UNIVERSITÉ DE MONTPELLIER
FACULTÉ DE MÉDECINE MONTPELLIER-NÎMES

THÈSE

Pour obtenir le titre de
DOCTEUR EN MÉDECINE

Présentée et soutenue publiquement
Par
Charlotte BOULLÉ

le 21 septembre 2021

TITRE

CARACTÉRISATION DU RISQUE D'EFFETS INDÉSIRABLES GRAVES LORS DU TRAITEMENT DE LA LOASE - IMPLICATIONS POUR LA PRATIQUE CLINIQUE ET EN SANTÉ PUBLIQUE

Directeur de thèse : Monsieur le Docteur Michel BOUSSINESQ

JURY

Monsieur le Professeur Éric DELAPORTE	Président du Jury
Monsieur le Professeur Vincent LE MOING	Assesseur
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Monsieur le Docteur Jacques GARDON	Membre Invité

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Remerciements

Aux membres de mon Jury :

Au Professeur Éric Delaporte,

A toi qui me connais et me fais confiance depuis maintenant tant d'années, toi qui m'as aidée à trouver ma voie dans la médecine, et sais te rendre toujours disponible, ma reconnaissance est immense, et je suis très touchée que tu aies accepté, après avoir dirigé ma thèse de sciences, de présider le Jury de ma thèse de Médecine,

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1 Introduction

Introduction

Dans ce premier chapitre, nous présenterons la problématique à laquelle nous nous sommes intéressés dans cette thèse, les objectifs des travaux réalisés et l'organisation du manuscrit.

1. Problématique

La loase (filariose à *Loa loa*) est souvent considérée comme une maladie bénigne mais les individus présentant une forte densité de stades larvaires du parasite (microfilaires) dans le sang risquent de développer une encéphalopathie après la prise de médicaments dits microfilaricides (c'est-à-dire détruisant les microfilaires), tels que la diéthylcarbamazine ou l'ivermectine. Les programmes de lutte contre l'onchocercose étant actuellement basés sur le traitement de masse des populations par ivermectine, ces événements indésirables graves entravent leur déploiement en Afrique centrale.

2. Objectifs

Ce travail vise à contribuer très modestement à une meilleure caractérisation du risque de survenue d'effets indésirables liés au traitement de la loase, afin d'aider à l'élaboration de stratégies de prise en charge optimales aux niveaux individuel et collectif. Plus précisément il s'agit de :

- **Mieux caractériser le niveau de risque individuel d'événement indésirable grave après traitement par ivermectine de sujets infectés par *Loa loa***

⇨ Article I : Étude de l'impact de facteurs individuels sur la modélisation du risque d'effet indésirable survenant après la prise d'ivermectine

- **Améliorer les critères d'imputabilité de l'ivermectine chez les sujets présentant un effet indésirable après traitement**

⇨ Article II : Étude de la possibilité d'inférer les charges microfilariennes pré-traitement à partir des valeurs mesurées après traitement (par exemple chez un sujet présentant un effet indésirable susceptible d'être dû à la prise du médicament)

3. Plan de la thèse

Cette thèse est composée de cinq chapitres principaux. Le corps de ce manuscrit de thèse sur article est rédigé en langue anglaise. Le chapitre 2 (*Background and key issues*) présente brièvement le cadre général des filarioses d'intérêt clinique, afin de resituer la problématique dans laquelle s'inscrit ce travail. Dans le chapitre 3, nous étudierons le risque individuel d'effet indésirable après traitement par ivermectine de sujets atteints de loase, afin d'améliorer la stratégie globale de prise en charge. Dans le chapitre 4, nous évaluerons dans quelle mesure la densité microfilarienne mesurée plusieurs jours après traitement permet d'évaluer la microfilarémie avant traitement, et donc la catégorie de risque dans laquelle se trouvait le patient. Cette évaluation permettrait de mieux apprécier l'imputabilité du médicament dans la survenue de l'effet indésirable, ce qui est essentiel dans le cadre des programmes de lutte basés sur les traitements de masse par ivermectine. Le chapitre 5 consistera en une courte conclusion, rédigée en langue française, mettant en perspective les résultats obtenus.

