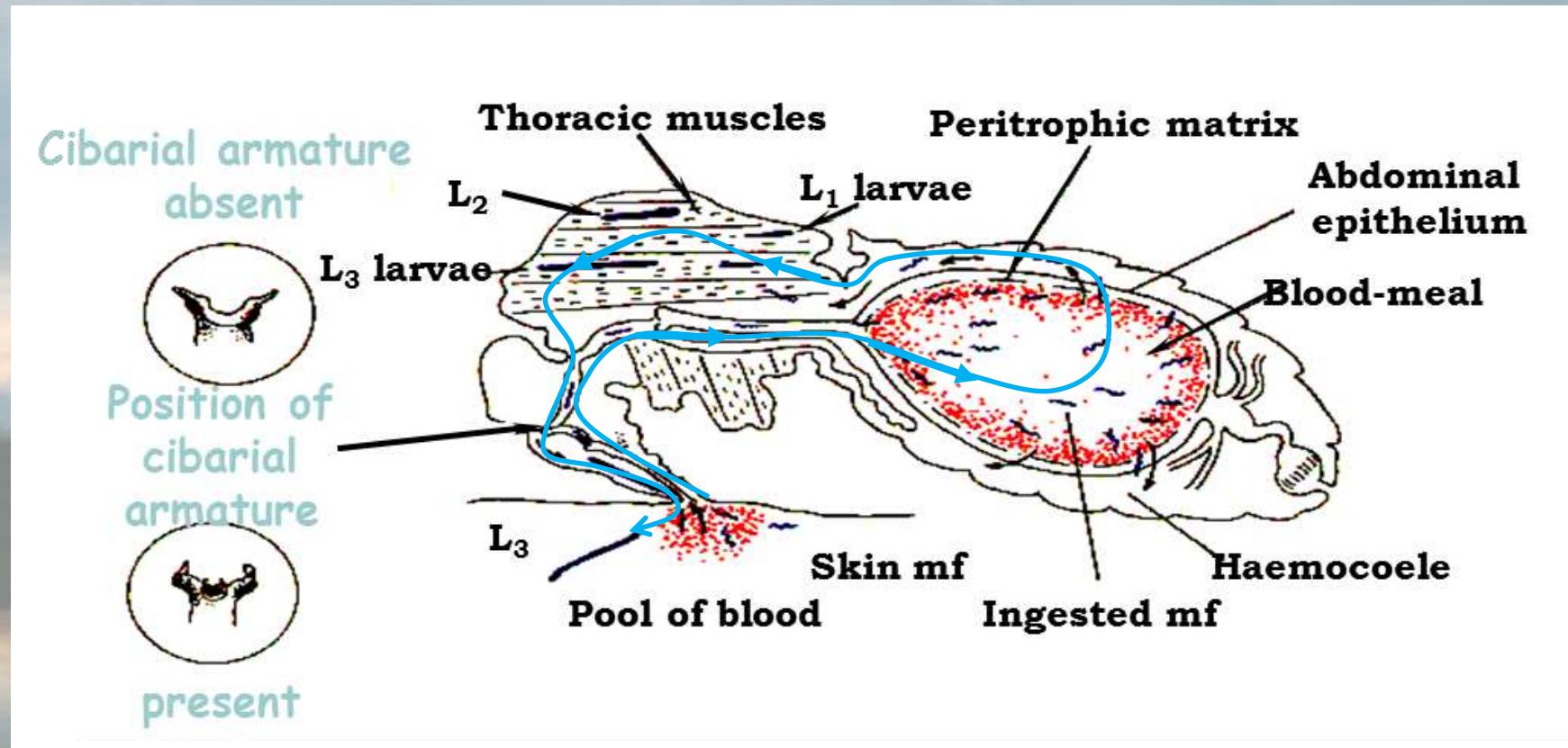
Cupp & Cupp (1997)



Ayesta et al. (1985)

¿Qué ocurre al interior del vector?

(mf → L1 → L2 → L3 (estadío infectante al ser humano))



Onchocerca volvulus

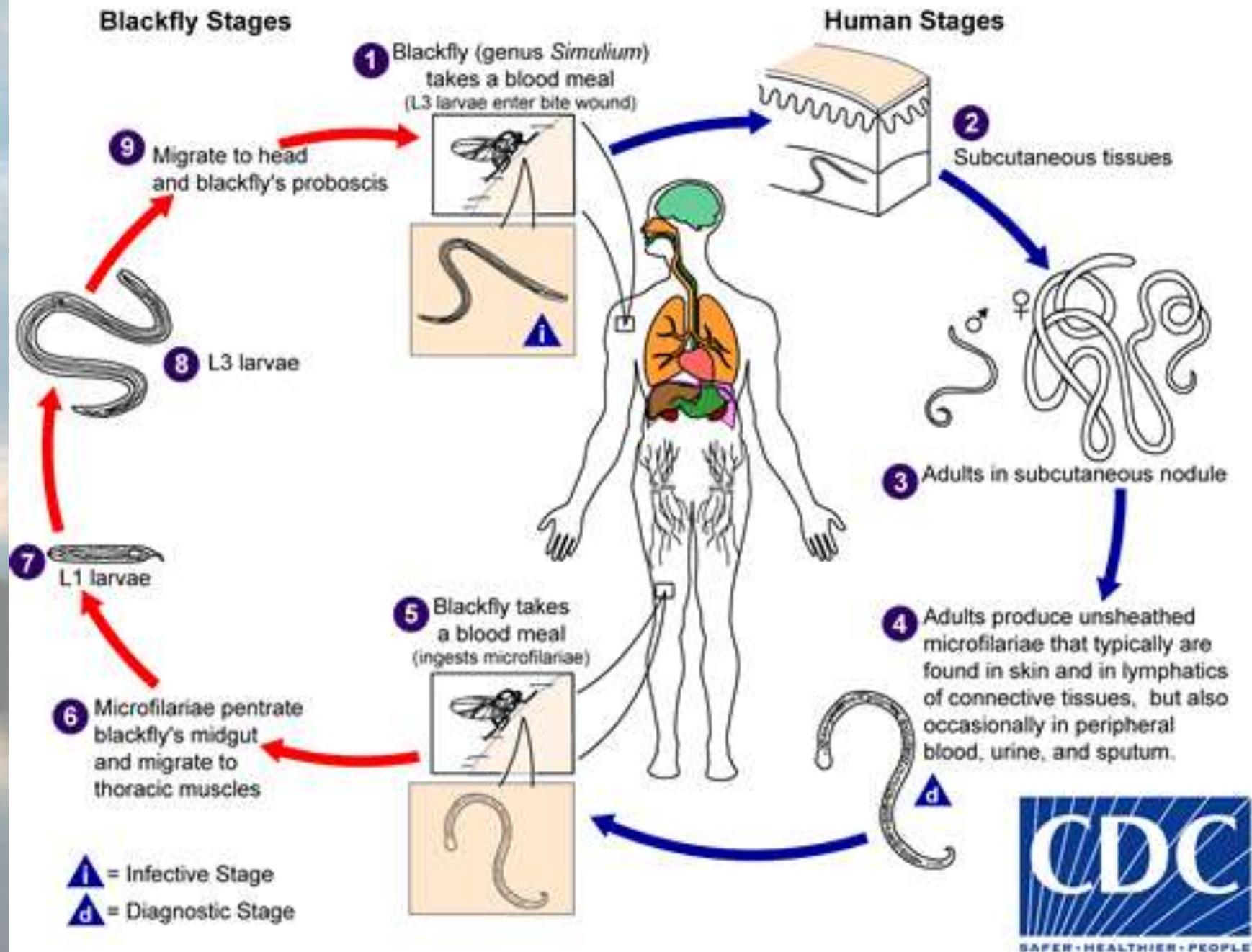


TABLE 54.1 Characteristics of Filarial Parasites and Guinea Worm and Common Clinical Manifestations in Humans

Species	Distribution	Vectors	Main Location of Adult Worms	Main Location of Microfilariae	Common Disease Symptoms
<i>Wuchereria bancrofti</i>	Tropics	Mosquito spp.	Lymphatic vessels	Blood	Lymphangitis, elephantiasis hydrocele
<i>Brugia malayi</i>	South and South-east Asia	Mosquito spp.	Lymphatic vessels	Blood	Lymphangitis, elephantiasis
<i>Brugia timori</i>	Eastern Indonesia, Timor Leste	Mosquito spp.	Lymphatic vessels	Blood	Lymphangitis, elephantiasis
<i>Loa loa</i>	Central and West Africa	Chrysops spp.	Connective tissue	Blood	Angioedema, "eye worm"
<i>Mansonella perstans</i>	Africa, Central and South America	Culicoides spp.	Serous membranes of body cavities	Blood	Usually symptomless
<i>Mansonella streptocerca</i>	Central and West Africa	Culicoides spp.	Skin	Skin	Usually symptomless
<i>Mansonella ozzardi</i>	Central and South America	Culicoides spp. <i>Simulium</i> spp.	Serous membranes of body cavities	Blood and skin	Usually symptomless
<i>Onchocerca volvulus</i>	Africa, Yemen, Central and South America	<i>Simulium</i> spp.	Skin	Skin	Rash, pruritus, papules, skin atrophy, nodules, visual impairment and blindness
<i>Dracunculus medinensis</i>	Africa	Copepods	Connective tissue, including skin	Not applicable	Pain, ulceration, emerging worm

