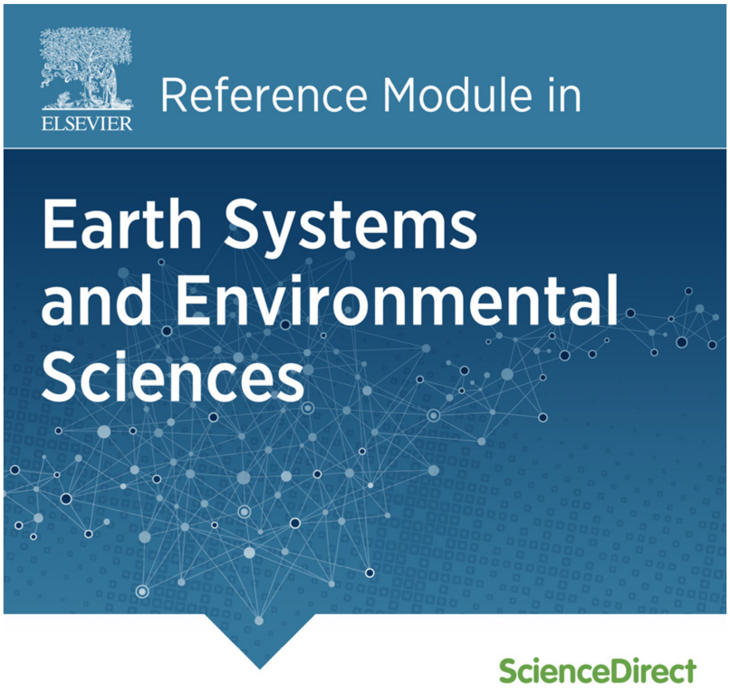

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Landscape Epidemiology of Human Onchocerciasis in Southern Venezuela☆

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Abbreviations

a.s.l.	Above sea level
AOCBR	Alto Orinoco-Casiquiare Biosphere Reserve
GIS	Geographical information systems
GPS	Global positioning systems
L1	First stage larva
L2	Second stage larva
L3	Third stage larva
RS	Remote sensing
s.l.	Sensu lato (broad sense)

Introduction: The Impact of Onchocerciasis on Human Health

Human onchocerciasis is a chronic infection caused by the filarial parasitic nematode *Onchocerca volvulus* and transmitted through the bites of *Simulium* vectors (black flies). More than 80 million people are exposed to the risk of infection with 37 million persons infected (according to the latest results of rapid epidemiological mapping of onchocerciasis), and 1 million with severely impaired vision. Most of the cases are observed in tropical Africa (99%), with the remainder in smaller, more discrete foci in Yemen and Latin America. Its impact on human health is through the clinical repercussions of the infection for the skin (causing cutaneous disease) and for the eyes (causing loss of vision and even blindness). However, onchocerciasis can have more insidious and subtle systemic effects, rendering the people infected more susceptible to the same and other infections and impairing their ability to respond well to vaccination. Mortality of the blind and of those sighted individuals with heavy parasite burdens has been well documented, particularly in savannah areas of West Africa.

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Onchocerciasis: A Vector-Borne Disease

A vector-borne disease is that in which the pathogen responsible for the disease is transmitted among people, or from a nonhuman mammal reservoir to susceptible individuals via an arthropod or invertebrate host in which the pathogen may multiply or develop into an infective stage. Examples are dengue (caused by a virus), plague (caused by a bacteria), malaria (caused by a protozoan), and onchocerciasis (caused by a nematode). Transmission of vector-borne diseases depends on the ecology of the vector and on the environmental determinants of vector and disease distribution. *Simulium* black flies were incriminated as the vectors of human onchocerciasis in Africa in 1926 by Blacklock. Although in 1917, Dr. Rodolfo Robles in Guatemala had suggested their role in the transmission of the disease. Since black flies breed in fast-flowing rivers, the disease is also known as 'river blindness.' The reason is that in endemic areas, those communities located in the proximity of such breeding sites may be at a higher risk of infection and eye disease. An endemic area is that in which the host–parasite–vector system has reached an equilibrium or steady state, characterized by a given proportion of infected people (prevalence of infection) with a given load of parasites per person and per fly (intensity of infection). When the prevalence and intensity of infection in the flies are combined with the density of vectors biting humans in a particular locality, it is possible to estimate the intensity of transmission, an important risk factor.

The Lifecycle of *Simulium*

Black flies are insects with complete metamorphosis, their lifecycle comprising four distinct stages: eggs, larvae, pupae, and adult males and females (Figure 1). The first three are aquatic stages. The duration of the black fly's lifecycle is variable, depending on the species and water and environmental temperatures, taking approximately in most of the cases 2 or 3 weeks in the tropics. Only female black flies feed on humans and other warm-blooded vertebrates as blood contains the necessary nutrients for egg development. The female flies lay their eggs on aquatic submerged or emergent substrates (trailing vegetation and rocks), and after 2–3 days, the larvae (which filter-feed on water microorganisms) emerge from eggs and anchor themselves to appropriate substrates. The larvae produce nonfeeding pupae in about a week, and a few days later, the black fly adults emerge. The females may live for as long as 3–4 weeks.

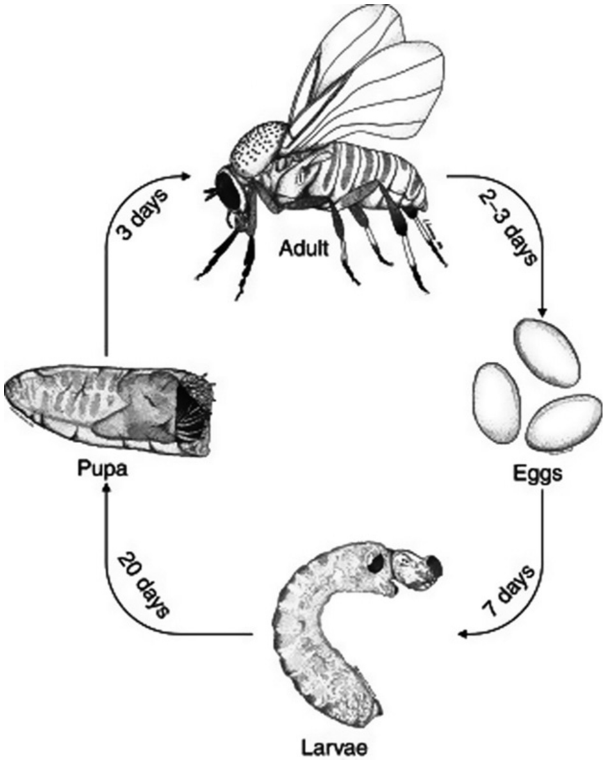

Figure 1 Lifecycle of *Simulium guianense* (illustration by Edmundo Guerrero).