2 Background and key issues

Background and key issues

Over 1 billion people in the world are currently affected by at least one of the so-called Neglected Tropical Diseases (NTDs). Twenty of them are listed by the WHO as of 2021, all of which carry a heavy burden, in terms of health and economic consequences to those populations living in countries already affected by poverty. More than half of the NTDs are parasitic diseases, two of them being filariases (World Health Organization, 2020). The five most common NTDs are soil-transmitted helminthiasis, schistosomiasis, lymphatic filariasis, trachoma and onchocerciasis.

1. Filariases

Filariasis are caused by nematodes (roundworms) transmitted by arthropods (mainly insects). Among the human filariases, three (lymphatic filariasis, onchocerciasis and loiasis) induce significant morbidity while others are much less pathogenic (mansonellosis). Filariae infecting animals can also, exceptionally, be found in humans (e.g. *Dirofilaria repens* or *D. immitis*). Here, we will review the main features of the three major human filariases, as their intertwined characteristics and epidemiology need to be considered as a whole, in order to better understand the challenges they pose.

1.1. Lymphatic filariasis

Epidemiology

Lymphatic filariasis (LF) is the most widespread filariasis, which causes the greatest burden among parasitic diseases after malaria with more than 800 million people still exposed to the disease. Fifty-one million people were actually affected in 2018, 2/3 of them exhibiting chronic manifestations, in India, sub-Saharan Africa, Latin America and Caribbean islands, South-East Asia and Pacific islands (Figure 1). This figure represents a 74% decrease since the start of the WHO's Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 2000 (World Health Organization, 2020).

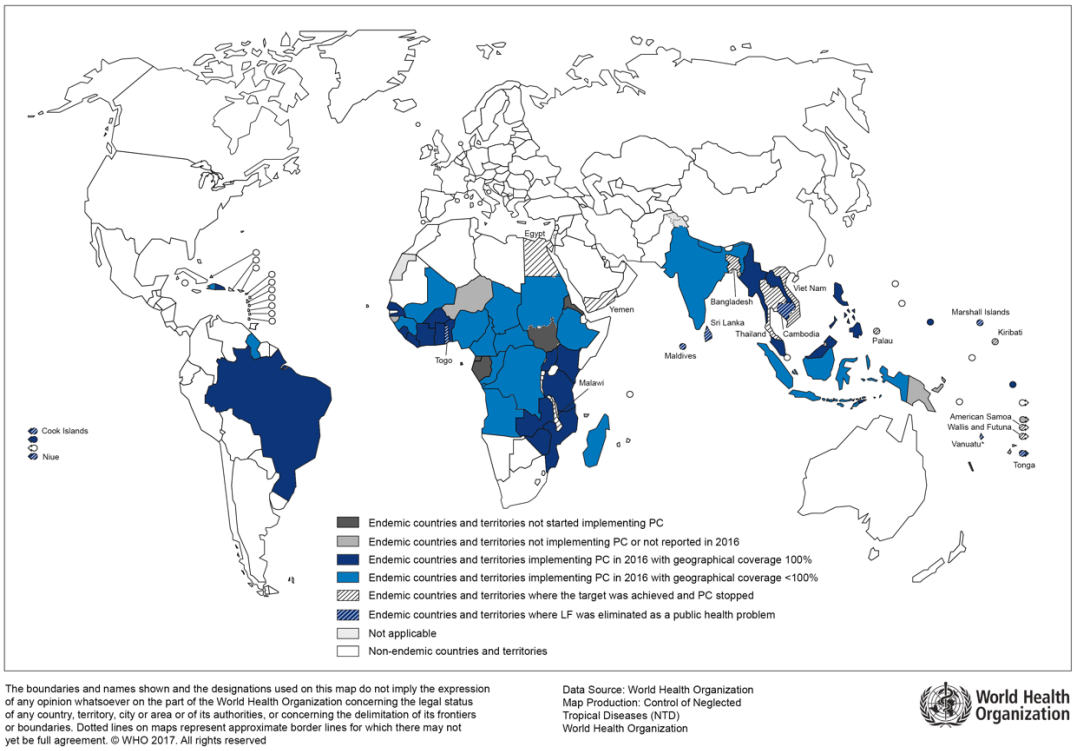

Figure 1. Distribution of lymphatic filariasis and status of preventive chemotherapy in endemic countries, 2016

