South Asian Journal of Parasitology

5(4): 29-44, 2021; Article no.SAJP.65039

Onchocerciasis in America: Venezuela One Step Away from its Elimination

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Somdet Srichairatanakool, Chiang Mai University, Thailand.
Reviewers:
(1) María del Carmen Marquetti Fernández, Cuba.
(2) Mara Ipa, Indonesia.
Complete Peer review History: https://www.sdiarticle4.com/review-history/65039

Review Article

Received 05 June 2021
Accepted 10 August 2021
Published 17 August 2021

ABSTRACT

Introduction: Onchocerciasis has been a threat to public health in the Americas for almost five centuries, affecting hundreds of thousands of people with the threat of severe dermatological conditions, visual impairment, and blindness. In Latin America, 13 foci of onchocerciasis were recognized, with 570,000 people at risk of infection by 2017.
Objective: To describe the progress of the onchocerciasis elimination programme for the Americas (OEPA) with emphasis on the experience of Venezuela.
Method: A literature review was developed, using databases: PubMed and Google Scholar, to identify articles published on the elimination process of onchocerciasis in America, finding 96 publications, including 14 documents from the World Health Organization and Pan American Health Organization.
Results: In the region of the Americas, the goal of eliminating onchocerciasis is close to happening, it has already been achieved in four of the six affected countries in the region: only Venezuela and Brazil continue to report transmission of the infection, in whose foci substantial progress has been made in interrupting transmission of the disease.

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Conclusions: Eliminating onchocerciasis in the South Focus of Venezuela and Amazonas-Roraima of Brazil constitutes the last step of this strategy. Changes to this strategy to achieve this included; the integration of the community to the distribution of treatment, the strengthening of the local health infrastructure, the design and implementation of operations research at the local level, financial sustainability and effective promotion.

Keywords: Onchocerciasis, elimination, America, ivermectin, Onchocerca volvulus.

1. INTRODUCTION

Onchocerciasis is part of Neglected Tropical Diseases (NTDs), [1] a group of 17 infectious pathologies that proliferate in ethnic minorities [2] and in conditions of poverty, especially in the tropical area [3]. It is the second world cause of infectious blindness [4] after trachoma [5]. It is present in 35 nations on three continents: Africa, America and Asia [6]. It mainly affects communities near rivers and fast-flowing streams [7], for which reason the disease is colloquially called "river blindness" [8].

Onchocerciasis is caused by the filarial nematode *Onchocerca volvulus* and transmitted through the bites of the Simulium black fly vectors [9].

Microfilariae were first discovered in 1874, almost 150 years ago, by John O'Neill, a British naval surgeon on the Gold Coast, Ghana, while examining skin cuts from so-called craw-craw patients suffering from dermatitis intense acute [10]. Patrick Manson in 1890 first identified microfilariae-releasing adult worms and in 1893 Rudolf Leuckart described their morphology of subcutaneous infestations as “Filaria volvuloxus”, now known as *Onchocerca volvulus* [11].

Microfilariae of *Onchocerca volvulus* are the main cause of the clinical manifestations of the disease, which include dermal manifestations and irreversible eye lesions that first result in impaired vision and finally total blindness [12]. The skin condition is the result of the migration of microfilariae from the subcutaneous nodules (onchocercomata), which harbor fertilized female and adult male filariae, into the adjacent skin. In the course of infection, an acute papular rash develops into a chronic papular dermatitis that may be associated with lichenification, development of papules, atrophy, and depigmentation. The skin manifestation may comprise so-called "leopard, elephant or lizard skin". In addition, edema and lymphadenopathy and the so-called "hanging groin" can occur [13].

Other pathogenic characteristics are the various neurological diseases, the nodding syndrome and epilepsy associated with autoimmunity [14,15,16], this association seems increasingly likely [17].

In 1993, the Onchocerciasis Elimination Program for the Americas (OEPA) was launched, a regional and international initiative [18] whose strategy is control (reduction of the incidence, prevalence, intensity, and morbidity and mortality) and elimination (reduction of the incidence of an infection to zero in a defined geographic area, with minimal risk of reintroduction) of the pathology [19]. In the past, vector control and nodulectomy were applied, but at present the intervention strategy is based on the massive administration of drug, in this case, ivermectin (available from 1987 with the donation of Mectizan® from Merck) in at least 85% of the population at risk of suffering from the disease [6].

Ivermectin is currently the only known safe and effective drug for mass treatment of onchocerciasis. However, it has limited macrofilaricidal activity, so treatments must be repeated for at least 12 to 15 years, which corresponds to the reproductive life of the adult worm when exposed to drug pressure [20].

The impact of massive treatment with ivermectin and supplemented with vector control in some countries has changed the global landscape of onchocerciasis. The elimination goal in the Americas was set in 2022, while for 12 African countries it is expected in 2030 [21]. Through the development, adjustment and optimization of control measures, transmission by the vector has been interrupted in foci of countries of the Americas (Colombia, Ecuador, and Mexico [6]), Uganda, Sudan, and elsewhere, followed by elimination of onchocerciasis [18].