Vector Bionomy and Transmission

Black flies are daytime biters, with host-seeking activity peaking around particular times of the day depending on the duration of the blood feeding and oviposition (egg-laying) cycles. Depending on intrinsic preferences and host availability, black flies obtain their blood meals, in a variable proportion, on human ('anthropophagy') and nonhuman ('zoophagy') hosts.

Black flies possess specialized mouthparts used to pierce the skin and ingest a blood meal containing microfilariae (the parasite stage infective to *Simulium*), which favors its role in onchocerciasis transmission. The relative abundance and biting density of different *Simulium* species may vary spatially, seasonally, daily, and hourly. Transmission intensity and onchocerciasis severity are the result of continuous exposure of individuals to *Simulium* bites. Consequently, quantification of host exposure (daily, monthly, and annually) is important for understanding the magnitude of transmission and the impact that control measures may effect on such transmission.

A high degree of anthropophagy and biting density may suggest given *Simulium* species as vectors of onchocerciasis but, additionally, the efficiency (known as vector competence) of such species in acquiring microfilariae, allowing their development to the infective stage, and surviving beyond this period is also important. A confirmed vector will be not only a competent experimental host for the parasite but also naturally infected with infective larvae indistinguishable from *O. volvulus*.

During the *Onchocerca–Simulium* interaction, a series of reciprocal effects on each other's survival at various stages of the parasite's lifecycle within the vector regulate the parasite population dynamics. As a result, the functional relationship between the number of microfilariae ingested for a given number of microfilariae in the skin and the number of infective larvae yielded within the black fly is a critical step in determining onchocerciasis transmission success. As an example, some species of *Simulium* vectors have a well-developed row(s) of sharp projections in the cibarium (a structure in the black fly's head) that may cause damage to ingested microfilariae, lowering the infective parasite yield and, consequently, rendering the vector less competent. Vectors with such 'cibarial armatures' however, may play an important vectorial role when their biting rates on humans are very high (as is the case of *S. ochraceum sensu lato* (s.l.) in Guatemala and *Simulium oyapockense* s.l. in the Amazonian focus). Since they destroy an important (but variable) proportion of ingested microfilariae, they suffer from lower levels of parasite-induced mortality but require higher densities of microfilariae in the skin to transmit successfully. By contrast, *Simulium* species with poorly or not at all developed cibarial armatures, such as *S. damnosum* s.l. in West Africa and *Simulium guianense* s.l. in the southern Venezuelan Amazonian focus, are often (but not always) more efficient vectors, playing important vectorial roles at lower biting rates and lower densities of microfilariae in human skin. However, if the parasite density in the skin is very high, the undamaged ingested microfilariae may induce high mortality in the flies, reducing the efficiency of transmission. (The word s.l. (broad sense) in the preceding text is used to denote that these vector species are in fact species complexes, including closely related, yet reproductively isolated but morphologically very similar species that can only be distinguished by cytogenetic and molecular genetics analyses and in a few cases morphologically.)

Vector density, vector competence, and vector survival are all important components of vectorial capacity, the latter parameter expressing the intensity of disease transmission in a particular space and season. However, the intensity of onchocerciasis transmission is usually estimated by measuring the annual biting rate (the number of bites potentially received by a person maximally exposed in a given locality), the annual infective biting rate (as above but calculated with the proportion of biting black flies harboring infective larvae), and the annual transmission potential (the average number of infective larvae potentially received by a maximally exposed person in a given locale).

The Lifecycle of *O. Volvulus*

The human population represents the only reservoir of human onchocerciasis. During an infective blood meal, the *Simulium* vector inoculates a third stage (L3) infective larvae *O. volvulus* through the wound produced by the black fly (Figure 2). These L3 larvae moult into L4 stage and develop within the human host into male and female adults that live in subcutaneous onchocercal nodules up to 10–13 years. Each year, the fertilized female worm may produce up to 0.5–1 million microfilariae that migrate typically to the skin but also to the blood, urine, and anterior chamber of the eye. When a black fly takes a blood meal from an infected person, it ingests microfilariae that migrate through the fly's abdomen to the thoracic muscles of the vector. In the fly's thorax, microfilariae first shorten and moult to become first stage (L1) larvae and subsequently moult into L2 larvae, which moult again into L3, infective larvae. Under tropical conditions of humidity and temperature, this takes place in about a week. Finally, the L3 larvae migrate to the head and mouthparts of the fly, becoming able to infect a new person when the fly takes another blood meal.

Onchocerca–Simulium Complexes

This close association between parasites and vectors has gradually developed into geographically and locally well-adapted *Onchocerca–Simulium* complexes. These complexes were first recognized in West Africa by cross-compatibility experimental infections of forest *S. damnosum* species with forest and savannah parasites, and savannah *S. damnosum* species with savannah and forest parasites. These studies revealed, across a series of bioclimes and localities, that Sudan-savannah *O. volvulus* developed