Pathogenesis

LF is caused by parasites belonging to the genus *Wuchereria* (*W. bancrofti*) in 90% of cases or, in some southeast Asian countries, to the genus *Brugia* (*B. malayi, B. timori*). The parasites are transmitted by mosquitoes belonging, according to the country and the environment, to several genera: *Anopheles* (that have the highest vector competence), *Aedes*, *Culex* or *Mansonia*. Adult female worms are up to 10 cm long and have a mean lifespan of 4-12 years. Embryos (microfilariae, mf), are 300 μm long, have a mean lifespan of 10 months and live in the lymphatic vessels close to pulmonary capillaries and circulate at night in the peripheral blood from which they are harvested when the mosquito vector takes a blood meal. In their intermediary host, mf undergo two molts and evolve into third-stage larvae (L3) which are called "infective" once they have reached the mosquito's head. L3s transmitted to a new human host during a subsequent blood meal reach the lymphatic vessels where they evolve into L4 larvae and then adult worms. After insemination by male worms, the females will produce mf (Figure 2). The periodicity of mf in peripheral blood results from co-evolution with its vector species, explaining the usual nocturnal peak (10:00 pm –

2:00 am) of the microfilaraemia, which corresponds with the main vectors (*Anopheles*) biting period (in the Pacific islands, *W. bancrofti* is transmitted by *Aedes* which bite by day, and the periodicity is "diurnal subperiodic"). Interestingly, the fecundity of adult female worms is conditioned by endosymbiontic bacteria belonging to the *Wolbachia* genus.

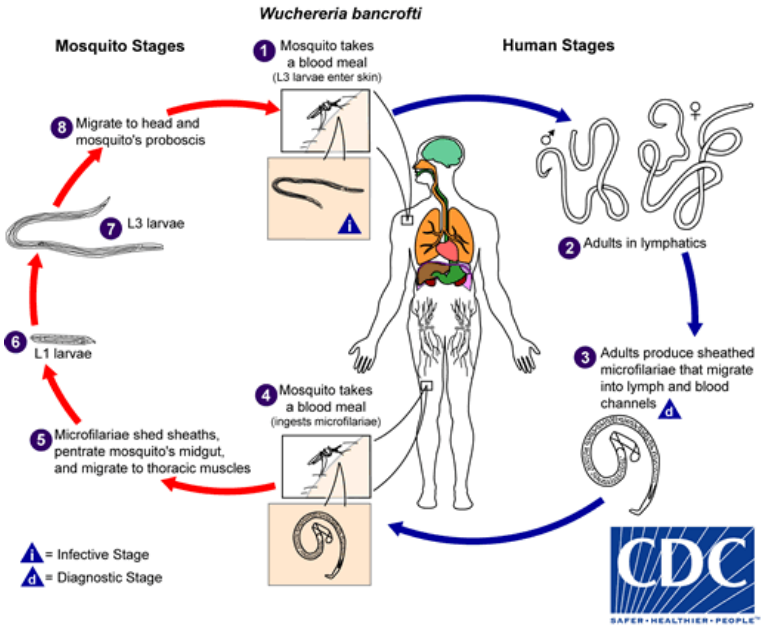

Figure 2. Life cycle of *Wuchereria bancrofti* within its intermediary and definitive hosts

Clinical features

Infected individuals are often asymptomatic. In the other case, the disease manifests as acute and chronic conditions (Figure 3).

Acute episodes last from a few days to more than a week, beginning within the months following the infection for genital manifestations such as scrotal lymphangitis or after one year for acute adenolymphangitis, affecting more frequently lower limbs in Africa, upper limbs in Oceania/French Polynesia (*W. bancrofti* var. *pacifica*), or popliteal fossa for those infected with *B. malayi*. Other manifestations include acute deep lymphangitis with fever, chest or abdominal pain, or acute superficial adenitis (inguinal, axillary). Filarial fever in the absence of lymphatic inflammation may also occur. Rarely, and mostly described in Asia, Brazil and Guyana, pulmonary manifestations under the form of feverish nocturnal asthma with weight loss occur, realizing the clinical picture called "tropical pulmonary eosinophilia" (TPE), which is characterized by a hypereosinophilia >3G/L, presence of eosinophils in the broncho-alveolar lavage fluid, and no

circulating mf (TPE results from a hypersensitivity reaction to the mf, which are opsonized with antifilarial antibodies, and then cleared from the circulation). Radiographs show increased broncho-vascular markings with a mottled appearance in the middle and lower lungs. Untreated, this condition evolves towards interstitial fibrosis and restrictive pulmonary disease. Acute conditions result from endothelial inflammation driven by adult worms.