Transmission in the Americas continues only in the Yanomami area, a large sparsely populated area in the Amazon rainforest, inhabited by the Yanomami indigenous people, comprising the

Amazonian focus of Brazil and the southern focus of Venezuela. This is an ecoepidemiologically unique approach with an at-risk population of approximately 35,000 people [22]. This area straddles the border between Venezuela and Brazil [23].

Given the proximity of the realization of this goal, set almost two decades ago, it is appropriate to describe the progress of the process of elimination of onchocerciasis in the Americas, with emphasis on the experience of Venezuela, since certain geographical and logistical factors have made it difficult to achieve that goal in less time.

2. METHODS

Between January and February 2021, a literature review was developed, using PubMed and Google Scholar as search engines and databases, to identify published articles on the elimination process of onchocerciasis in America. The following search terms were used for matches in title or topic: "onchocerciasis", "elimination of onchocerciasis in America", "elimination of onchocerciasis in Venezuela", "elimination of onchocerciasis in the southern focus". Of the articles found in the primary search, (22 publications) their bibliographic references were observed, searching for said full-text citations through the respective PubMed (PMC free article), CrossRef and Google Scholar links. Official documents of the WHO and PAHO that address the subject under study was included (14 documents). Opinion articles and editorials were excluded. A total of 96 publications in Spanish, English and Portuguese were included (Fig. 1).

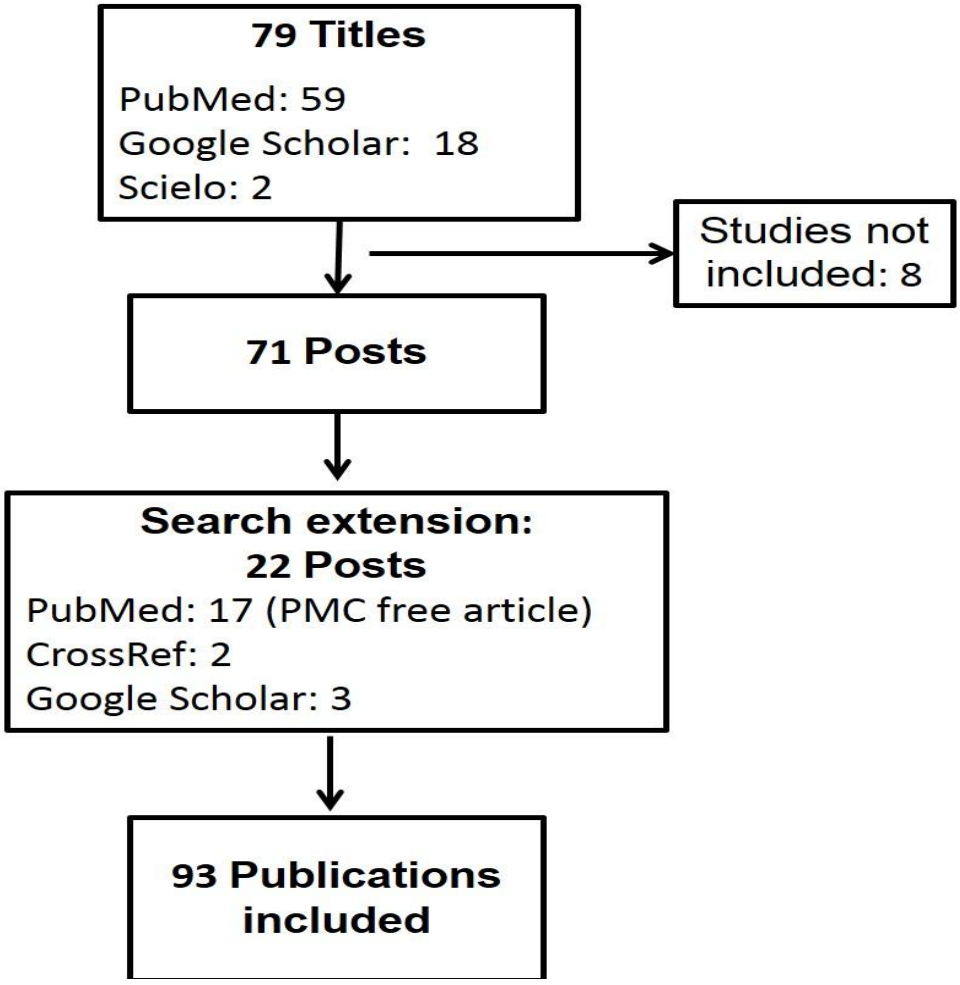

Fig. 1. Selection diagram of studies on elimination of onchocerciasis

3. RESULTADOS Y DISCUSION

3.1 Onchocercosis. General Considerations

Onchocerciasis, also known as river blindness, is an infection caused by the filarial nematode, *Onchocerca volvulus* [24]. It is transmitted by several species of the genus *Simulium*, known as the black fly [25]. Microfilariae (mf) induce the characteristic manifestations of the disease, including acute and chronic dermatitis and skin atrophy, lymphadenitis, and ocular fibrosis and inflammation that can lead to blindness.