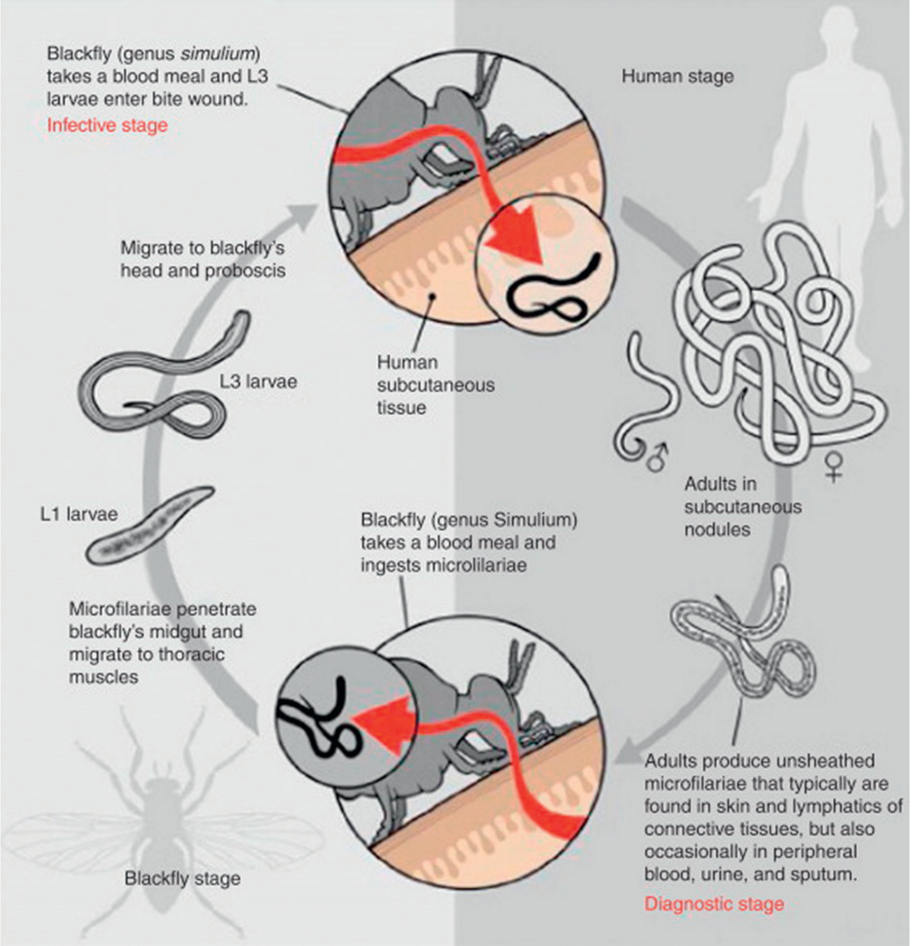

Figure 2 Lifecycle of *Onchocerca volvulus* (illustration by Giovanni Maki, derived from a CDC image at http://www.dpd.cdc.gov/dpdx/HTML/Filariasis.htm). From Basáñez MG, Pion SDS, Churcher TS, Breitling LP, Little MP, and Boussinesq M (2006) River blindness: A success story under threat? *PLoS Medicine* 3: e371.

very little or not at all in forest flies and *vice versa*. The existence of two parasite forms or 'strains,' transmitted by different vector species, and with different pathogenicity to the eye was later confirmed by experimental infections of the cornea of rabbits and by molecular biology (DNA sequence) methods. Cross-infection experiments also showed that West African parasites did not develop as well in Guatemalan and north Venezuelan vectors as did the local parasite populations. Similar differences between *Onchocerca–Simulium* complexes were noted between southern (Amazonian) and north-eastern Venezuelan foci of onchocerciasis. In an evolutionary context, host–parasite interactions are expected to result in geographical patterns of adaptations in which parasites are better able to infect their local host populations.

Focal Geographical Distribution of Latin American Foci

Local adaptation of parasites, black flies, and human populations most likely explains the focal geographical distribution of onchocerciasis in Latin America, where the parasite was probably imported from the African continent through the slave trade some centuries ago. Thirteen onchocerciasis foci have been described in Mexico, Guatemala, Colombia, Ecuador, Brazil, and Venezuela (**Figure 3**).

In Venezuela, there are three onchocerciasis foci: north-eastern, north-central, and southern or Amazonian focus. The last one comprises endemic areas in the rainforest of the Upper Caura and Upper Orinoco River region, affecting the indigenous Yanomami population and extending beyond the border with Brazil to join the Yanomami Brazilian focus. This is the largest focus in Latin America, with areas of high intensity of transmission and significant presence of severe ocular lesions and blindness before the start of mass treatment with ivermectin.

Figure 3 Focal geographical distribution of onchocerciasis foci in Latin America (illustration by Eric Calderón, derived from a figure prepared by the Onchocerciasis Elimination Program for the Americas (OEPA) (IACO, Inter American Conference on Onchocerciasis, 2006)).

Parasite, Vector, and Human Populations as Part of the Disease Ecosystem

The transmission dynamics of onchocerciasis takes place in several unique assemblages comprising parasite, vector, and human populations and their associated biota. Different landscape and ecosystem types are associated with distinct *Onchocerca–Simulium* complexes and, consequently, with different onchocerciasis transmission intensities, degrees of severity, clinical manifestations, and epidemiological patterns. In 1964, the Russian parasitologist Eugene Pavlovsky published a seminal book on the relationship between landscape and transmission dynamics of infectious diseases in which he formulated his theory of the natural focality of infections and stated that such diseases have a defined habitat preference, very much like a species. The parasite–vector–reservoir host of infection-associated biota system was denominated after Pavlovsky 'pathobiocoenoses' or natural nidi (foci) of disease. Dynamic equilibrium among different components of this complex system accounts for the existence of great heterogeneity in the intensity of infection, which, in turn, is determined by spatial heterogeneity and the mosaic structure of landscapes and ecosystems. Work by Duke in Africa and Dalmat in Guatemala in the late 1950s to early 1960s demonstrated the influence of environmental factors such as distance to vector-breeding sites and altitude above sea level (a.s.l.) on the risk of onchocerciasis infection.

Remote Sensing, Geographical Information Systems, and Landscape Epidemiology

Complex systems, such as vector-borne infections, require systemic approaches to further their understanding. Landscape or spatial epidemiology provides a holistic approach for the analysis of relationships between elements of physical and cultural environment involved in the risk of infection. This discipline has its roots in epidemiology and landscape ecology, and proposes that by identifying significant geomorphologic, climatic, biotic, and cultural features of a landscape or geographical area, as well as their seasonal changes, it is possible to predict spatial and temporal variations in exposure and the risk of infection. Landscape features have long been recognized as important determinants of transmission in malaria, onchocerciasis, and other vector-borne diseases.

Recent introduction of remote sensing (RS), global positioning systems (GPS), geographical information systems (GIS), and spatial statistics as tools for the analysis of the risk of vector-borne infections has allowed a fast development of landscape epidemiology or ecoepidemiology.