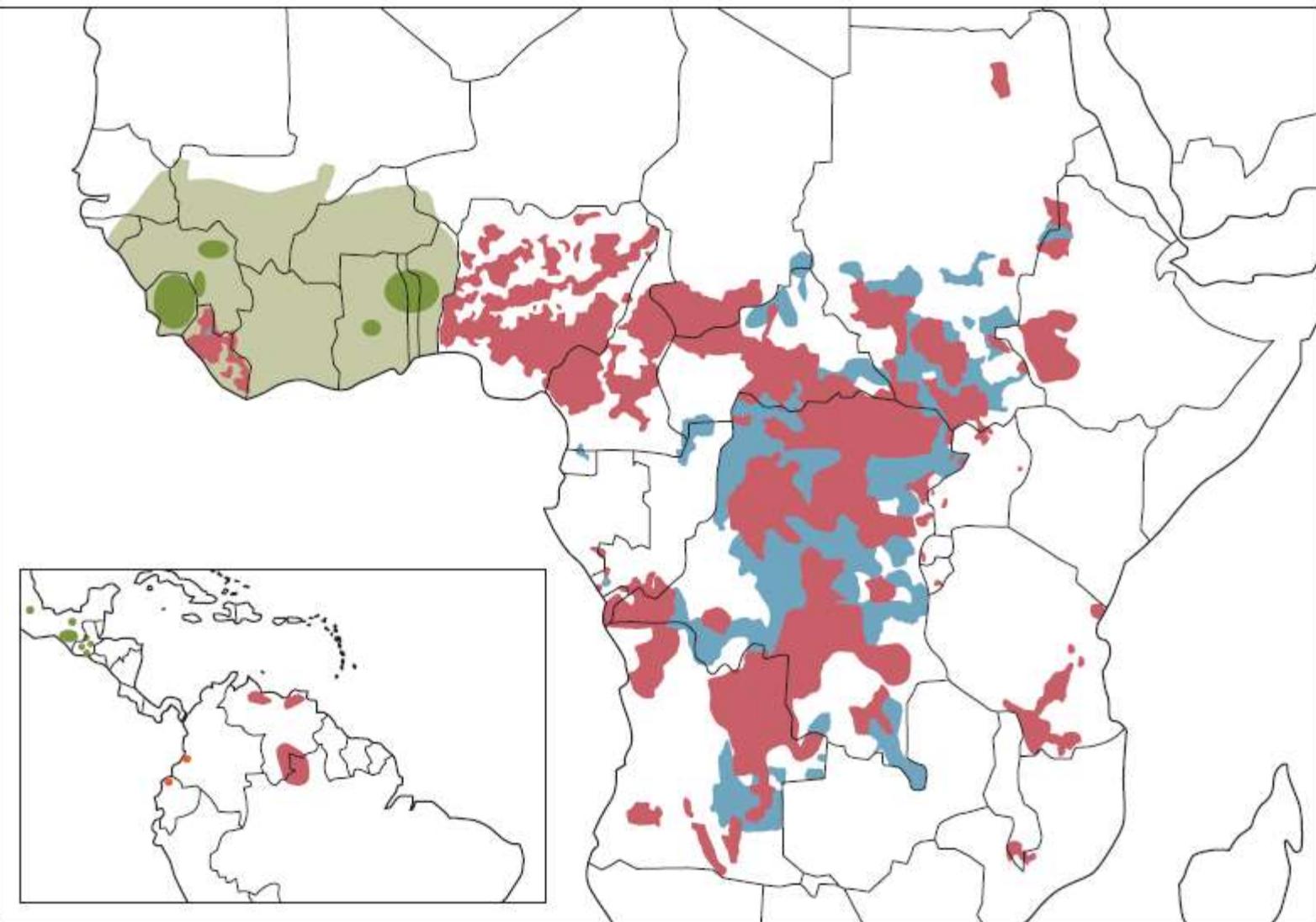


Figure 54.14 Geographical distribution of human onchocerciasis in Africa and Latin America. Red areas are under ivermectin treatment, blue areas need further mapping, orange areas are for special intervention, and ivermectin distribution has been suspended in areas shown in green. (Modified after Basanez MG, Pion SD, Churcher TS, et al. River blindness: a success story under threat? *PLoS Med* 2006;3:e371 and Cupp EW, Sauerbrey M, Richards F. Elimination of human onchocerciasis: history of progress and current feasibility using ivermectin (Mectizan®) monotherapy. *Acta Tropica* 2011;120(Suppl 1):S100–S1008.)

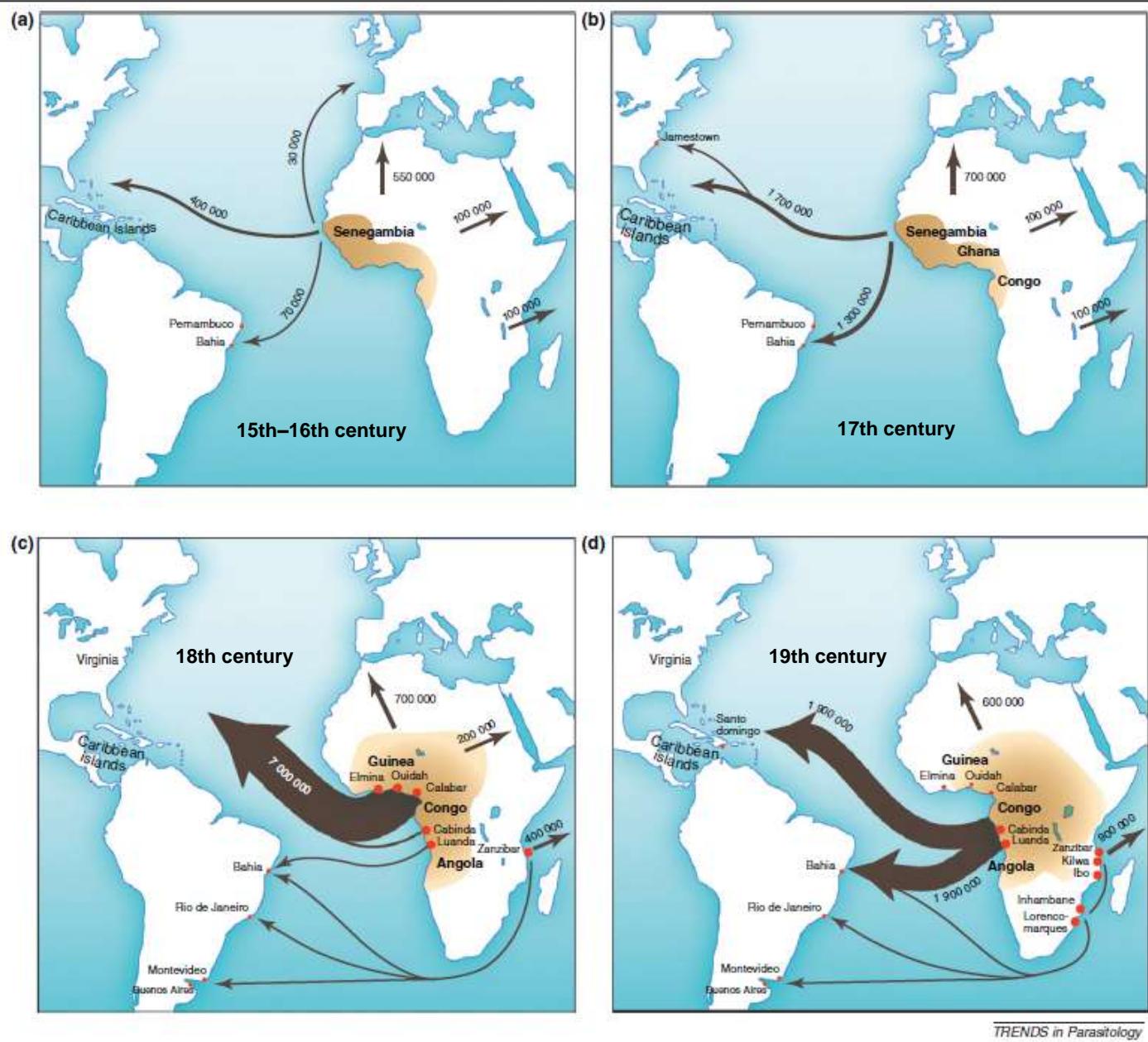


Figure 1. Trend in direction and numbers of African slaves transported over time. (a) 15th–16th century. (b) 17th century. (c) 18th century. (d) 19th century. Data source: UNESCO.

Importancia epidemiológica

- The World Health Organization estimated in 1995 that about **17.7 million** individuals worldwide were infected with *O. volvulus* with **270 000 cases of blindness** and **500 000 with severe visual disability**
- More than 99% of all onchocerciasis cases are in sub-Saharan Africa.
- Additional mapping surveys completed in 2005 led to revised estimates for Africa with **37 million people infected** and **90 million people at risk**.

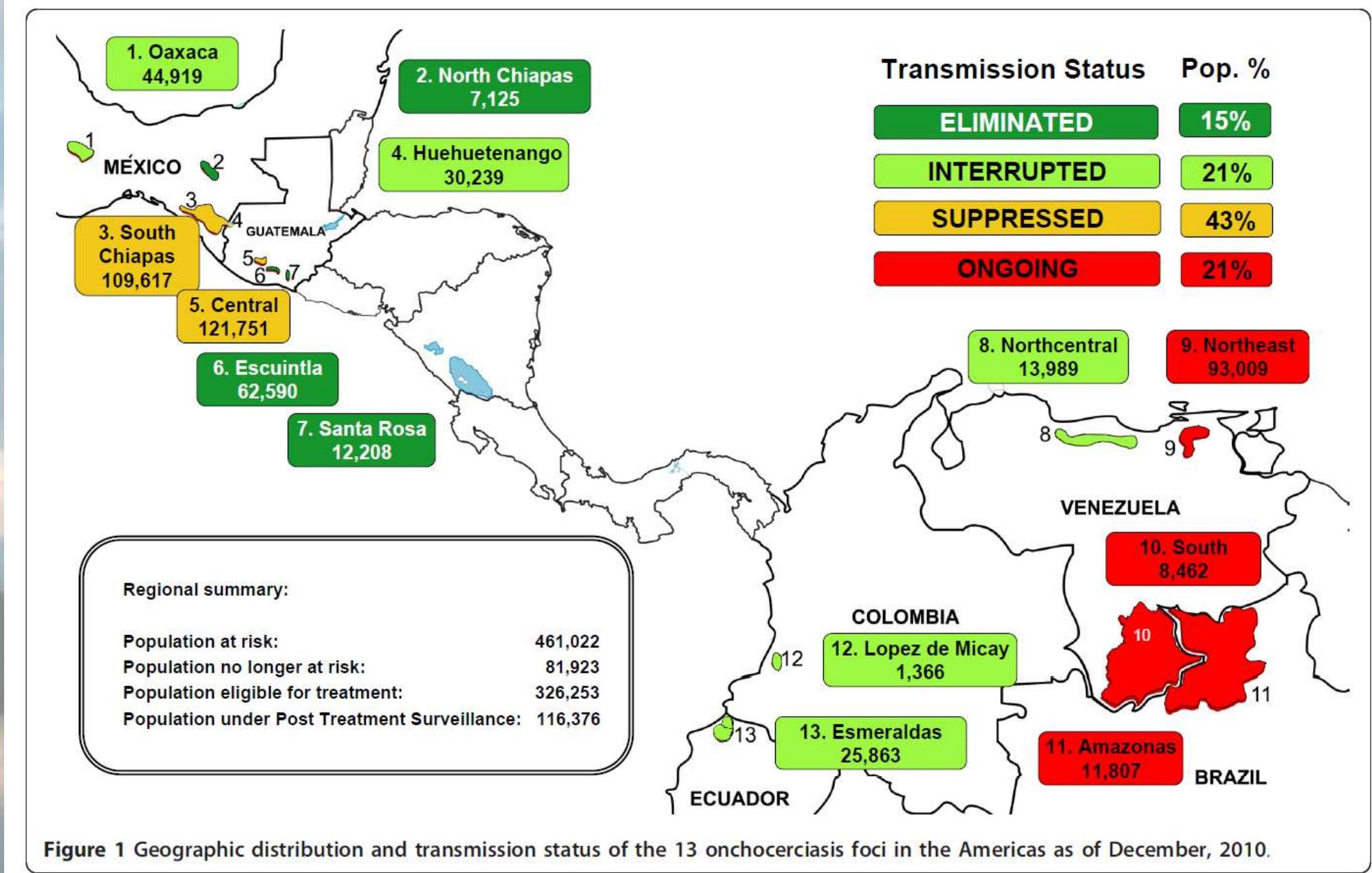


Figure 1 Geographic distribution and transmission status of the 13 onchocerciasis foci in the Americas as of December, 2010.