The cutaneous manifestations have been well described by Murdoch et al [26]. which include: acute and chronic papular oncodermatitis, scratch marks, lichenification, and typical pigmentary skin changes known as leopard skin. The main ocular findings in onchocerciasis include changes in the cornea, such as sclerosing keratitis and snowflake opacities, torpid iritis characterized by typical pear-shaped deformity of the iris, secondary cataracts, choroidoretinopathy, and optic neuritis [27].

Diagnosis is usually made by direct visualization of the larvae emerging from superficial skin biopsies. In some cases, the mf can also be observed directly in the slit lamp as they migrate and remain in the anterior chamber of the eye [28].

Onchocerciasis came to the Americas through the slave trade. From the beginning of the 16th century, slaves from the highly endemic areas of West Africa were taken to Central and South America, carrying with them the parasite, which when finding suitable species of Simulium the infection was transmitted to the American indigenous population [29]. The spread of the disease through work and other migrations, and the presence of different vectors in the environment, explains the presence of onchocerciasis in Ecuador, Colombia, Guatemala, Mexico and Venezuela [30], and genetic tests for parasites confirm this link [31].

Given the impact of onchocerciasis in the Americas, it is not surprising that there has been critical early scientific research on the disease, conducted by a researcher from an affected country. Dr. Rodolfo Robles (1878-1939), a physician from Guatemala, who conducted studies in patients with onchocerciasis, which led to the discovery in 1915 that the disease was caused by *O. volvulus*. In recognition of this important contribution to research, onchocerciasis is also called “Robles disease” [32].

3.2 Onchocerciasis as a Public Health Problem in the World

The Global Burden of Disease Study estimated in 2017 that there were 20.9 million prevalent *O. volvulus* infections worldwide: 14.6 million of the infected people had skin disease and 1.15 million had vision loss [33]; therefore, onchocerciasis is considered the second infectious cause of blindness in the world, after trachoma [34]; representing a major public health problem in many parts of the world [35]. The disease is endemic in 31 countries in sub-Saharan Africa[33] and parts of Central and South America [35].

Onchocerciasis has been a threat to public health in the Americas for almost five centuries, affecting hundreds of thousands of people with the threat of severe dermatological conditions, visual impairment, and blindness [36]. In Latin America, 13 foci of onchocerciasis were prevalent, distributed in Brazil, Colombia, Ecuador, Guatemala, Mexico and Venezuela, where around 570,000 people were considered at risk of infection in 2017 [37].

Although rarely life-threatening, onchocerciasis causes chronic suffering and severe disability with approximately 1.5 million disability-adjusted life years (DALYs) lost each year due to this disease. Severe itching associated with the disease only accounts for 60% of these DALYs [38]. In some hyperendemic communities, every second infected person eventually goes blind [39].

3.3. Historical Management of Onchocerciasis

Treatment of onchocerciasis before 1990 was with a combination of diethylcarbamazine (DEC), also known as banocide for the microfilaria and suramin for the adult worm, but were subject to severe adverse events [40]. Massive nodulectomies were also performed, particularly in America. This made sense because the onchocerciasis variant in this region was often associated with a preponderance of nodules on the head, which theoretically made ocular injury more likely. However, the long-term effectiveness of this strategy is questionable, given that a study

carried out in Ecuador showed a reappearance of nodules in hyperendemic areas [41].

The fortuitous discovery of the microfilaricidal potential of ivermectin radically changed the possibility of controlling onchocerciasis by chemotherapy. In 1974 the team of Satoshi Omura et al. isolate an organism from the soil of a golf course near the town of Ito: *Streptomyces avermitilis,[42]* and they sent it to Merck, Sharp & Dohme (MSD) laboratories. William Campbell, took care of its evaluation and in 1975 in different soil samples sent, isolated and identified several derivatives of 16-membered macrocyclic lactone (known as avermectins) [43], which have high anthelmintic activity [44].

In 1981, ivermectin was marketed as a broad-spectrum anthelmintic drug in veterinary medicine, particularly for *Dirofilaria immitis* (dog heartworm). In 1982, MSD researchers reported activity against *O. volvulus* [45]. The immediate concern was whether ivermectin caused optic neuritis and secondary optic atrophy, as did DEC. A randomized controlled trial conducted in the state of Kaduna, Nigeria, compared ivermectin with placebo and found that there was a significant difference in the incidence of optic neuritis between the two groups [46]. The incidence ratio of optic neuritis (ivermectin versus placebo) was 0.90 (95% confidence interval [CI]: 0.54-1.51) for subjects with microfilarial loads of 0-10 mf per mg of skin and 0.52 (CI: 0.29-0.93) for subjects with more than 10 mf per mg of skin. This suggested that ivermectin reduced the incidence of optic neuritis in subjects with loads greater than 10 mf per mg of skin, but had little effect in those with lower loads. The implication was that sustained annual supply of ivermectin could prevent a substantial proportion of onchocercal blindness. In the same trial, it was established that ivermectin did not precipitate optic neuritis within 2 weeks after ingestion, as did DEC [47]. This trial and others [44,48] established the safety and efficacy of ivermectin.