RS involves satellite technology including high-temporal-resolution satellites, which provide multitemporal climatologic (temperature and humidity) data, and multispectral medium- to high-spatial-resolution satellites, which provide accurate information about land cover. The GIS has the capacity to store and integrate georeferenced field (environmental, sociocultural, and epidemiological) data with climatologic and land cover information provided by satellite technology and display such data in thematic maps.

Initial application of these approaches for vector-borne diseases attempted to characterize and map vector habitats, usually working on a local scale. More recently, the focus has shifted to identifying and mapping landscape elements that collectively define vector and human population dynamics related to the risk of disease transmission, usually focusing on larger areas with lower resolution. The use of spatial analysis tools may allow to associate epidemiological variables (infection prevalence, intensity, and incidence) with landscape features (altitude, topography, geological substrate, and vegetation cover). Thus, environmental variables may help to predict spatially varying infection risk and establish priorities for control interventions.

A Case Study: Onchocerciasis in the Southern (Amazonian) Venezuelan Focus

The Environment: The Alto Orinoco-Casiquiare Reserve Biosphere

Transmission of onchocerciasis in the Venezuelan part of the Amazonian focus (straddling Venezuela and Brazil) takes place in the headwaters of the Caura and Paragua rivers, Bolivar State, and in the Alto Orinoco-Casiquiare Biosphere Reserve (AOCBR) (southeastern part of Amazonas State), the largest biosphere reserve (83 830 km^2) in the world in the intertropical region. This area that forms part of the Guianan Shield, of ancient origin (3600 million years), is composed by a complex mosaic of lithologic and geomorphologic units. According to the Venezuelan botanist Otto Huber, there are three main lithologic groups: an igneous–metamorphic basement (the Guianan Shield), a sedimentary cover (mainly the Roraima Group), and younger intrusive rocks of volcanic origin.

This complex lithologic mosaic and the ancient origin of the Guianan Shield, coupled with repeated cycles of erosion forces, resulted in a highly structured landscape in which the following units are recognized (Alto Orinoco-Casiquiare Reserve Biosphere Project/Ministry of Environment/Venezuela):

(a) sedimentary lowland river plains and peneplains (<200 m a.s.l.), corresponding to the plains and peneplains of the Orinoco river and lower course of its main affluent rivers, with geological basement composed of sand, clay, and sandy quartz;
(b) hill lands (200–600 m a.s.l.) with numerous rounded hills, undersubstrate made of igneous or volcanic basement rocks;
(c) valleys with alluvial sediments that are generally deeply incised river courses on upland plateaus, mountainous, or hill land areas;
(d) mountainous areas characterized by higher altitude and higher slope ground (slope of the Parima Mountains);
(e) upland plateau areas (600–1500 m a.s.l.) characterized by higher altitude and lower ground slope (Parima and Unturan Mountains);
(f) highland or 'tepuis' with flat-topped summits at altitudes between 2000 and 2600 m with vertical walls (escarpments) up to 1000 m long and peaks reaching up to 3000 m a.s.l. (Figure 4).

Onchocerciasis transmission occurs in the Upper Orinoco river basin. The Upper Orinoco extends from its source in the slope of Cerro Delgado Chalbaud in the Parima Mountains – close to the border with Brazil – to the mouth of the Casiquiare River that connects the Orinoco and the Amazonas Rivers. Main tributaries of the Orinoco in the Upper Orinoco Basin are the Cunucunuma, and the Padamo and Ocamo Rivers on the northern side (all three originating in the Parima Mountains), and the Mavaca River on the southern side (originating in the Unturán Mountains). The 360-km-long Siapa River has its headwaters in the Tapirapecó Mountains situated in the border with Brazil and is a tributary of the Casiquiare River. The Upper Siapa River is a nearly unexplored area where there is endemic onchocerciasis. The Caura and Erebato Rivers in the Bolivar state are both tributaries of the middle course of the Orinoco River. Their headwaters are located in the Maigualida Mountains, close to the border with the Amazonas State in Venezuela and Brazil.

Figure 4 Duida-Marahuaca 'tepui' with flat-topped summit in the lowland plains of the Orinoco river.

Lowland rainforest river plains (<200 m a.s.l.) and other landscape under 500 m a.s.l. present a macrothermic ombrophilous climate, with mean annual temperature >24 °C, more than 2000 mm of mean annual precipitation and <2 dry months in the year. Hill lands, mountains, and plateau areas above 500 m a.s.l. present submesothermic ombrophilous climate, with 18–24 °C of mean annual temperature and similarly more than 2000 mm of mean annual precipitation and <2 dry months in the year. The average rainfall increases from the north to the south and from the east to the west, reaching 4000 mm of annual rainfall in the southwestern part of the region (San Carlos de Rio Negro).

The complex geomorphologic and landscape mosaic of the AOCBR and the variety of climate regimens determine a great biodiversity of flora with striking endemic species. Forest cover accounts for 83% of the total surface area of Venezuelan Guayana. An altitudinal or orographic zonation of vegetation has been recognized, with different altitudinal vegetation cover: lowland and basimontane forest complex (<400 m a.s.l.), submontane and montane forest complex (400–1200 m a.s.l.), and savannah with shrubs (800–1200 m a.s.l.).

The Human Population and the Use of Space

The Yanomami

The AOCBR is the habitat of the Yanoama indigenous group, representing one of the last largest seminomadic ethnic groups living from the products of the rainforest. The human population afflicted by onchocerciasis belongs mainly to this ethnic group, which has more than 25 000 members and 4 very well-preserved linguistic subgroups in Venezuela and Brazil (Yanomami, Yanomam, Yanam, and Sanema). They live in the forest, scattered in more than 200 villages, practicing shifting cultivation, hunting, and gathering of forest products (Figure 5).