Eventually, LF is most famous and feared for the chronic obstructions that follow the repetition of acute episodes, that are due to adult worms, resulting in hydrocele, lymphoedema, lymphatic varices, chyluria (as a consequence of pyelo-lymphatic fistula), among others.

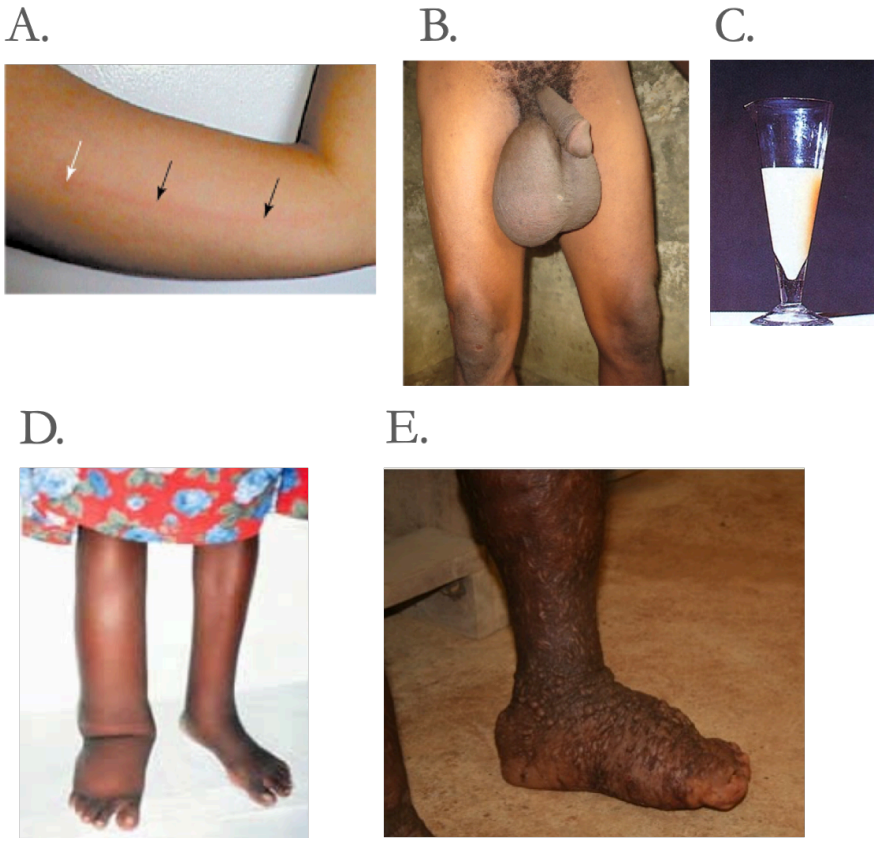

Figure 3. Clinical manifestations of lymphatic filariasis.

A. Acute lymphangitis. B. Hydrocele. C. Chyluria. D. Lower limb lymphedema. E. Elephantiasis

Diagnosis

Direct:

- **Gold standard**: detection of mf by microscopic examination of **calibrated thick blood smear** (TBS) or concentrated blood samples. The blood has to be collected at the time of high mf density, i.e. usually by night (10:00 pm to 2:00 am), or during the day in the Pacific

islands. Puncture fluid from an effusion can also be examined (without periodicity, since of lymphatic origin). Concentration methods can be applied to diagnose LF with low mf densities. Some individuals can present what is called an "occult filariasis", i.e., an infection without circulating mf.

- Visualization of motile live worms ("filarial dance sign") by ultrasonography of the scrotum, inguinal lymph nodes, or breasts.
- Exceptionally visualization of fragments of the adult worms on a lymph node biopsy (although this is not a recommended diagnostic procedure).