Ivermectin is a drug that kills mf in the skin and temporarily inhibits mf release by adult worms [49]. Therefore, although it works quickly to reduce the amount of mf in the skin, it depletes mf for only a few months, after which mf reappears at levels 20% or more of the pre-treatment state within a year [50]. This microfilarial density appears to be sufficient for transmission to continue [51]. The reason for this rather limited effect of ivermectin is that it does not kill long-lived adult worms and that its embryocidal activity appears to be restricted mainly to the late stages of microfilarial development, leaving early embryogenesis intact [52]. Studies using albendazole showed only a very transient effect on early embryogenesis [50]. Thus, newly infected people would continue to enter the cycle of transmission, and elimination of onchocerciasis would remain a distant goal that could not be achieved without better medications [53].

America's experience with onchocerciasis has played a prominent role in the study of this disease throughout history [54]. In such a way that, Duke et al. [55], (who worked in America) were the first to raise the concept that repeated ivermectin treatments (two or 4 times a year) were partially macrofilaricidal. Furthermore, the long-term operational effect of repetitive treatments twice a year on survival and mating of adult worms in the Americas, showed that six-monthly treatments for 6 to 7 years with high coverage rates were equivalent to between 10 to 13 years of vector control [49]. Therefore, the elimination strategy has been based on safe and effective high treatment coverage for several years (due to the long life cycle of the adult parasite) and for more than one cycle per year [56].

This strategy of scaling up in the Americas region from one to two times per year of mass drug administration (MDA) began around the year 2000, based on a series of previous studies, first in Africa [57,58,59,60] and a 3-year pilot study in Guatemala [61], confirming the effectiveness of this regimen. This has allowed more than 500,000 people to no longer need ivermectin in the Americas and children born in 11 previously endemic foci in the last decade are free of the risk of onchocerciasis and its associated pathologies [62].

The mass distribution of ivermectin revolutionized the approach to onchocerciasis control at that time, and MDA has since been promoted toward other neglected tropical diseases [63].

While ivermectin monotherapy through MDA has had a positive impact on skin and eye morbidity and the incidence of blindness, these gains may be fragile due to the potential for drug resistance and the need for treatment sustained for up to 15 years [64].

In 1987, just before the publication of the first issue of the Community Eye Health Journal, the pharmaceutical company MSD made an unprecedented commitment to donate Mectizan® (Ivermectin MSD), for the time necessary to control onchocerciasis [65].

3.4 The Onchocerciasis Elimination Program in America

As Dadzie et al points out.,[66] onchocerciasis has long been the focus of attention in the international community, due to its associated morbidities, including blindness, skin diseases, and an association with childhood epilepsy [67].

OEPA's original goal was to reach a point where ivermectin treatment could be successfully and safely withdrawn. Given the encouraging progress in three of the six endemic countries at that time, the Annual Inter-American Conference on Onchocerciasis (IACO) in 1996 concluded that the development of internationally accepted standards for certification of the elimination of onchocerciasis transmission was urgently needed [68]. The Program Coordinating Committee (PCC) began to draft these criteria in 1997. This work included the conceptual control / elimination algorithm [66]. During the same period, President Jimmy Carter invited the then Director-General of WHO, Gro Harlem Brundtland, to lead this issue. WHO rejected the idea of having elimination guidelines that were only applicable to the Region of the Americas, and convened a consultative meeting in Geneva in 2000 to develop global guidelines that would involve experts from OEPA, the Onchocerciasis Control Program of Africa. West (OCP) and the African Onchocerciasis Control Program (APOC). OEPA-based algorithms later appeared in the first WHO Guidelines for Certification of Human Onchocerciasis Elimination: Criteria and Procedures [59].

Compared with much of Africa, onchocerciasis in the Americas was generally less severe. However, many American foci were hyperendemic for the disease due to extremely high annual bite rates of less efficient vectors (black flies) due to their cibarial armature in Guatemala and Mexico. However, *S. exiguum* in Ecuador has a vectorial capacity equivalent to that of the savanna *S. damnosum*, [70] and the hyperendemic communities in Ecuador had community reference prevalences greater than 90%, a situation very similar to that observed in most of the hyperendemic African communities. However, transmission of *O. volvulus* was eliminated in Ecuador after 9 years of treatment twice a year [71]. Around the same time that MDA was stopped in Ecuador, Diawara's 2009 study in Mali and Senegal proclaimed proof of the principle of elimination of onchocerciasis in Africa with mass treatment of ivermectin alone [72].