The Yanomami are the southernmost and largest Yanoama subgroup, numbering more than 10.000 people. The majority of their territory is situated within the Parima-Tapirapecó National Park, a large section of which was declared the biosphere reserve of Alto Orinoco-Casiquiare in 1991. At the time of the latest census, the total Yanoama population in Venezuela was 13 347 persons. Thus, they represent one of the most numerous indigenous group in the Amazonas State. Up until the first part of the twentieth century Yanomami population was concentrated mainly in the Parima highlands. Around that time, due to the increase in population they started to migrate in small groups towards the lowlands where they eventually have had the first sustained contacts with the missionaries in 1950s on the banks of the Orinoco River. Ever since then, the Yanomami experienced population decrease, accelerated culture change and increased dependency on western goods and food. At the present time, more traditional Yanomami communities are situated in remote mountainous regions close to headwaters of various rivers, whereas other communities that are situated in lowland river plains have had more permanent contact with western society and therefore in their increased dependency on western goods and technology. The neighbouring Sanema have had sustained contact with western society long before the Yanomami (referred by Humboldt when he visited La Esmeralda). Akin to the Yanomami from the lowlands who experienced major culture change and are now involved in various government health and education programmes, the Sanema are more stationary and less dependent on tropical forest products.

Venezuelan Yanomami and Sanemá occupy approximately more than 250 distinctive communal houses (known as *shaponos*). Approximately 11.427 Yanomami and Sanemá in 205 communal houses live in the onchocerciasis endemic area of the Venezuelan part of the Amazonian focus and are exposed to the risk of infection. The *shapono* is a large circular structure varying in size from 20 to 100 m in diameter (Figure 6).

A community can number between 20 and 200 inhabitants. Although it appears as one continual single structure, the *shapono* consists of a number of separate compartments (or separate 'houses'), covered with a leaf-thatched roof sloping from the outer edge toward the open circular clearing (central plaza). The central area is intended for festivities and other collective events such as

Figure 5 Yanomami population in the Amazonian focus of human onchocerciasis.

Figure 6 A communal house ('shapono') and two deforested areas for shifting slash and burn agriculture.

shamanic sessions and cremation ceremonies. The space under the *shapono's* roof is reserved for domestic activities whereby each family group occupies a specific hearth.

Each *shapono* is a sovereign whole, interlinked with other neighboring communities through a vast network of kinship ties. The intercommunal links between family members are based on marriage alliances and blood ties. Very often, neighboring communities stem from the same mother community. The suffix 'theri' after the name of each *shapono* means 'people of,' while the name itself indicates a certain geographical feature, animal, or plant (Smole, 1976).

Gardens (*hikari thë ka*) are situated within easy reach of each *shapono*. A section of the forest is cleared for gardening activities, first by the felling of large trees with axes, and then by burning of the undergrowth. Each family has its own garden section, which is cultivated exclusively by Yanomami men. The main crop consists of numerous trees of the banana family. The staple food is plantain (*kuratha*), a tree-like herbaceous tropical plant related to the banana family. The bulk of their meat supplies come from a wide range of wild animals, although it is generally agreed that their principal food supply (85% according to Chagnon, 1992) comes from cultivated food.

In their exploitation of natural resources, Yanomami use a network of established forest paths spreading out from the collective house and its garden area that tie together distinguished sites such as hunting and gathering camps, old gardens, and geographical features. Thus, the Yanomami ethnogeographic organization of space appears to be reticular and structured by a crisscrossing network of sites (points) and routes (lines). Crisscrossing this web of paths and places is another network made up of named rivers and streams, which constitutes another primary spatial reference.

Micro- and macromovements of villages and gardens

Yanomami are seminomadic people following two patterns of migrations: micro- and macromigrations. Micromigrations are short village movements that take place every 2–3 years and are caused by the need to establish new gardens or to replace the deteriorated roof of a collective house. Macromigrations, on the other hand, are long village movements caused by internal disputes and intercommunal warfare (Chagnon, 1992). Macromovements involve a major change of the place of residence and are the result of a complex pattern of alliances and conflicts that involve population increase, fission of communities, and dispersion into new areas. Once a village reaches a certain number of inhabitants, it will undergo a process of fission due to the increased internal disputes. Often these splinter groups will reunite with each other for protection against a common enemy. In addition to these patterns of migration, Yanomami are engaged in seasonal movements of hunting and food gathering (*wayumi*) as well as in regular visits to other shaponos for the purpose of exchanging trade items, attending funerary rituals, or visiting relatives. Micro- and macromovements, as well as the seasonal movements and visitations, expose the Yanomami to different landscapes and risks of onchocerciasis infection, providing connectivity between otherwise localized nodes of transmission.

The *Simulium* Vectors in the Amazonian Venezuelan Focus: A Multivector–Host System

Three main vectors of onchocerciasis have been recognized in the Amazonian focus of onchocerciasis based on their vector competence (as established by feeding experiments), biting rates on humans (as established by human-landing catches), and natural infection rates (as measured by fly dissection or other methods of parasite detection):

(a) *S. oyapockense* s.l. is the main vector in hypoendemic communities (with low intensity of transmission) located in the lowland forested plains of the Orinoco river and its main tributaries (<200 m a.s.l.). In this landscape, *S. oyapockense* s.l. is the dominant anthropophagic species, with relative abundance close to 100% and high biting density (mean daily biting rate = 1920 bites per person per day). This species possess a well-developed cibarial armature and damages a high proportion of ingested

Figure 7 Breeding site of *Simulium guianense* s.l.

microfilariae. As a consequence, it has a low vector competence. *S. oyapockense* s.l. breeds in large and perennial lowland rivers such as the Orinoco. The breeding sites are productive throughout the year, giving place to stable high-density adult-biting populations.

(b) *Simulium incrustatum* contributes to the transmission of onchocerciasis in mesoendemic and hyperendemic areas. Although *S. incrustatum* possesses an armed cibarium, it may destroy a lower number of microfilariae than *S. oyapockense* and partly as a result, it can yield an output of infective larvae significantly higher than that of the latter for a given number of microfilariae in the skin. Consequently, the vector competence of *S. incrustatum* and its survivorship once infected are higher than those of *S. oyapockense* s.l. This species may play a more important role in onchocerciasis transmission than previously thought. *S. incrustatum* breeds in smaller tributaries of highland rivers, being more susceptible to seasonal variation in river flow. Daily biting rates are higher in the drier months than in the rainy season. This species reaches its highest relative abundance in the Upper Ocamo plateau upland savannah area, between 800 and 1200 m a.s.l. In this geographical area most of communities are hyperendemic; *S. incrustatum* may be the only antropophilic biting simuliid present in the region, reaching high density biting rates ($>$ 3000 bites per person per day).(c) *S. guianense* s.l. lacks cibarial teeth and is the most efficient vector in the hyperendemic areas of the Upper Orinoco region in spite of its relatively low biting density. *S. guianense* s.l. is the dominant anthropophagic species during the transition between dry and wet seasons in the hill lands under volcanic substrate between 200 and 400 m a.s.l., with medium to high biting density (600–2500 bites per person per day) and in plateau upland savannah areas of the Parima Mountains with biting density between 100–500 bites per person per day. *S. guianense* s.l. breeds in rapids and waterfalls of clear-water rivers, surrounded by riparian forest lying between hill lands with undersubstrate of volcanic rocks (Figure 7). At least one of these breeding sites is localized very close to some of the most hyperendemic communities in the riverside of the Orinoquito River.