Pan American
Health
Organization



World Health
Organization
REGIONAL OFFICE FOR THE
Americas

[Home](#) [Health Topics](#) [Programs](#) [Media Center](#) [Publications](#) [Data](#) [Countries and Centers](#) [About PAHO](#)

Colombia, el primer país de las Américas que elimina la oncocercosis

Bogotá, Colombia, 16 de noviembre del 2011 (OPS/OMS)—Colombia se ha convertido en el primer país del continente americano que logra eliminar la oncocercosis (también conocida como ceguera de los ríos) dentro de sus fronteras, según lo anunciado por las autoridades sanitarias colombianas en la XXI Conferencia Interamericana sobre Oncocercosis, celebrada en Bogotá la semana pasada.



Crédito: OMS/TDR/Mark Edwards



Figure 54.15 Skin microfilaria of *O. volvulus* (haematoxylin). (Courtesy of D.W. Buttner)

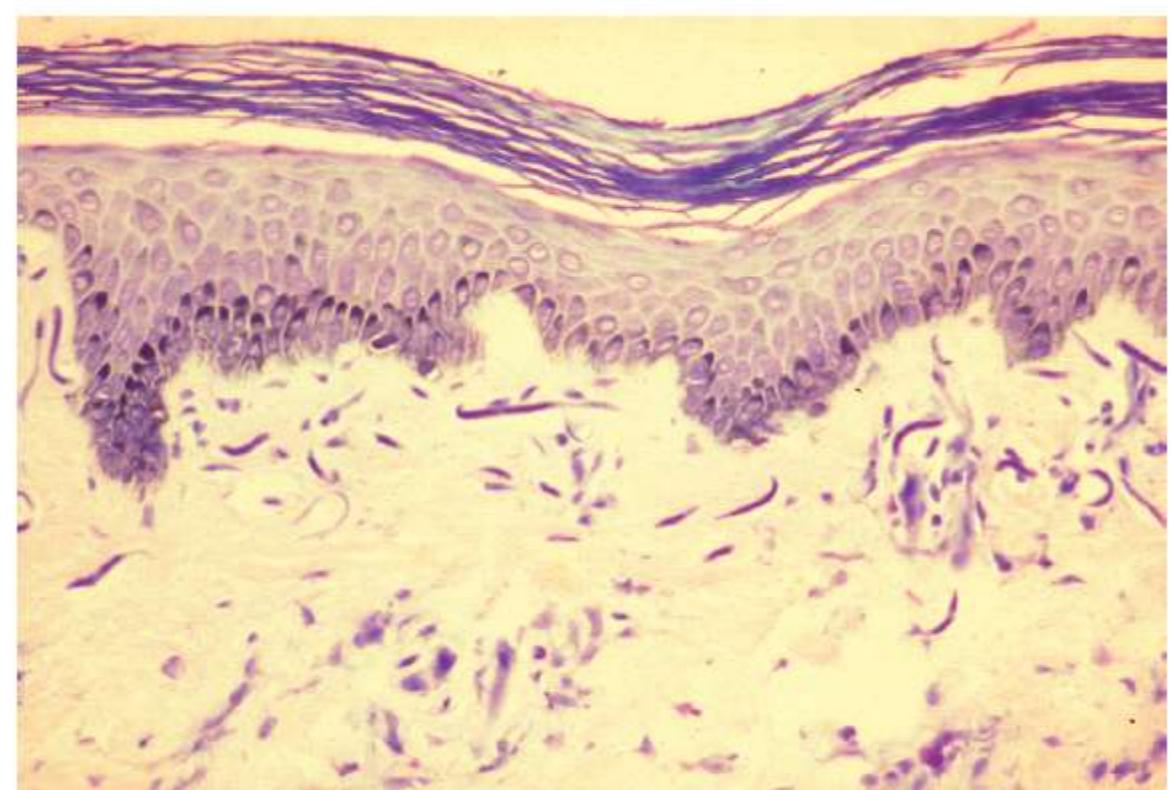


Figure 54.16 Microfilariae of *O. volvulus* in subcutaneous tissue. (Courtesy of D.W. Buttner)

Erradicación en Colombia (2011)

- Primer país del continente que logra eliminar la oncocercosis
- Tres años de vigilancia (2007-2010) y pruebas intensivas, realizadas tras la suspensión del tratamiento de la enfermedad en el 2007.
- Los esfuerzos abarcan 16 años, a cargo del
 - Instituto Nacional de Salud,
 - Ministerio de Salud y Protección Social,
 - Programa para la Eliminación de la Oncocercosis en las Américas (OEPA)
 - Organización Panamericana de la Salud/Organización Mundial de la Salud (OPS/OMS).
- El único foco de transmisión de la enfermedad en el país era una comunidad remota de 1.366 personas en el Departamento del Cauca, situado en la costa sudoeste.
- La estrategia de eliminación consistió en proporcionar a los residentes de esa comunidad tratamiento con el medicamento antiparasitario ivermectina dos veces al año durante más de 13 años; el medicamento fue donado por su fabricante, el Laboratorio Merck®.

TABLE 54.1 Characteristics of Filarial Parasites and Guinea Worm and Common Clinical Manifestations in Humans

Species	Distribution	Vectors	Main Location of Adult Worms	Main Location of Microfilariae	Common Disease Symptoms
<i>Wuchereria bancrofti</i>	Tropics	Mosquito spp.	Lymphatic vessels	Blood	Lymphangitis, elephantiasis hydrocele
<i>Brugia malayi</i>	South and South-east Asia	Mosquito spp.	Lymphatic vessels	Blood	Lymphangitis, elephantiasis
<i>Brugia timori</i>	Eastern Indonesia, Timor Leste	Mosquito spp.	Lymphatic vessels	Blood	Lymphangitis, elephantiasis
<i>Loa loa</i>	Central and West Africa	Chrysops spp.	Connective tissue	Blood	Angioedema, "eye worm"
<i>Mansonella perstans</i>	Africa, Central and South America	Culicoides spp.	Serous membranes of body cavities	Blood	Usually symptomless
<i>Mansonella streptocerca</i>	Central and West Africa	Culicoides spp.	Skin	Skin	Usually symptomless
<i>Mansonella ozzardi</i>	Central and South America	Culicoides spp. <i>Simulium</i> spp.	Serous membranes of body cavities	Blood and skin	Usually symptomless
<i>Onchocerca volvulus</i>	Africa, Yemen, Central and South America	<i>Simulium</i> spp.	Skin	Skin	Rash, pruritus, papules, skin atrophy, nodules, visual impairment and blindness
<i>Dracunculus medinensis</i>	Africa	Copepods	Connective tissue, including skin	Not applicable	Pain, ulceration, emerging worm

Skin manifestations of arthropod-borne infection in Latin America

Adrián Bolívar-Mejía^a, Camila Alarcón-Olave^b, and Alfonso J. Rodriguez-Morales^{c,d}

^aFaculty of Health, Universidad Industrial de Santander, ^bFaculty of Medicine, Universidad Autónoma de Bucaramanga, Bucaramanga, Santander, Colombia, ^cFaculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Risaralda, Colombia and ^dWorking Group on Zoonoses, International Society for Chemotherapy, Aberdeen, UK

Correspondence to Alfonso J. Rodriguez-Morales, Department of Community Medicine, Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Risaralda 660003, Colombia. Tel: +57 300 8847448; e-mail: arodriguezm@utp.edu.co

Curr Opin Infect Dis 2014, 27:288–294

DOI:10.1097/QCO.0000000000000060

ONCHOCERCIASIS

Onchocerciasis (river blindness), is a disease caused by the filarial nematode *Onchocerca volvulus*, transmitted by species of the genus *Simulium* [33[black small square][black small square]]. This involves skin and eyes, being the second leading cause of infectious blindness in the world, mainly affecting Africa and some Latin American countries which traditionally has included Brazil, Ecuador, Guatemala, Venezuela, Mexico and Colombia (being declared eradicated there in 2013) [34[black small square][black small square]]. In Ecuador, Guatemala and Mexico, transmission also was interrupted [33[black small square][black small square]].

Skin manifestations can range from very mild to severe complex alterations with significant aesthetic and functional sequelae [35,36]. The severity of these lesions will depend on the parasite inoculum, the strain, the exposure time, the time evolution of the lesion and the host immune response. Thus, the first clinical manifestations are associated with the appearance of an itchy rash, which can occur with or without edema [35,36]. The natural evolution of skin lesions has been described in four phases, which are: an acute popular onchodermititis phase; followed by the appearance of onchocercomas, subcutaneous nodules within which are encapsulated adult worms and whose size may reach 10 cm, configuring the second phase, chronic popular onchodermititis; followed by the third phase, lichenified onchodermititis; and finally atrophy and depigmentation, phases in which the skin condition is severe enough to produce atrophy, wrinkling and skin depigmentation, conferring the affected individual with an older appearance [35-37].

Onchodermatitis

Michele E. Murdoch

Watford General Hospital, Watford, UK

Correspondence to Dr Michele E. Murdoch, BSc FRCP, Consultant Dermatologist, Department of Dermatology, Watford General Hospital, Watford, Herts WD18 0HB, UK

Tel: +44 1923 208036;
e-mail: michele.murdoch@whht.nhs.uk

Current Opinion in Infectious Diseases 2010,
23:124–131

Purpose of review

This review is timely because awareness of the burden of disease from onchodermatitis has increased significantly over recent years. Recent progress in the field is reviewed with emphasis on publications within the past 2 years.