In 2000 the Onchocerciasis Elimination Program for the Americas began the use of twice yearly treatments with high coverage rates, and by doing so made possible the elimination of onchocerciasis in four of the six affected countries in the region: in 2013, Colombia, after 16 years of work [56], was the first country in the world where the WHO verified the elimination of onchocerciasis [56,73], followed by Ecuador in 2014 [71,74], Mexico in 2015 [75,76] and Guatemala in 2015 [77,78] verified by WHO in 2016 [78]. Only Venezuela and Brazil continue to report transmission of the infection, particularly deep in the Amazon rainforest, on their common border.

Although the risk of re-emergence of onchocerciasis or reintroduction in Colombia due to immigration of infected individuals is considered very low, given; a) the remote location of people, b) the transmission of onchocerciasis was eliminated in the Esmeraldas focus in Ecuador, the closest of the foci, and c) migration of infected persons from foci in Brazil and Venezuela seems highly unlikely. Nevertheless, surveillance has been established to detect any possible reintroduction and should be maintained until elimination of onchocerciasis is achieved throughout the Region of the Americas [56].

4. ONCHOCERCIASIS IN VENEZUELA

4.1 Historical Aspects

Onchocerciasis was first reported in Venezuela in 1948 in the Northeast region of the country. A short time later, a new focus was discovered in the North-Central region, and subsequently, a new transmission area was described in the southern region of Venezuela, bordering the focus of Brazil [79].

In 1982 the presence of the parasite was reported among the Sanemá indigenous people of Alto Caura, south of Bolívar State, and later the Alto Caura focus was described [80], which is part of the Amazon focus. The epidemiological,

parasitological, and entomological studies of human onchocerciasis in the State of Amazonas in Venezuela, initiated by Rassi, continued in detail starting in 1981 by the multidisciplinary team of the Amazon Center for Research and Control of Tropical Diseases "Simón Bolívar" (CAICET). This team began its investigations in the Sierra de Parima and the Alto Orinoco [81], to more recently explore and describe the characteristics and transmission of the disease along the Ocamo-Putaco, Orinoco-Orinoquito rivers [82], Padamo, Mavaca [83], and Siapa river [84,85].

4.2 North Focus

4.2.1 Geographic location

In Venezuela, the endemic area of the north is located in the mountainous area of the coast and is composed of two foci that are geographically separated but similar in their epidemiology, namely, the North-Central focus [86] and the North-Eastern focus [87] in the latter, the infection is transmitted by *Simulium metallicum* sensu lato Bellardis [88,89] and around 108,968 people of the rural population are at risk [90]. The North-Central focus [86] covers 6 administrative states (Fig. 2) and 45 endemic communities. The population at risk (14 835 individuals) corresponded to approximately 12% of the total population at risk in the country. The North-Eastern focus [87], on the contrary, it includes 3 administrative states (Fig. 2) but 465 endemic communities of approximately 94,583 inhabitants, corresponding to 79% of the total population at risk in the country. The residents of both endemic areas are mainly part of the rural population dedicated to agricultural activities [89].