Geographical Patterns of Onchocerciasis in Southern Venezuela

The proportion of people with skin microfilariae of *O. volvulus* (prevalence of infection) and the intensity of infection (number of microfilariae per milligram of skin) reflect a number of factors related to:

(a) human behavior associated with a risk of exposure to infection (age, absence of clothes, subsistence activities, and movement patterns);
(b) human (immune) response to infection exposure;
(c) species of black flies present in the locality, biting density, and vector competence;
(d) landscape and environment in which the human–vector interaction takes place.

The prevalence of onchocerciasis in a community is stable through the years in a defined locality without treatment or intervention. However, it increases with age (Figure 8).

The relationship between prevalence and intensity of infection is nonlinear. In the southern Venezuelan focus, the intensity of infection increases with prevalence of infection up to 50 microfilariae mg^{-1} of skin. After this value, the prevalence reaches a plateau while the intensity of infection continues to increase up until 300 microfilariae mg^{-1} of skin (Figure 9). Those communities with prevalence of onchocerciasis $<$20% are classified as hypoendemic; those with prevalence $\geq$20% but lower than 60% are regarded as mesoendemic, and those communities with prevalence $\geq$60% are known as hyperendemic.

Hyperendemic communities are associated in all foci with increased risk of irreversible ocular lesions (cumulative inflammatory lesions in the cornea that do not regress but cause progression to eye damage and irrecoverable loss of vision). The prevalence of irreversible lesions is generally under 5% of the general population in nonhyperendemic communities (prevalence of

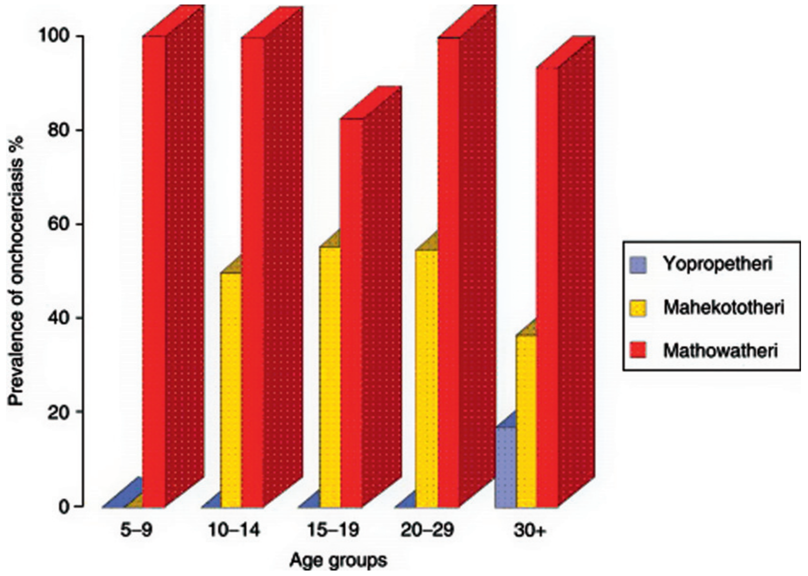

Figure 8 Prevalence of onchocerciasis by age group in hypoendemic (Yopropetheri), mesoendemic (Mahekototheri), and hyperendemic (Mathowatheri) communities of the Amazonian Venezuelan onchocerciasis focus.

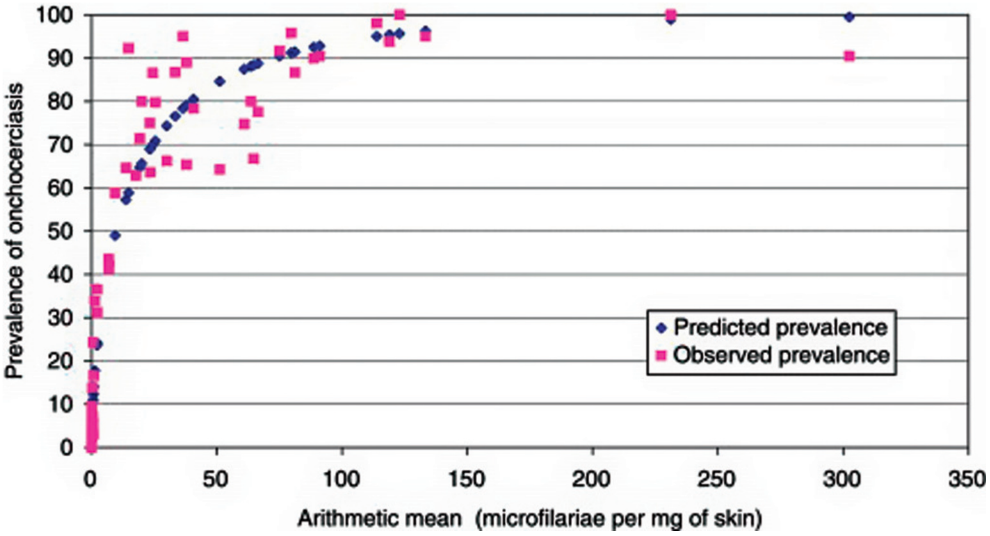

Figure 9 Relationship between the prevalence and the intensity of infection by *Onchocerca volvulus* microfilariae in the Amazonian focus.

onchocerciasis <60%) in foci from Guatemala, southern Venezuela, and West African savannah areas. However, in hyperendemic communities, the prevalence of irreversible ocular lesions increases in some foci of West Africa up to 25% of general population. In the southern Amazonian Venezuelan focus, this figure reached up to 18% in some communities before the introduction of regular mass ivermectin treatment.