Recent findings

Advances have been made in understanding immunopathogenesis and in diagnosis and treatment. The World Bank/WHO African Programme for Onchocerciasis Control (APOC), which uses annual community-directed treatment with ivermectin (CDTI) via the Mectizan Donation Programme, now covers 19 African countries. Development of ivermectin resistance is a concern. Unlike ivermectin, which is a microfilaricide, doxycycline, which targets *Wolbachia* endosymbiotic bacteria, sterilizes adult female worms and has a macrofilaricidal effect. Moxidectin, which sterilizes or kills adult worms has started a phase III trial with ivermectin. Additional primary healthcare interventions have been successfully integrated with CTDI. In Latin America, transmission has been interrupted in half of the original endemic foci and Colombia is the first nation to have achieved countrywide interruption of transmission. The first report of elimination using ivermectin in an African setting is a milestone. Two African foci using vector control plus CTDI have reported vector elimination.



Figure 54.17 *O. volvulus* nodule on the body.



Figure 54.18 Onchocerciasis: Papular skin lesions. (Courtesy of D.W. Buttner)



Figure 54.19 Onchocerciasis: Depigmentation and leopard skin.
(Courtesy of D.W. Buttner)



Figure 54.20 Onchocerciasis: Sowda. (Courtesy of D.W. Buttner)



380. «Inglés colgantes» y elefantiasis escrotal

La afectación de los ganglios linfáticos inguinocrurales puede dar lugar al cuadro denominado «ingles colgantes». Estos tres pacientes africanos muestran alteraciones anatómicas especialmente graves causadas por oncocercosis.



Figure 54.22 Onchocerciasis: Hanging groin. (Courtesy of D.W. Buttner)

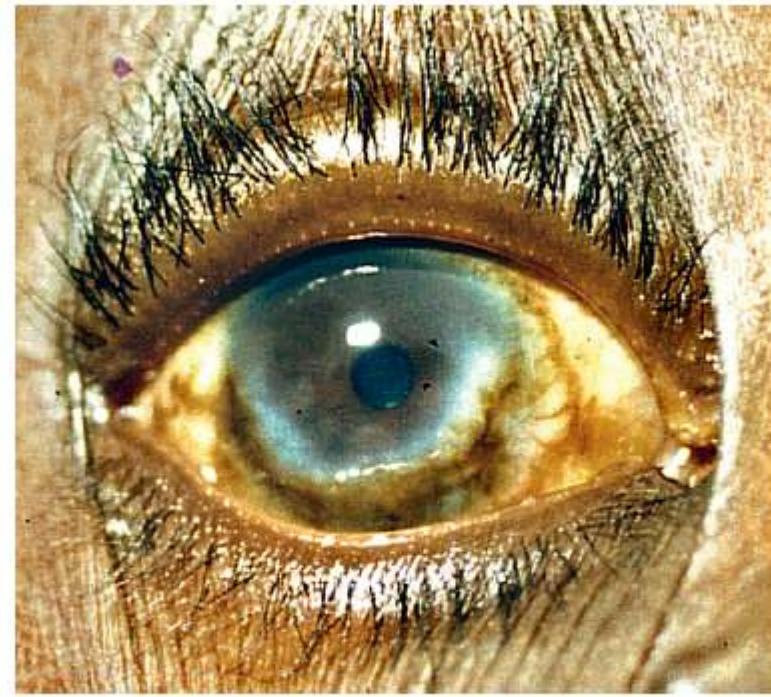


Figure 54.23 Onchocerciasis: early sclerosing keratitis. (Courtesy of D.W. Buttner)



379.
Despigmentación
Atrofia pretibial y despigmentación en un paciente con oncocercosis tardía (quemada). Este trastorno se denomina a veces «piel de leopardo». Se puede producir una atrofia de la piel, que adquiere el aspecto de «tejido de papel».



381. Facies leonina por oncocercosis en Guatemala
Las estimaciones relativas al número de personas infectadas en el continente americano son imprecisas, aunque, por ejemplo, al menos 2 millones de personas viven en las áreas endémicas de Venezuela. En América Central, la oncocercosis (erisipela de la costa) se caracteriza por un aspecto eritematoso de la cara y de la parte superior del tronco. Se observa en jóvenes, generalmente menores de 20 años de edad, con infecciones intensas. Las placas o pápulas con una tonalidad morada se pueden observar en América Central, generalmente en pacientes de edad mayor. Este trastorno, denominado «mal morado», da lugar en ocasiones a un aspecto de facies leonina, como se observa en la imagen.



Figure 54.24 Onchocerciasis: advanced sclerosing keratitis. (Courtesy of D.W. Buttner)

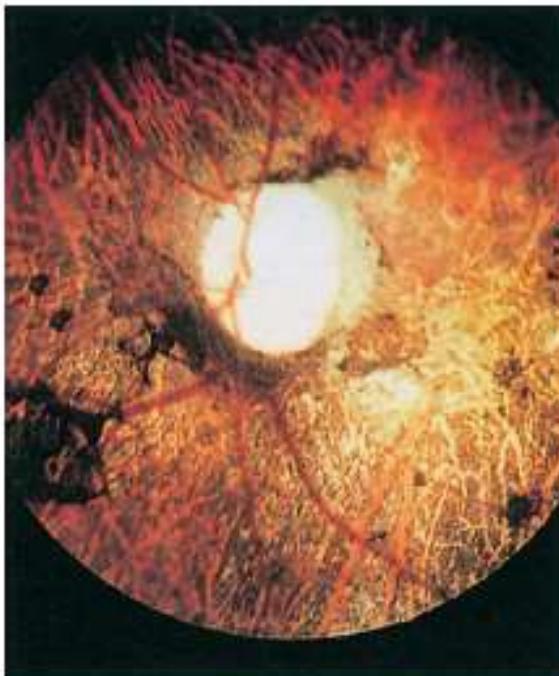


Figure 54.25 Skin snip to diagnose *O. volvulus* infection. (Courtesy of D.W. Buttner)



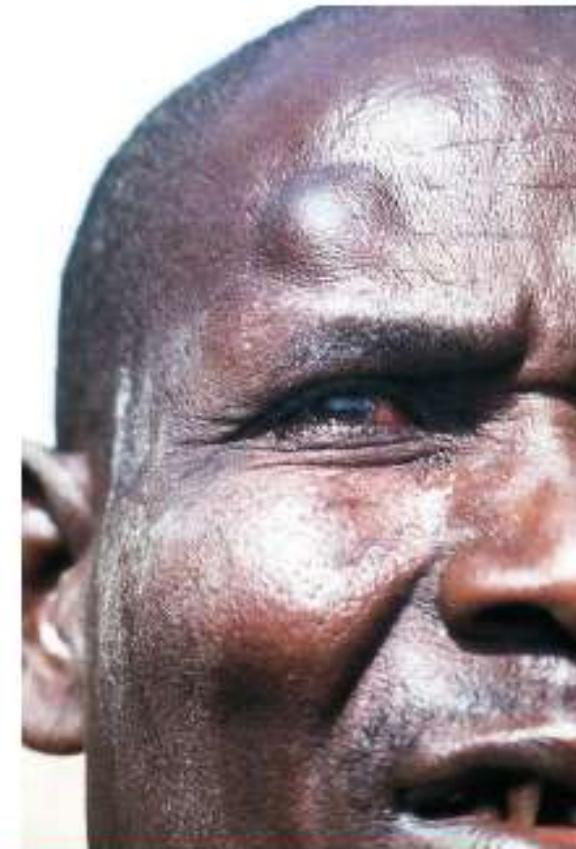
386. Afectación corneal temprana

La reacción tisular asociada a las microfilarias muertas en la córnea da lugar a la aparición de zonas de opacificación «en copo de nieve», como se observa en la imagen. Esta queratitis puntiforme puede desaparecer con el tiempo. La infección intensa por microfilarias puede causar una queratitis progresiva y esclerosante que con frecuencia induce ceguera.



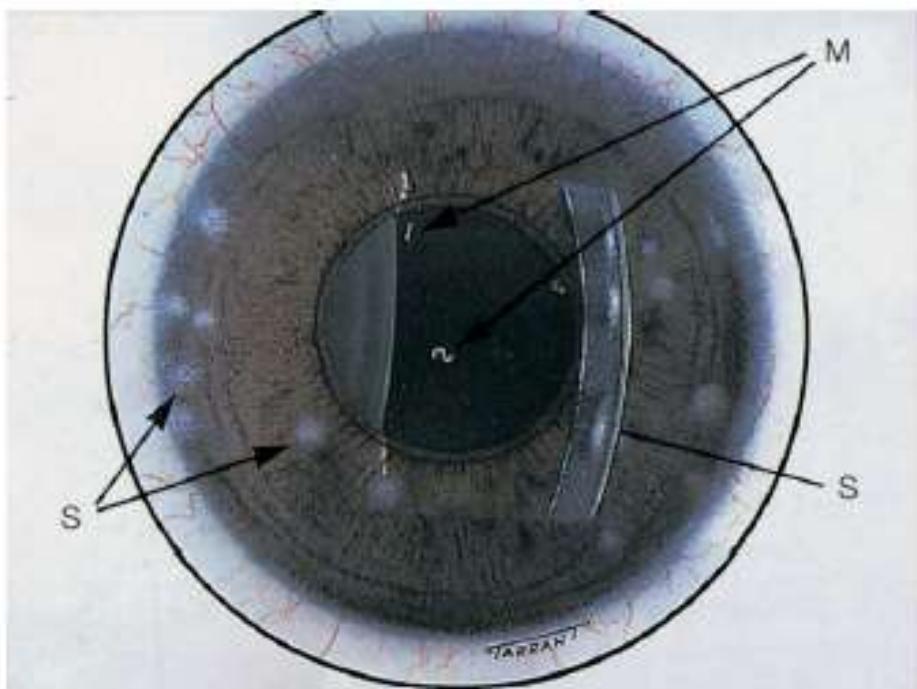
387. Atrofia óptica

La lesión causada por las microfilarias en los segmentos anteriores del ojo puede dar lugar a diversas lesiones coroidoretinianas; finalmente puede aparecer una atrofia óptica, como se observa en la imagen.



388. Ceguera de los ríos

A partir del gusano hembra existente en el nódulo de *Onchocerca volvulus* localizado en la cabeza de este paciente ciego de Burkina Faso pueden haber penetrado grandes cantidades de microfilarias en los tejidos oculares, causando finalmente ceguera.