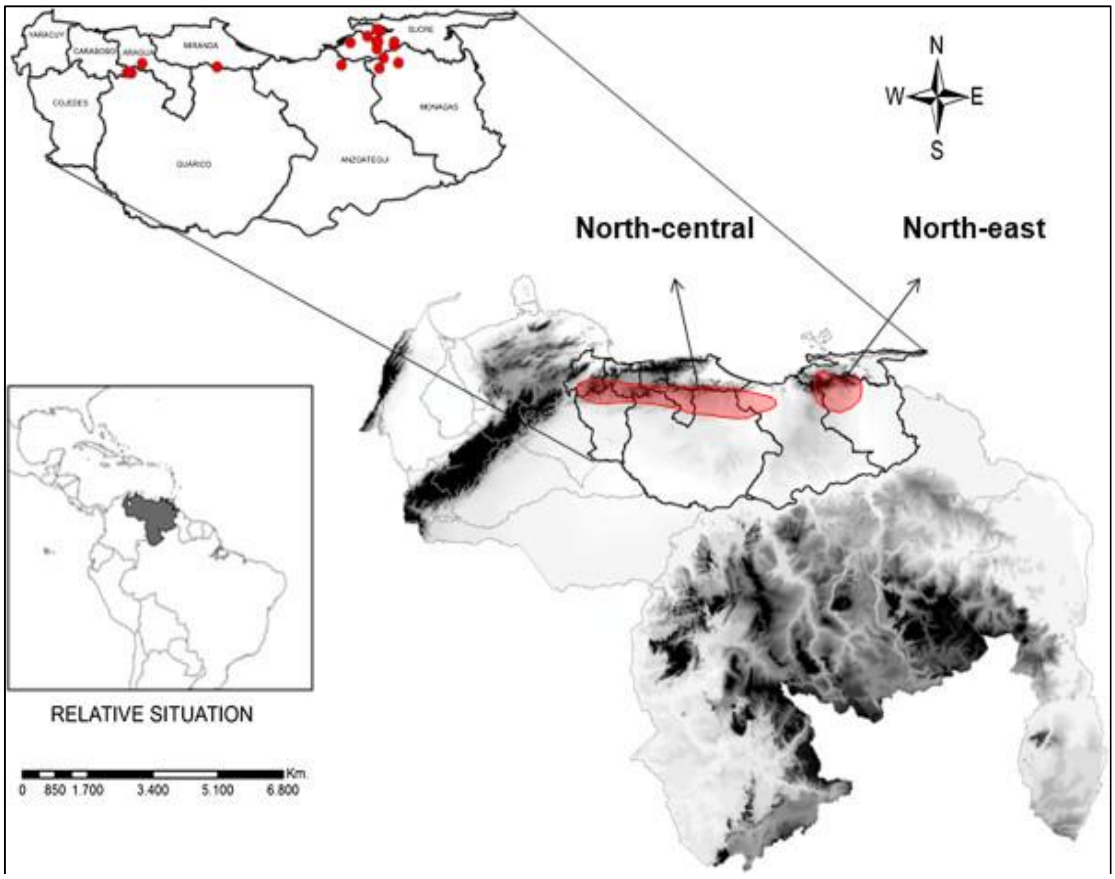

Fig. 2. Map of Venezuela showing the nine states where onchocerciasis has been endemic in the northern region of the country. The red areas on the map represent the two endemic foci. The red dots on the expanded states correspond to those communities (sentinel and extra-sentinel) where periodic comprehensive epidemiological evaluations (EEP) were carried out to monitor the impact of treatment on parasite transmission in both foci [91]

4.2.2 Achievements and progress

The results of the entomological evaluations carried out between 2007 and 2009 allowed the study of a total of 24 038 females of *S. metallicum* in sentinel and extra-sentinel communities, which when examined by PCR were negative for *O. volvulus* DNA. The results of the serological studies revealed that IgG4 Ov-16 antibodies were not being produced in the 2,089 children <15 years of age examined in the study communities after 8 to 10 years after MDA. Finally, the results of epidemiological surveys show that the prevalence of *O. volvulus* mf in the sentinel community represented a significant decrease from a 2% prevalence of mf in the skin and a geometric mean of 0.1 microfilariae per skin section in the community (CMFL) during 2001 at zero levels from 2005 onwards. These figures have maintained that level until 2010, when 20 rounds of treatment had been achieved. No prevalence of mf in the cornea (MFC) or prevalence of microfilariae in the anterior chamber of the eye (MFAC) were found among the inhabitants during 2010. Epidemiological studies showed that the prevalence of mf of *O. volvulus* in the focus (El community Piñal) decreased from a specific prevalence of 33.3% of mf in the skin to zero during 2012, after 24 rounds of treatment [91].

The prevalence of <1% mf of *O. volvulus* in the cornea and anterior chamber of the eye, as well as <1% of mf of *O. volvulus* in the skin, were the last criteria required by the WHO to confirm the interruption of the parasite in the 6 sentinel communities of both foci. In general, the entire population examined had <1 mf for skin and eyes in the years 2010 (North-Central Focus) and 2012 (North-Eastern Focus), respectively, with the exception of 3 communities in the North-Eastern focus. These last results were counted in 3 identified persons (one in each community) who left the communities and were absent from treatment during the last years of the MDA; therefore, particular control measures were applied to these people at the end of 2012. Currently, the findings obtained by Convit et al. [91] strongly suggest that neither eye nor skin diseases are attributable to *O. volvulus* infection in the northern area of Venezuela.

Convit et al.[91] have reported evidence of local interruption of *O. volvulus* transmission by *Simulium metallicum* in 510 endemic communities located in northern Venezuela after 10–12 continuous years of biannual ivermectin treatment. For this reason, they have asserted that onchocerciasis infection no longer represents a significant risk to public health in this endemic area.

Faced with this accumulation of evidence, the OEPA notified: in the North Central Focus, the transmission was eliminated in 2014; transmission was eliminated in the North-Eastern Focal in 2017. In the North Central Focal, no treatment was administered as of 2011, after verifying by epidemiological evaluations that transmission had been interrupted and 3 years after the post-epidemiological surveillance post-treatment, it was found that the transmission remained interrupted and therefore onchocerciasis had been eliminated. In the Northeast Focus, treatment was also stopped because it was found that transmission was interrupted after several rounds of treatment with good coverage [92].