Pretreatment observations from this focus showed that the prevalence of any onchocercal ocular lesions was greater than 50% and that of bilateral blindness was 1.4% of the population. Onchocercal cutaneous lesions were observed in 69.49% (papular onchodermatitis) and 13.56% (skin atrophy) of the whole population in hyperendemic communities. The impact on public health of onchocerciasis indicates that it is of outstanding importance to characterize the habitat of hyperendemic communities in order to predict the presence of severe ocular lesions.

A cline has been described in some river systems where infection prevalence increases with increasing altitude a.s.l. However, in other river systems, equivalent increases in altitude do not translate in increasing infection prevalence, suggesting that not only altitude and its associated changes in vector species, but also river-specific factors are important determinants of onchocerciasis risk. Using landscape epidemiology approach, GPS, and GIS, more than 60 Yanomami communities were georeferenced and mapped. Spatial and non spatial analysis showed that sociocultural and environmental variables (ethnic group, low index of cultural change, strong slope steepness, small river order, volcanic rock under-substrate and high biting density of *S. guianense*) were significantly associated with hyperendemic communities and related to certain types of landscape (hill lands, mountains, and plateaus). There is a clear geographical distribution pattern of hyperendemic onchocerciasis in the Upper Orinoco region, with clustering of hyperendemic communities on hill lands, mountainous, and plateau areas near the border with Brazil. Clustering of hypoendemic communities were observed along the main course of the Padamo and Mavaca Rivers and in the plains of the Orinoco River (Figure 10).

Different multivariate analysis methods showed clustering of hypoendemic communities in the lowland rainforest plains, with an undersubstrate of sand, clay, and sandy quartz, near the Orinoco River and its main tributaries (Figure 11), where the main vector is *S. oyapockense* s.l. In this kind of landscape, up to 65% of communities are hypoendemic.

Clustering of hyperendemic communities was observed in three types of landscape:

(a) Hill lands with undersubstrate of volcanic rocks between 200 and 400 m a.s.l., with macrothermic climate, in the slope of the Parima Mountains, with vigorous basimontane forest. The richness in nutrients of the parental rock and those received from the upper slopes, as well as the very humid macrothermic climate, probably explains the tall, dense, evergreen basimontane forest that predominates in this landscape. More than 90% of *Simulium* vectors collected in this area along several years have been *S. guianense* s.l., the main vector of onchocerciasis in the Amazonian focus, reaching high daily biting rates (up to 2500 bites/person/day). The majority of communities found in this kind of landscape are hyperendemic (Figure 12).

(b) Mountainous or plateau areas, with granite undersubstrate, at higher altitude and steepness of the slope ground, near smaller rivers with waterfalls. The soils are poor, and the climate is submesothermic (>18 °C mean annual temperature) with a pronounced dry period from December to March. The flora and vegetation are not uniform, with montane forest of medium to tall trees, semideciduous forest of smaller trees and shrubs, and open savannah areas with evergreen riparian or 'gallery forest' along the riversides. The most efficient vector in these hyperendemic areas is *S. guianense* s.l., reaching high relative abundance and medium simuliid biting density (Figure 13). (c) Forested and savannah Plateau highland areas in the Upper Ocamo river, where *S. incrustatum* is the most abundant antropophilic vector and may also play a relevant role the transmission of onchocerciasis. Most of the communities in this type of landscape are hyperendemic.

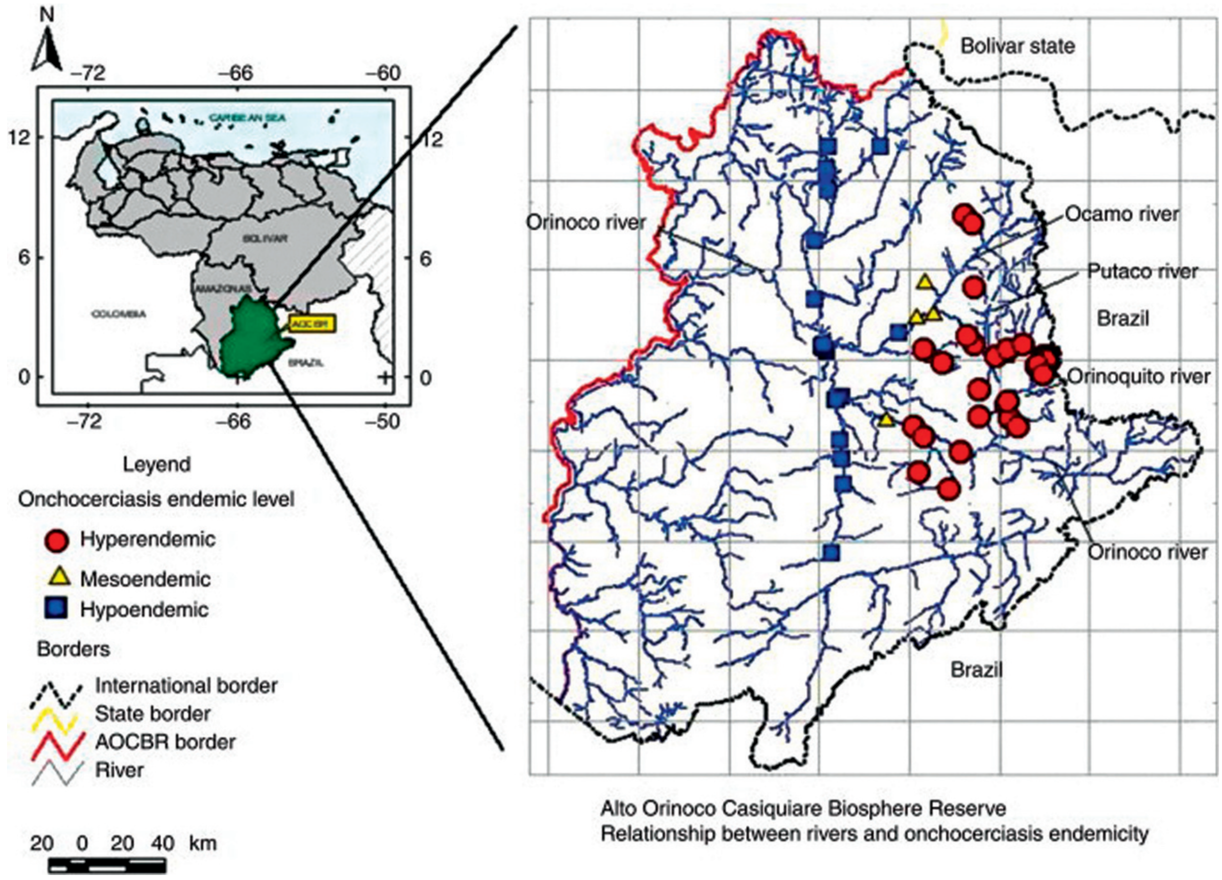

Figure 10 Geographical distribution of hypo-, meso-, and hyperendemic communities.