389. Estudio del ojo con lámpara de hendidura

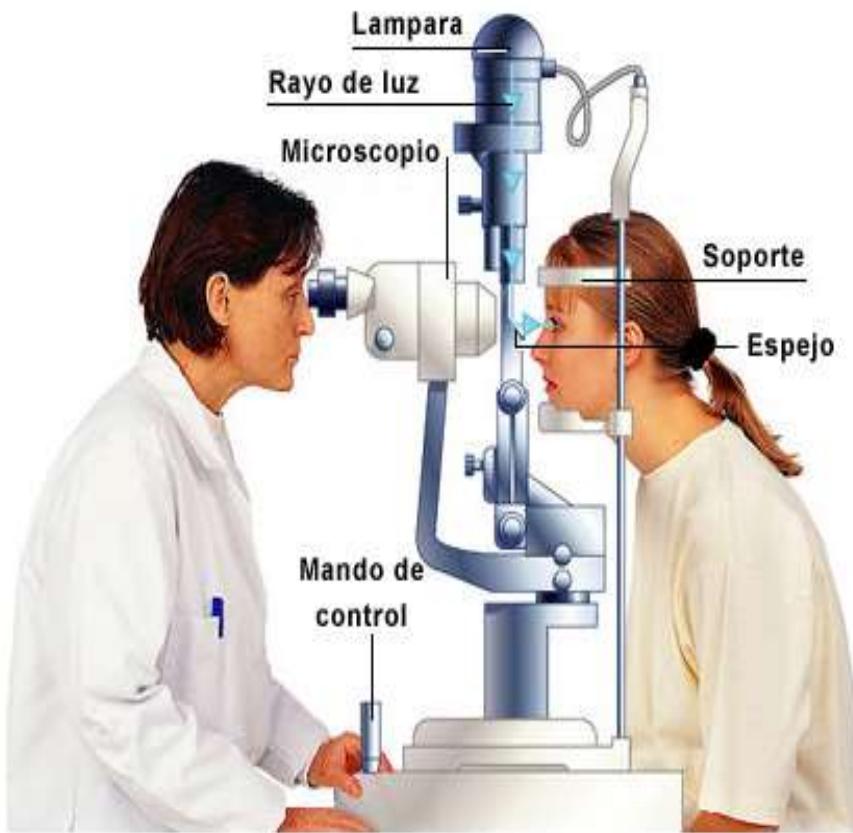
El estudio mediante lámpara de hendidura revela a menudo la presencia de numerosas microfilarias (M) en la cámara ocular anterior. Se pueden observar mejor en el cuadrante inferior interno. En la córnea se observan las zonas de opacificación «en copo de nieve» (S).



390. Nodulectomía

En algunos casos tempranos es posible prevenir las alteraciones oculares graves mediante la escisión de los nódulos que contienen los gusanos adultos, lo que impide la producción continuada de microfilarias, que son los elementos patógenos causantes realmente de la enfermedad. La nodulectomía se ha llevado a cabo con frecuencia en América Central y en América del Sur. Las medidas de control (mediante el uso de productos larvicidas) en el continente americano sólo han dado buenos resultados hasta el momento en México y, en menor grado, en Guatemala.

Lámpara de hendidura



Maniapure, Bolívar, Venezuela, 2007



AJRM 2007



AJRM 2007



AJRM 2007



AJRM 2007

Muestras de piel

Skin Snips

Microfilariae



382. Técnica de corte de la piel

Se corta un pequeño fragmento de piel –a menudo de la parte posterior de los hombros, de las regiones ilíacas o de la pantorrilla– y se coloca en una gota de suero salino sobre un portaobjetos cubierto con un cubreobjetos, en donde se deja durante varios minutos a temperatura ambiente. La biopsia por punción, tal como se observa en la imagen, permite la obtención de una muestra de tamaño estándar para la valoración cuantitativa de la cantidad de microfilarias. Un método más sencillo consiste en levantar la piel con la punta de una aguja y cortar un pequeño fragmento con un bisturí.



376. Nódulos de *Onchocerca* en las crestas ilíacas de una mujer africana

Las filarias adultas permanecen encapsuladas en material fibroso y forman nódulos en los tejidos subcutáneos. En África, los nódulos se localizan predominantemente en la parte inferior del cuerpo, mientras que en América Central lo hacen principalmente en la cabeza y en la parte superior del tronco.

377. Corte macroscópico de un nódulo

En este corte macroscópico de un nódulo se observan madejas de gusanos adultos situados sobre una matriz de células inflamatorias y de material fibrinoide en el que están incluidas las microfilarias liberadas por los gusanos hembra. ($\times 2$)

378. Microfilarias en una biopsia cutánea

Tras su salida del útero del gusano hembra, las microfilarias migran hacia la piel y el ojo. El tratamiento con una sola dosis del microfilaricida dietilcarbamazina puede desencadenar una respuesta alérgica intensa, la «reacción de Mazzotti», debido a la rápida destrucción de las microfilarias residentes en la piel. (Se puede observar una reacción similar en la piel con larvas de microfilarias de *Mansonella streptocerca*). (Hematoxilina y eosina, $\times 350$)

Case-control Studies on the Relationship between Onchocerciasis and Epilepsy: Systematic Review and Meta-analysis

Christoph Kaiser^{1*}, Sébastien D. S. Pion², Michel Boussinesq²¹ Basic Health Services Kabarole & Bundibugyo Districts, Fort Portal, Uganda, ² Institut de Recherche pour le Développement, UMI 233, Montpellier Cedex 5, France**Table 2.** Case-control studies on the onchocerciasis-epilepsy relationship: study areas characteristics and odds ratios (OR).

[Reference] ^a , year of study; country; study area	Pre-control onchocerciasis endemicity level ^b	Duration of onchocerciasis control before study (years) ^c	Onchocerciasis endemicity level at time of study ^b	OR mf (95% CI) ^d	OR Nod (95% CI) ^d
[29,39] ^a 1991; Cameroon; Mbam & Kim and Mbam & Inoubou, 17 villages	Hyper (Pmf>69%)	0	Hyper (Pmf>69%)	4.17 (0.45–38.32)	2.82 (1.43–5.56)
[20] ^a 1994; Uganda; Kabarole district, 13 villages	7 villages hyper, 6 meso/hypo	3 CDTI	7 hyper (Pmf>60%), 6 meso/hypo	1.67 (0.61–4.57)	2.77 (0.92–8.33)
[30] ^a 1996; CAR; Ouham and Ouham-Pende divisions, dispensaries in 3 towns	Area meso/hyper	5 CDTI	Meso/hyper	1.17 (0.82–1.68)	NA
[31,42] ^a 1998; Mali; Tyenfala and Baguineda sub-divisions, 18 villages	7 villages hypo, 11 meso/hyper	11 CDTI+VC for 4 years (1994–1997)	All hypo (Pmf 9% and 23%)	2.04 (0.40–10.40)	NA
[18] 1993; Uganda; Kabarole district, two villages	1 village hyper, 1 village hypo	2 CDTI	1 hyper (Pmf 63%), 1 hypo (Pmf 19%)	7.31 (3.19–16.73)	NA
[38] 1994; Burundi; Bururi province, Buyengero & Burambi divisions	Area meso/hyper	0	Meso/hyper	2.49 (1.38–4.50)	NA
[32] 1995; Benin; Dassa-Zoumé sub-division, one town and neighboring villages	Area meso/hyper	1 CDTI+VC for 7 years (1988–1995)	Meso (Pmf 47%)	2.56 (0.78–8.41)	NA
[33–35] 1996; Burkina; Bougouriba province, 12 villages	Area hyper	VC for 16 years (1975–1990)	Hypo (Pmf 13%)	0.84 (0.29–2.40)	NA
[41] 1996; Tanzania; Ruvuma region, Songea district, one village	Area hyper	0 ^e	Hyper (Pmf 68%)	3.50 (1.21–10.17)	NA
[44] 2000; Cameroon; Sanaga maritime division, Logbikoy hospital	Area hyper	1 CDTI ^e	Hyper (Pmf>80%)	3.76 (1.31–10.74)	0.98 (0.55–1.75)
[40] 2004; Cameroon; Sanaga maritime division, one village	Area hyper	3 CDTI ^e	Hyper (PNod 62.5%)	NA	1.38 (0.42–4.51) ^f
[36,37,45] 2005; Tanzania; Morogoro region, Ulanga district, Mahenge hospital	Area meso/hyper	8 CDTI	Meso	3.77 (2.18–6.52)	NA
Pooled studies (random effects model)				2.49 (1.61–3.86)	1.74 (0.94–3.20)

^aThe first four studies are those achieving control for intensity and time of exposure and gender. In these studies people with epilepsy were matched for gender, age and place of residence to one or two people without epilepsy; in the study by Kaiser et al. (2011), 5 of 38 pairs were not matched for sex.

^bPmf = prevalence of skin microfilariae (mf) in subjects aged ≥ 5 years; PNod = prevalence of nodules in males aged ≥ 20 years; Hypo = hypoendemic ($\text{Pmf} < 35\%$ or $\text{PNod} < 20\%$); Meso = mesoendemic ($35\% \leq \text{Pmf} < 60\%$ or $20\% \leq \text{PNod} < 40\%$); Hyper = hyperendemic ($\text{Pmf} \geq 60\%$ or $\text{PNod} \geq 40\%$).

^cCDTI = Community-Directed Treatment with Ivermectin; VC = Vector control.

^dOR mf = Odds ratio for epilepsy in patients with skin mf; OR Nod = Odds ratio for epilepsy in patients with nodules; 95%CI = 95% Confidence interval; NA = not assessable.

^ePassive ivermectin treatment had been organized in these areas before the implementation of the CDTIs organized by the African Program for Onchocerciasis Control (APOC).

^fOR calculated on the number of persons examined (6 of the 36 controls were "missing" for nodule palpation). If all the missing controls had nodules, the OR would be 1.00 (0.31–3.19) and if none of them had nodules, the OR would be 1.96 (0.62–6.22).