4.3 South Focus

4.3.1 Epidemiology

The southern focus comprises endemic areas in the rainforest of the Alto Orinoco, Alto Siapa and Alto Caura basins (in Venezuelan Guiana), affecting the Yanomami indigenous group and extending beyond the border with Brazil to join the Brazilian Yanomami area to form the Amazon focus of onchocerciasis [93]. The Venezuelan part of the outbreak encompasses 12 geographic areas: Padamo; Ocamo, Mavaca; Banana plantation; Guaharibos; Orinoquito; Parima, Chalbaud, Ventuari; Uasadi, Caura and Siapa [94] (Fig. 3).

By 2019, according to data published by the OEPA, in the South Focus, there is a population at risk of 16,761 people distributed in 363 communities [92]. This is the largest focus by area in Latin America [74]. The Southern Focus shows an epidemiological spatial gradient, which includes areas of high intensity of transmission with substantial levels of skin and eye morbidity observed before the start of the elimination program. In the hyperendemic communities of the focus, skin disease was highly prevalent, with 24% of the population affected by lichenified oncodermatitis and 10% with skin atrophy [95]. The pre-treatment prevalence of oncho-proximal nodules, especially in the head, was 29%, reaching 51% in some communities (for example, in Orinoquito). Lymphatic lesions, including hanging groin, previously described in

Africa, have also been reported [81]. Similarly, ocular pathology (50% prevalence of punctate keratitis, and 75% prevalence of MFAC) was an important clinical manifestation attributable to onchocerciasis. In some hyperendemic communities in the Parima area, the prevalence of any ocular lesion associated with onchocerciasis was greater than 50%, reaching up to 70% in those individuals aged ≥40 years. The prevalence of irreversible eye injuries such as sclerosing keratitis (cumulative inflammatory lesions in the cornea that do not regress but cause progression to ocular damage and irrecoverable loss of vision) reached up to 17% in the Orinoquito area. Bilateral blindness due to onchocerciasis was observed in 0.45% of the general population [81].

4.3.2 Historical aspects of the Amazon Focus

In the Amazon Focus, the annual distribution of ivermectin began in 1993 only in a few communities and with a low average therapeutic coverage, less than 60% until 2000. As of that date, the onchocerciasis elimination program in Venezuela was reorganized drastically under OEPA's strategic plan and began semi-annual ivermectin treatment, with increasing coverage. The frequency of treatment increased further from two to four times a year in 45 communities during 2009 and currently, this quarterly treatment regimen has been extended to 192 of 241 (80%) of the endemic communities. This treatment approach was adopted to accelerate the interruption of transmission, that is, accelerate the death of adult worms, especially in areas with a very high density of vector bites, in communities whose prevalence and intensity of mf seemed to have reached a new level, or in communities that had recently been identified and incorporated into the program in later stages [94].