Figure 11 Lowland rainforest plains of the Orinoco river and its main tributaries.

Figure 12 Rainforest hill lands close to the main sentinel community of Coyowetheri (Orinoquito).

Figure 13 Upland plateau savannah area with gallery forest (800 m a.s.l.) (Parima Mountains).

Control Measures

The control strategy of the Onchocerciasis Elimination Program for the Americas is aimed at eliminating the eye disease produced by *O. volvulus* and interrupting its transmission where deemed possible through mass administration of ivermectin (a drug that kills the microfilariae and temporarily inhibits their production by the female adult worms) twice a year in all endemic areas in Latin

America. Regular ivermectin treatment reduces by more than 95% the numbers of microfilariae in the skin 2 months after treatment and reduces infection of the black flies (particularly of those with well-developed cibarial armatures, which are particularly less competent at lower levels of microfilariae in the skin). The strategy is based on evidence obtained in Guatemala and Ecuador where interruption of transmission has been accomplished after repeated ivermectin treatment rounds, with coverage (proportion of the population treated) higher than 85% of the eligible population. (It should be noted that in the areas of Guatemala and Ecuador where this has been achieved, the prevailing vectors, *S. ochraceum* s.l. and *S. quadrivittatum*, respectively, possess well-developed cibarial armatures.) This strategy has made it possible to interrupt transmission in 11 out of 13 onchocerciasis foci in Latin America. The Yanomami population in Brazil and in the southern Venezuelan focus (approximately 25.000 indivisuals) is now the only population at risk living in areas with persistent transmission of the infection in the American continent. In the southern Venezuelan focus, the 85% goal of coverage treatment with ivermectin was reached in the year 2006. In-depth epidemiological evaluations, conducted in 2008 in the hyperendemic upland savannah areas of the Parima Mountains in the border with Brazil, showed that infection intensity had decreased by 99%, and eye disease (due to corneal lesions induced by microfilarial death) by 96%. The persistence of infection prompted the program to introduce 3-monthly mass treatment in hyperendemic communities in an attempt to interrupt transmission in this geographical area. After four years of this treatment schedule onchocerciasis transmission was interrupted in centinel communities with the pretreatment highest level of transmission. However, the existence of isolated Yanomami communities without contact with the Venezuelan State, the seminomadic characteristics of the human population (providing connectivity between otherwise relatively isolated pockets of transmission), the multivector system of transmission, the variety of landscapes in which transmission can occur, and the extent of the geographical endemic area suggest that transmission will persist in the core of the Amazonian focus for some time, representing thus a continuing challenge for the elimination of onchocerciasis in the whole continent.

Concluding Remarks and Future Directions

In the Venezuelan part of the Amazonian focus, different landscapes associated with different *Onchocerca–Simulium* complexes and the human infection reservoir are associated with different infection intensities and risk levels. The specific environmental preferences of the *Simulium* vectors, and the migration patterns of the human population, determine locally and regionally the spatial and temporal distributions of parasites, vectors, and endemicity levels. Main sociocultural and environmental risk factors have been identified. On the whole, risk of onchocerciasis infection is higher in the Yanomami than in the Sanema. The risk of infection increases with age and duration of exposure and lower degree of cultural change. In different localities, the risk of infection is higher at peak biting density hours and during those months with higher monthly transmission potentials (e.g., the transition between dry and rainy seasons for areas where *S. guianense* s.l. is the prevailing species).

The relative risk of infection and of severe ocular lesions is significantly higher in certain types of landscape, characterized by key environmental variables. Among these, hill lands with undersubstrate of volcanic rocks at medium altitude (200–400 m a.s.l.) (associated with *S. guianense* s.l.), and mountainous and plateau landscapes with granite undersubstrate at higher altitudes (400–1200 m a.s.l.) (associated with *S. incrustatum* and *S. guianense*) are the landscapes with the highest intensity of infection and annual transmission potentials (highest risk of infection). Seasonal migrations as well as micro- and macromovements of the Yanomami population through different geographical areas and landscapes expose the human population to different risks of infection and provide an opportunity for the infection to persist. The heterogeneity in onchocerciasis transmission is associated with the mosaic structure of landscapes, the use of space and resources from the tropical rainforest by the Yanomami, and the diversity and complexity of a multivector system of transmission. Local ecoregional mapping using environmental and anthropic variables may be useful to predict onchocerciasis risk in isolated communities. Risk maps and remote sensors are making important contributions to predict the presence of indigenous communities without contact with the Venezuelan Health System in areas of high risk for hyper-endemic onchocerciasis.

In the Amazonian focus, onchocerciasis occurs in a network of interconnected nodes, the degree of connection depending on both vector and human movement, the latter being possibly more important or better documented. This spatial structure has important repercussions for onchocerciasis transmission and control, as some landscapes that by themselves may not be able to sustain endemic transmission may receive an important and periodic influx of heavily infected people from highly endemic areas that prevail in other types of landscapes, making it possible for otherwise relatively poor vectors to allow microfilariae of *O. volvulus* to complete their lifecycle successfully. This continual exchange of parasites between the different landscapes and their vectors, by virtue of human migration, will also weaken potential barriers to gene flow, such that the various *Onchocerca–Simulium* complexes will not become as differentiated as those, say, in West Africa. This may allow spread of onchocerciasis to currently nonendemic areas with susceptible black fly species, and also may call for spatially explicit and anthropology-based research avenues for onchocerciasis control.

The transport of *Onchocerca* parasites along the reticular nature of the Yanomami use of space may indeed be very diffusive, necessitating treatment in all landscapes, but if particular networks could be identified as being responsible for most transmission, a more targeted approach could be beneficial. Spatially explicit approaches to the understanding of onchocerciasis population dynamics and its control are very much an uncharted territory.

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