Am. J. Trop. Med. Hyg., 70(5), 2004, pp. 556–561
Copyright © 2004 by The American Society of Tropical Medicine and Hygiene

A LONGITUDINAL STUDY OF IMPACT OF REPEATED MASS IVERMECTIN TREATMENT ON CLINICAL MANIFESTATIONS OF ONCHOCERCIASIS IN IMO STATE, NIGERIA

EMMANUEL C. EMUKAH, EDITH OSUOHA, EMMANUEL S. MIRI, JUDE ONYENAMA, UCHE AMAZIGO,
CHRISTOPHER OBIJURU, NKEIRU OSUJI, JOSEPHINE EKEANYANWU, STANLEY AMADIEGWU,
KENNETH KORVE, AND FRANK O. RICHARDS

*National Office, Global 2000 Program of The Carter Center, Jos, Nigeria; Ministry of Health Imo State Nigeria; African Program for
Onchocerciasis Control—World Health Organization, Ougadougou, Burkina Faso; The Carter Center, Atlanta, Georgia*

TABLE 2

Onchocerciasis: Prevalence of selected morbidity indicators in the Imo State, Nigeria cohort, baseline 1995 compared to 2002 re-examinations

Village	No.	Nodule rate		Leopard skin		Papular rash		Visually impaired	
		1995	2002	1995	2002	1995	2002	1995	2002
Ndiawa	48	31%	25%	13%	13%	17%	2%	17%	2%
Uhiowerre	49	55%	6%	10%	10%	10%	4%	10%	0%
Umungwa	46	41%	13%	17%	17%	0%	0%	0%	0%
Umuoriaku	48	21%	21%	19%	19%	19%	8%	19%	6%
Ubakuru	45	47%	16%	11%	11%	0%	0%	0%	0%
Ikpem	56	89%	13%	11%	11%	5%	0%	23%	0%
Amano	71	93%	20%	14%	14%	28%	0%	25%	0%
Umuawuchi	48	71%	31%	15%	15%	35%	0%	27%	0%
Total	411	59%	18%	14%	14%	15%	2%	16%	1%

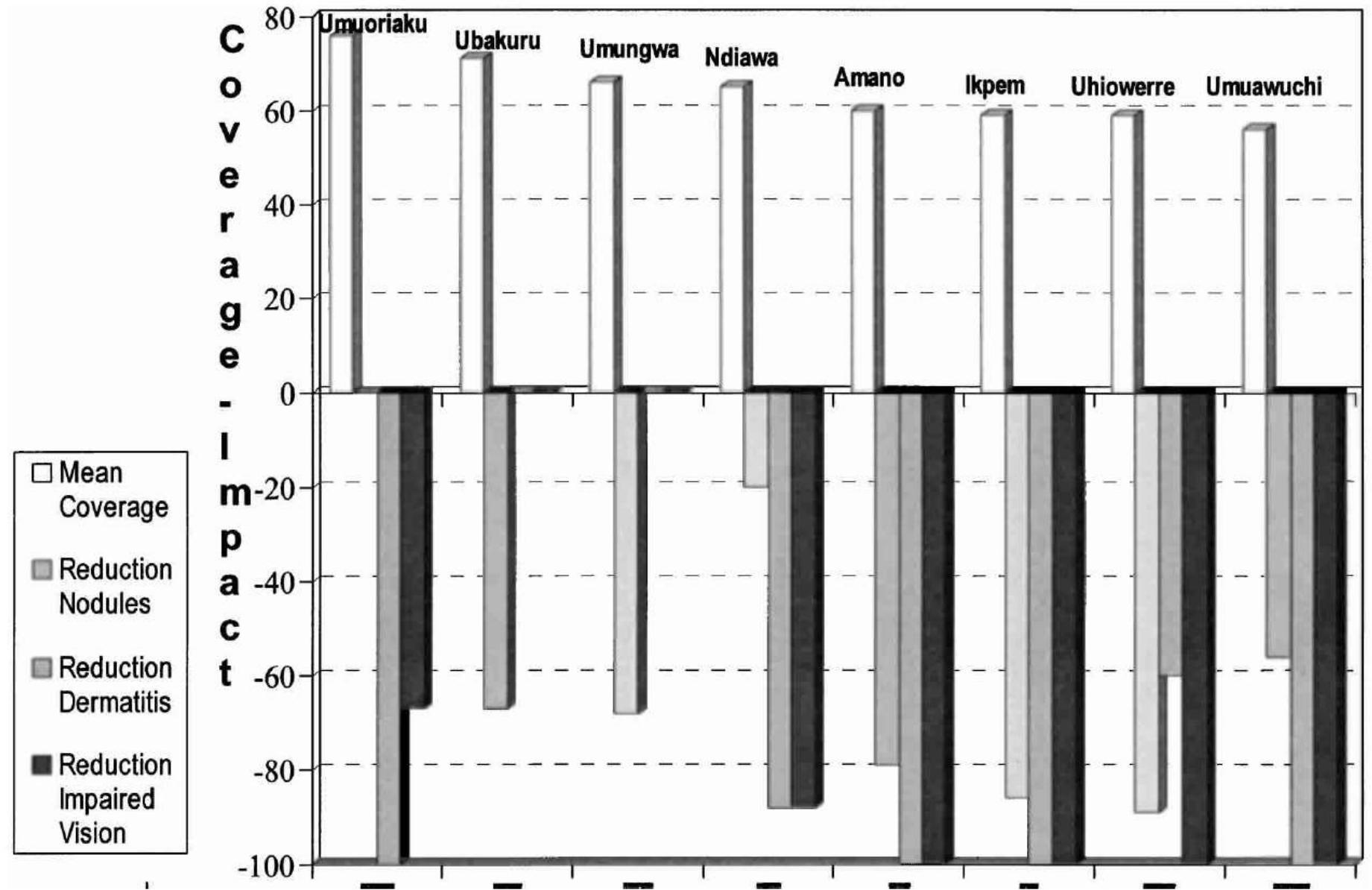


FIGURE 2. Mean total ivermectin population coverage compared with the impact on prevalence of selected morbidity indicators by community.

Onchocerciasis in Anambra State, Southeast Nigeria: endemicity and clinical manifestations

Evaristus Chibunna Mbanefo,¹ Christine Ifeoma Eneanya,¹ Obioma C Nwaorgu,¹ Moses Obiefuna Otiji,² Victor Mmaduabuchi Oguoma,¹ Bernice Amala Ogolo³

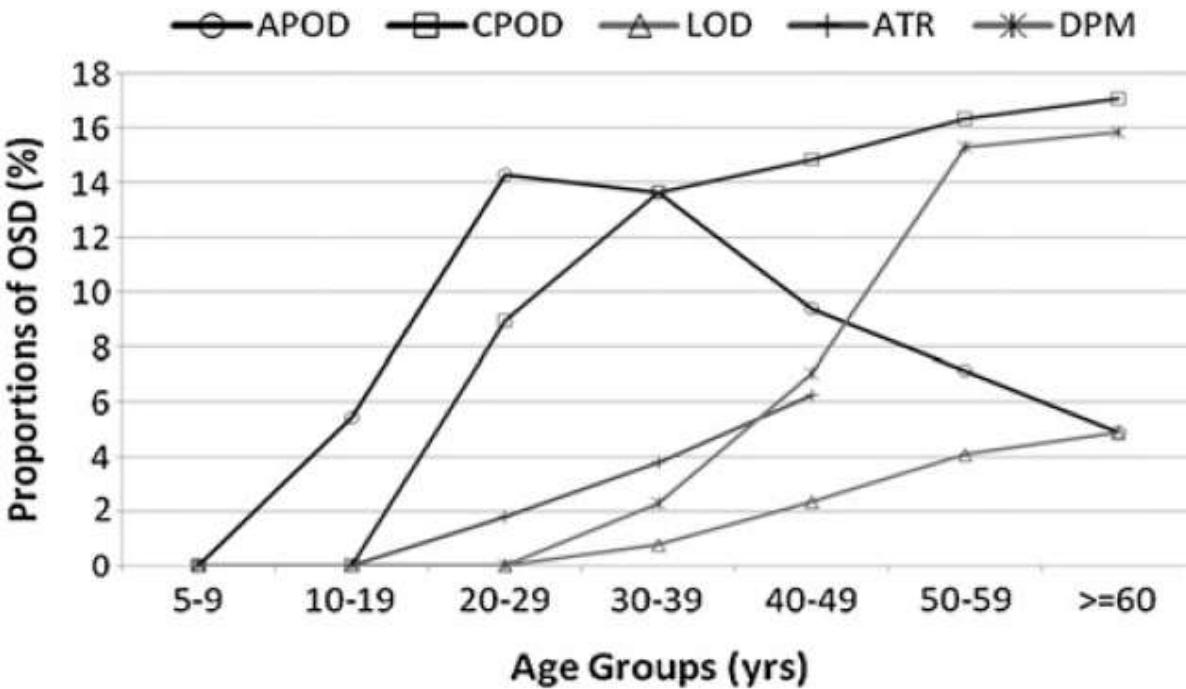
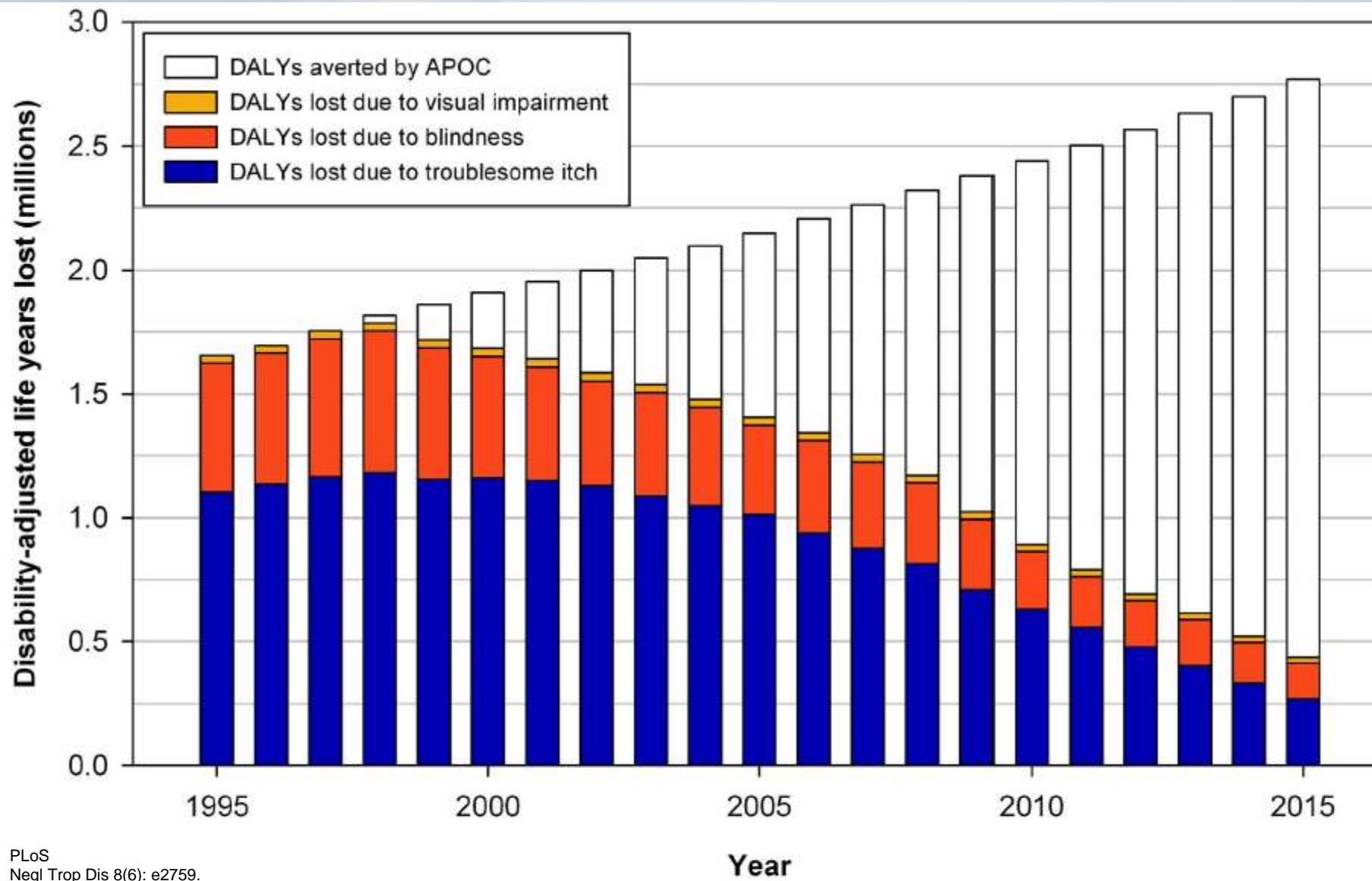