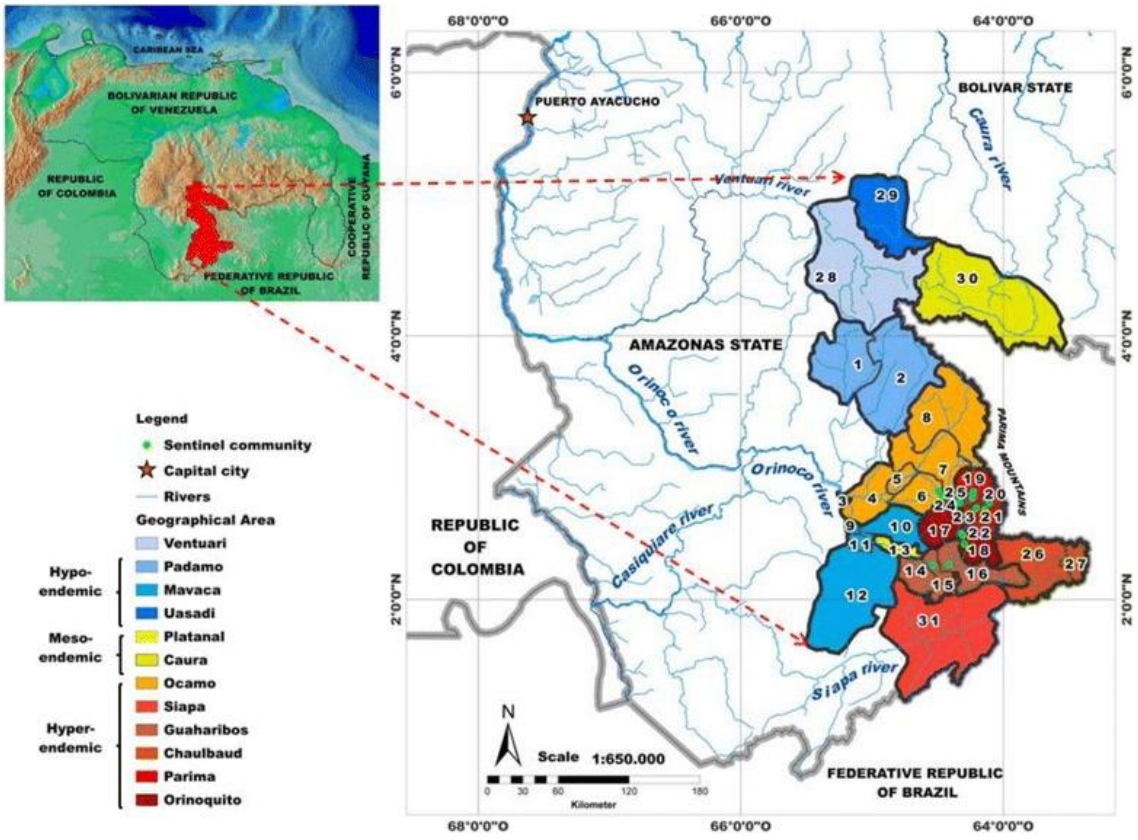

Fig. 3. Venezuelan part of the focus of Amazon onchocerciasis. The legend lists the 12 geographic areas of the outbreak colored by the basal endemicity of the infection by *O. volvulus*, from the lowest (light blue) in Ventuari to the highest (dark red) in Orinoquito [94]

4.3.3 Achievements and progress

The Southern Focus remains the only persistent focus of infection in Venezuela [74], and where OEPA has declared that the transmission continues [92].

As mentioned above, the WHO criteria to certify the focal interruption of parasite transmission are: absence or near absence of L3 larvae in the head of black fly vectors (measured by PCR), a 99% reduction in the intensity of transmission (measured by potential seasonal transmission), and the absence of detectable *O. volvulus* infection (by parasitological or immunological diagnosis) in children [69].

In this sense, the prevalence of *O. volvulus* mf in most communities decreased notably from pre-treatment levels. According to the results of the most recent epidemiological evaluation (2008–2009 for Awei and 2013–2015 for the rest), 8 out of 16 communities (Awei, Kanoshewë, Niayopë, Masiriki, Arokofita, Okiamo, Warapawë and Pokoshiprare) had zero mf in skin and eyes, and 7 of the 8 remaining communities had CMFL <1 mf / ss. There was also a notable decrease in the prevalence of CFM and the prevalence of CFM, with the prevalence of CFM decreasing to zero in 5 communities [94].

In contrast, the Hasupiwei, Pashopëka, Koyowë, Kakarama, Waharafitha, Matoa, Yaurawë and Toumawei communities still show mf in the skin and eyes, with a prevalence of CFM of up to 12%. Of these communities, the last four had a baseline prevalence of microfilaridermia ≥95% [94].

The results of the Ov-16 seroprevalence surveys carried out in 2013 by geographic sub area describe: 26 children aged 1 to 10 years (from 6 communities) were seropositive out of a total of 396 examined (6.6%; 95% CI 4.3 –9.5%). Most of the seropositive children (22/26, 85%) were grouped in 5 communities of the Orinoquito subzone. However, the prevalence for children aged 1 to 5 years was 1.8% (4/218), with only 3 communities (Koyowë, Matoa and Yaurawë) showing specific antibodies against *O. volvulus* for this age group [94].

Botto et al. [94] reports that these data suggest that before reaching the epidemiological state of interruption, the focus has begun to show a decrease to very low or negative parasitological results in the skin, eyes (indicators of reversible morbidity) and flies, which suggests that the treatment has suppressed the transmission of the infection. Reductions of 81% in fly infectivity and reductions of 97% in potential for seasonal transmission have been achieved, with an overall prevalence of 7% in Ov-16 seroprevalence among children up to 10 years of age and 2% among children under 5 years of age, providing evidence of suppression of *O. volvulus* transmission by the most competent vector of the outbreak, *S. guianenses*, in previously hyperendemic to holoendemic areas.

The semi-nomadic characteristics of the population, the remoteness of the Yanomami territory, the hologenic status of some areas and the continuous identification of new endemic communities in the Venezuelan part of the Amazon focus constitute the main challenges for the elimination of onchocerciasis in the Amazon focus.

The use of high spatial resolution satellite data to identify remote communities in the rainforest is a strategy currently used in an attempt to delineate the scope of the outbreak and the distribution of transmission zones.[93] At present, as a new strategy, Yanomami personnel have begun to be incorporated into the ivermectin distribution tasks, as well as the identification of new communities, this strategy has been implemented since 2019 with excellent results, which are still in progress.

5. CONCLUSIONS

Eliminating onchocerciasis in the South Focus of Venezuela and Amazonas-Roraima of Brazil is the last step to achieve the goal of elimination of onchocerciasis from the Americas.

The OEPA experience in the future will provide lessons on the real possibilities of eliminating a disease.

The impact of the massive administration of ivermectin has allowed that currently no new cases of blindness associated with onchocerciasis have been reported.

Key tools for meeting OEPA's objectives are the integration of the community into the distribution of treatment, the strengthening of the local health infrastructure, the design and implementation of operations research at the local level, financial sustainability and effective promotion.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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