Figure 1 Frequency of different classes of OSD by age in Ayamelum local government area of Anambra State, Nigeria (2009). Subjects aged 50 years and above were excluded from examination for atrophy to avoid inclusion of atrophy due to aging. APOD, acute papular onchodermatitis; CPOD, chronic papular onchodermatitis; LOD, lichenified onchodermatitis; ATR, atrophy; DPM, depigmentation.



PLoS
Negl Trop Dis 8(6): e2759.

Figure 1. Disability-adjusted life years (DALYs) lost due to onchocerciasis from 1995 to 2015. The total height of the bars (colored plus blank) represents the estimated number of DALYs lost in a counterfactual scenario without ivermectin mass treatment (increasing trend due to population growth). The colored part of each bar represents the estimated actual number of DALYs lost (declining trend due to ivermectin mass treatment). The blank part of each bar therefore represents the annual number of DALYs averted by ivermectin mass treatment in the total APOC population.

doi:10.1371/journal.pntd.0002759.g001

African Programme for Onchocerciasis Control (APOC)

Diagnóstico

► Microfilariae of *Onchocerca volvulus* in tissue.

Microfilariae of *Onchocerca volvulus* are unsheathed and measure 300-315 µm in length. The tail tapers to a point and is often sharply bent. The nuclei do not extend to the tip of the tail. Microfilariae typically reside in skin but may be found in blood or urine during heavy infections, or invade the eye and cause a condition known as river blindness.



Figure A: Microfilariae of *O. volvulus* from a skin nodule of a patient from Zambia, stained with hematoxylin and eosin (H&E). Image taken at 1000x oil magnification.

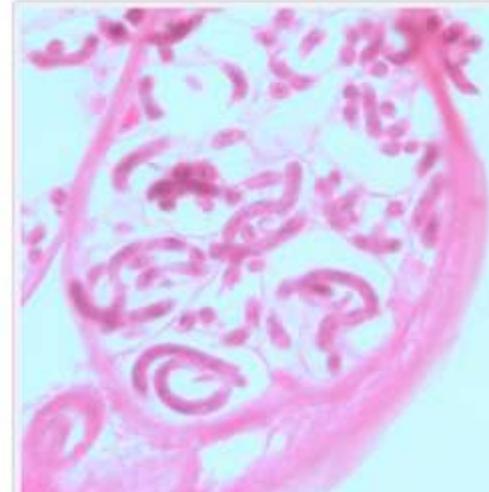


Figure B: Microfilariae of *O. volvulus* within the uterus of an adult female. The specimen was taken from the same patient as in **Figure A**. Image taken at 500x magnification, oil.

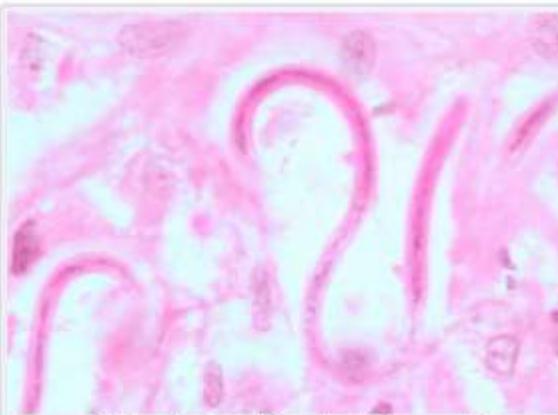


Figure C: Microfilariae of *O. volvulus* from a skin nodule of a patient from Zambia, stained with H&E. Image taken at 1000x oil magnification.



Figure D: Coiled microfilaria of *O. volvulus*, in a skin nodule from a patient from Zambia, stained with H&E. Image taken at 1000x oil magnification.

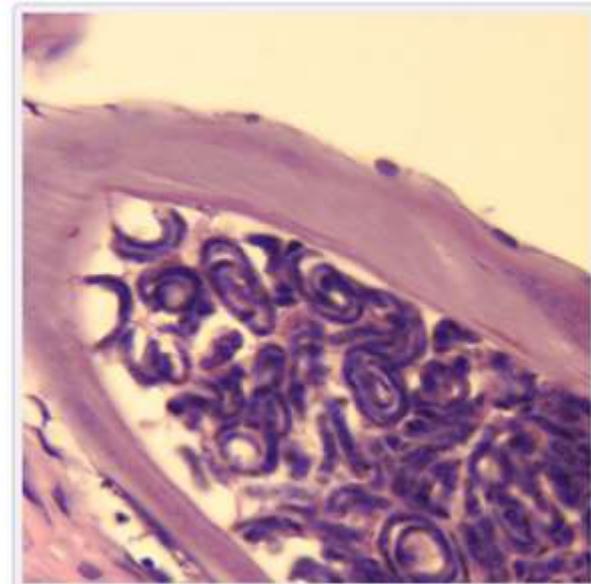


Figure E: Cross-section of an adult female *O. volvulus*, stained with H&E. Note the presence of many microfilariae within the uterus.

Diagnóstico

▼ Adults of *O. volvulus* in tissue.

Adult males of *Onchocerca volvulus* measure 15-45 mm in length; females are 30-50 cm. Adults usually reside in nodules (onchocercomas) in subcutaneous tissue.

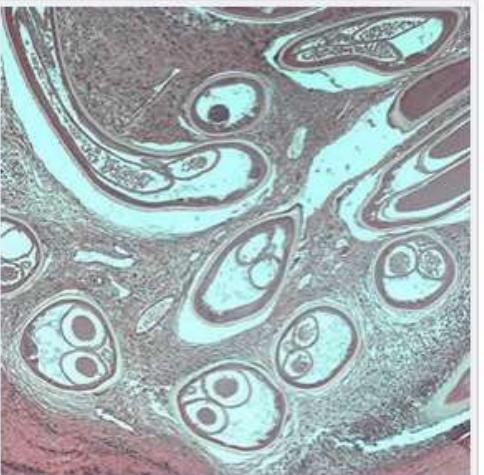


Figure A: Adult of *O. volvulus* in a subcutaneous nodule, stained with hematoxylin and eosin (H&E).

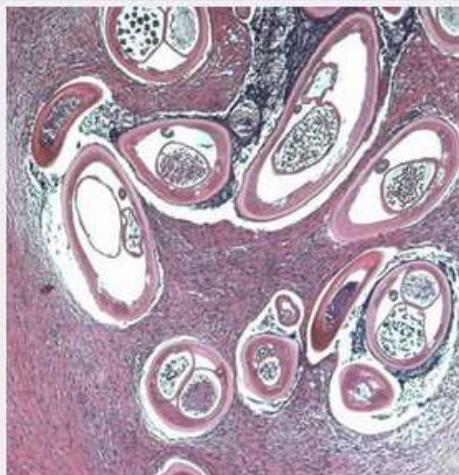


Figure B: Adult of *O. volvulus* in a subcutaneous nodule, stained with hematoxylin and eosin (H&E).

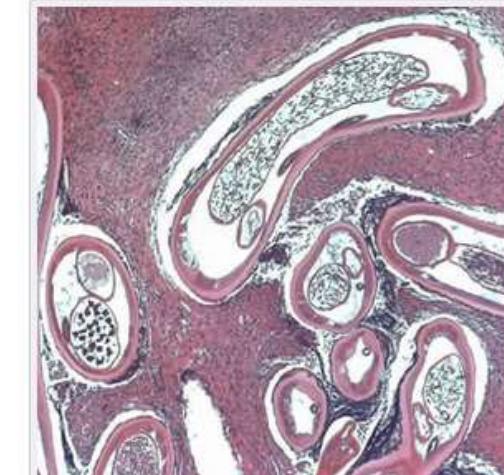


Figure C: Adult of *O. volvulus* in a subcutaneous nodule, stained with H&E.

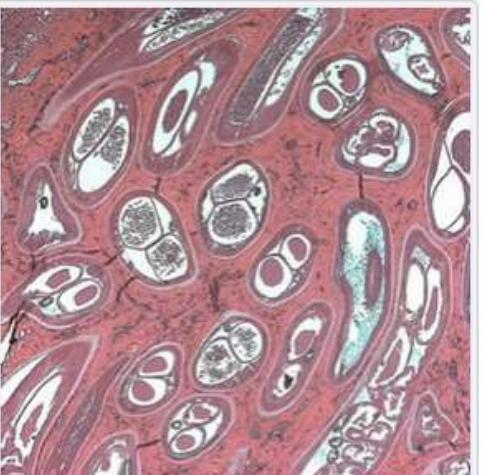


Figure D: Adult of *O. volvulus* in a subcutaneous nodule, stained with H&E.

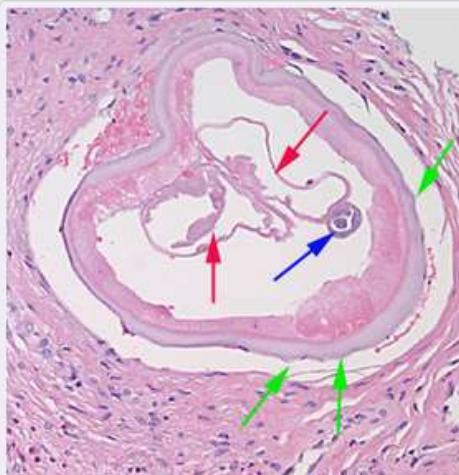


Figure E: Cross-section of an adult female *Onchocerca* sp. from the biopsy of a scalp nodule from a patient from Liberia. Note the presence of the intestine (**blue arrow**), uterine tubes (**red arrows**) and some cuticular nodules (**green arrows**). Also notice the weak musculature under the thick cuticle. Image courtesy of Drs. Philip LeBoit and Paul Borbeau.

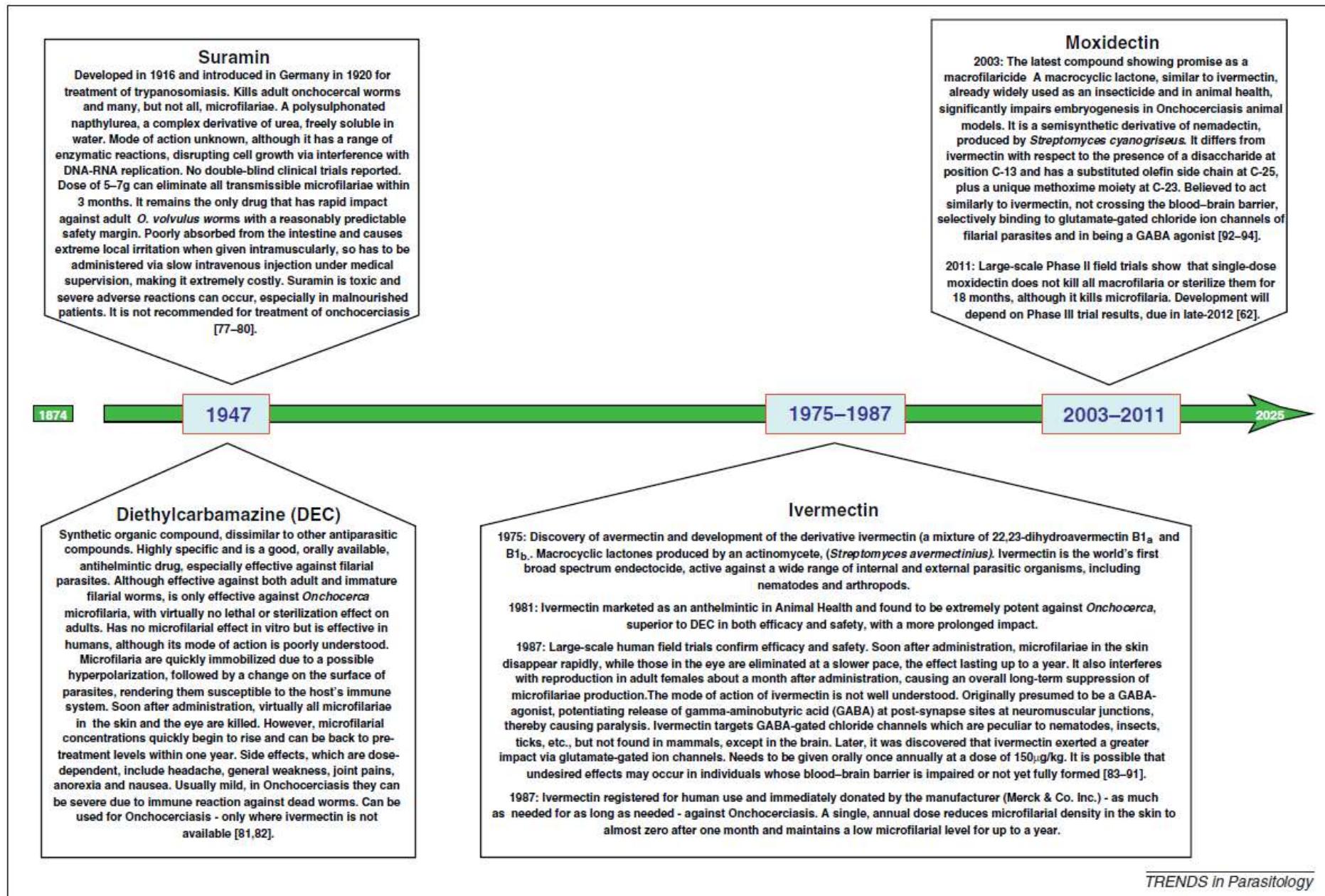


Figure 2. Timeline of major anti-onchocerciasis drugs [62,77–94].

Prevención de picaduras de insectos

Janet M. Torpy. Insect Bites and Stings
JAMA July 3, 2013 Volume 310, Number 1

Preventing insect bites



^aIf skin is exposed use DEET insect repellent and wash off after use.

Control vectorial



391. Fumigación de BTI desde helicóptero sobre una zona de cría de *Simulium damnosum* en el río Milo (República de Guinea)

En la operación internacional Onchocerciasis Control Programme se utilizaron con frecuencia avionetas y helicópteros de fumigación. Tras la aparición de resistencia al insecticida temephos (Abate®) se empezó a utilizar de manera generalizada el agente biológico *Bacillus thuringiensis israelensis* H14 (BTI) para destruir las fases acuáticas de *Simulium damnosum* en una campaña que tuvo una duración de 30 años y que redujo espectacularmente la transmisión de *Onchocerca volvulus* en la mayor parte de las áreas endémicas de África occidental y central. Sin embargo, el riesgo de reinvasión de las áreas infestadas por moscas infectadas situadas fuera de las zonas controladas sigue constituyendo una amenaza.



Contents lists available at ScienceDirect

International Journal for Parasitology

journal homepage: www.elsevier.com/locate/ijpara



Vaccines to combat river blindness: expression, selection and formulation of vaccines against infection with *Onchocerca volvulus* in a mouse model



Jessica A. Hess^a, Bin Zhan^{b,c}, Sandra Bonne-Année^a, Jessica M. Deckman^a, Maria Elena Bottazzi^{b,c}, Peter J. Hotez^{b,c}, Thomas R. Klei^d, Sara Lustigman^e, David Abraham^{a,*}

^a Department of Microbiology and Immunology, Jefferson Medical College, Thomas Jefferson University, 233 S. 10th Street, Philadelphia, PA 19107, USA

^b Department of Pediatrics, National School of Tropical Medicine, Baylor College of Medicine, Houston, TX 77030, USA

^c Sabin Vaccine Institute and Texas Children's Hospital Center for Vaccine Development, 1102 Bates St, Ste. 550, Houston, TX 77030, USA

^d Department of Pathobiological Sciences, LSU School of Veterinary Medicine, Louisiana State University, 1909 Skip Bertman Drive, Baton Rouge, LA 70803, USA

^e Laboratory of Molecular Parasitology, Lindsley F. Kimball Research Institute, New York Blood Center, 310 E 67th St, New York, NY 10065, USA

Table 1Characteristics of seven antigens selected for further development into a vaccine against infection with *Onchocerca volvulus*.

Characteristics of the <i>O. volvulus</i> protective protein					Characteristic of nematode orthologous proteins Protection in other filaria or nematode animal models
Antigen accession #(kDa)	Identity (Function)	Localisation	Immunogenicity	In vitro assays	
Ov-CPI-2 M37105 (17)	Onchocystatin, (Cysteine protease inhibitor)	Hypodermis; basal layer of cuticle; separation of L3/L4 cuticles; secretory vesicles; ES Lustigman et al. (1996)	Human Chimpanzee (Lustigman et al., 1991)	Human – Ov L3 molt inhibition Cho-Ngwa et al. (2010)	-Ls-cystatin (<i>Ls</i>) Pfaff et al. (2002) -Ac-cystatin (Ac) (Hotez, unpublished data) -Ls-cystatin (mutated) (<i>Ls</i>) Babayan et al. (2012)
Ov-103 M55155 (15)	Novel, nematode specific	L3: basal layer of the cuticle; hypodermis; basal lamina; channels; multivesicular bodies. Mf: surface	Human (Lustigman, unpublished data)	Human – Ov L3 molt inhibition (Lustigman, unpublished data) Human – killed Mf Lustigman et al. (1992)	-Ac-SAA-1 (Ac) Zhan et al. (2004)
Ov-RAL-2 U00693 (17)	Novel, nematode specific	Granules of glandular esophagus; Hypodermis	Human Mice (S. Lustigman, unpublished data)	Human – Ov L3 molt inhibition (Lustigman, unpublished data)	-rWb-SXP/Bm14 (<i>Bm</i>) Wang et al. (1997) -rAs16 (<i>As</i>) Tsuji et al. (2003,2004) -rAc-16 (Ac) (P. Hotez, unpublished data)
Ov-ASP-1 AF020586 (25)	Novel, homologue of vespid venom allergen 5 and the PR-1 protein family	Granules of glandular esophagus; ES	Human Mice MacDonald et al. (2004)	Jird – killed <i>Bm</i> L3 and Mf Anand et al. (2011)	-Bm-ASP-1(<i>Bm</i>) Anand et al. (2011) -Ac-ASP-2 (Ac) Goud et al. (2004)
Ov-ALT-1 U96176 (15)	Novel, filariae specific	Granules of glandular esophagus; cuticle; channels Joseph et al. (1998)	Human MacDonald et al. (2002)	Jird – killed <i>Bm</i> L3 and Mf Anand et al. (2011)	-Bm-ALT-1 (<i>Bm</i>) Gregory et al. (2000) <i>Bm</i> -ALT-2 (<i>Bm</i>)
Ov-B20 L41928 (52/65)	Novel, nematode specific	Cuticle; hypodermis; ES product	Cattle anti- <i>Ol</i> Abdel-Wahab et al. (1996)	ND	-Cross protection (Av) Jenkins et al. (1996) and Taylor et al. (1995a,b)
Ov-RBP-1 L277686 (20/22)	Novel, nematode specific; Retinoid binding protein	Body wall; ES product Tree et al. (1995)	Human Mpagi et al. (2000)	ND	-Cross protection (Av) (Jenkins et al. (1996) and Taylor et al. (1995a,b))

Ac, *Ancylostoma ceylanicum*; *As*, *Ascaris suum*; *Av*, *Acanthocheilonema viteae*; *Bm*, *Brugia malayi*; ES, excretory-secretory product; *Ls*, *Litomosoides sigmodontis*; Mf, microfilaria; ND, Not determined; *Ov*, *Onchocerca volvulus*; *Ol*, *Oncocerca lienalis*; *Wb*, *Wuchereria bancrofti*.

Conclusiones

- Enfermedad infecciosa tropical parasitaria transmitida por vectores, aún de considerable carga en África y algunas regiones de América Latina.
- En algunos países, se está en vías de eliminación y erradicación.
- En Colombia se logró ya erradicar.
- Importante, mantener la vigilancia entomológica.
- Seguir el avance en control en países aún endémicos.



Tanzania, África del Este, 2006.