Indirect:

- Pan-filarial serology (does not allow for species diagnosis).
- Detection of circulating antigens of adult worms by ELISA or rapid diagnostic tests (RDT); the first widely used RDT (the immunochromatographic card test, ICT) has now been replaced by the Alere Filarial Test Strip (FTS) (Weil, Lammie and Weiss, 1997; Weil *et al.*, 2013; Chesnais *et al.*, 2017). Main drawback: cross-reactivity with false positive results in case of high infection with *L. loa*, warranting diurnal TBS to assess *L. loa* microfilaraemia, and/or examination of nocturnal TBS to search *W. bancrofti* mf (Bakajika *et al.*, 2014; Wanji *et al.*, 2015; Pion *et al.*, 2016; Hertz *et al.*, 2018).
- Detection of highly specific circulating antibodies (IgG4 anti-Ag Wb123) (Alhassan *et al.*, 2015).
- PCR used in research settings (Rao *et al.*, 2006).
- Moderate blood eosinophilia, raised during acute lymphangitic episodes.

In French travel medicine departments, usually only the TBS is available. Depending on the clinical presentation, ultrasonography can be useful (for instance in case of hydrocele).

Treatment

Sensitivity to antimicrobial drugs:

- **Doxycycline** (DOX): macrofilaricidal through its action on the endosymbiotic *Wolbachia* symbiotic bacteria necessary to adult worms' fertility and viability.
- **Diethylcarbamazine** (DEC): microfilaricidal, minor debated effect on adult worms.
- **Albendazole** (ALB): microfilaricidal, and partially embryotoxic.
- **Ivermectin** (IVM): microfilaricidal.

Recommended regimen:

Outside endemic areas, individual treatment is warranted for imported cases.

The optimal therapeutic regimen consists of 4 weeks (in the absence of clinical manifestations) or 6 weeks (in their presence) of DOX treatment (100 mg bid) followed by a single dose of DEC (6 mg/kg) after 3 months, respecting the usual contraindications. This is the only curative scheme leading to the elimination of the adult worms.

B. malayi infections can be cured by DOX (100 mg qd) for 6 weeks, followed by a single dose of DEC + ALB.

TPE (due to *W. bancrofti* or *B. malayi*) warrants treatment by DEC (2 mg/kg/8h) for 2-3 weeks. Retreatment may be necessary.

Programmatic considerations

LF caused by *W. bancrofti* is targeted for elimination as a public health problem and for worldwide eradication by annual mass treatment. Eradication of *Brugia* species is not achievable due to the proven existence of domestic and wild animal reservoirs. Since the beginning of the GPELF, 17 countries and territories are now acknowledged as having achieved elimination of LF as a public health problem. Five additional countries are under surveillance to demonstrate that elimination has been achieved on their territory. Eradication can be obtained through the obtention of prolonged interruption of the transmission in concerned areas. This is mainly achieved through the strategy of preventive chemotherapy with repeated mass drug administration (MDA), consisting in delivery of medication to all the population living in endemic areas, without prior individual diagnostic. Because drugs that can be administered as single doses lack activity on adult worms, treatment has to be prolonged over several years (in relation with the lifespan of adult worms), with good treatment coverage. Since the start of the GPELF, 20 years ago, MDA requirement has been lowered by 43%, 50 countries still require it, including 10 where the intervention has not yet been delivered once in some endemic areas. Economic benefits of the program were above 100 million dollars saved as of 2015 (World Health Organization, 2020).

The WHO recommends several MDA regimens, depending on the **co-endemicity** of lymphatic filariasis with **onchocerciasis** and **loiasis**. The choice is governed by the fact that the sensitivity to antifilarial drugs varies according to the filarial species and that some drugs can induce serious

adverse events in subjects infected with *O. volvulus* and/or *L. loa* (World Health Organization, 2021a). These issues will be further developed below (*see: Loiasis, treatment, p53*):

- In countries which are onchocerciasis- and loiasis-free:
  DA: DEC (6 mg/kg) + ALB (400 mg)
  or **IDA**: IVM (200 μg/kg) + DEC (6 mg/kg) + ALB (400 mg)
- In countries with onchocerciasis: **IA**: IVM (200 μg/kg) + ALB (400 mg)
- In areas co-endemic with loiasis: **ALB** (400 mg) alone twice a year (Pion *et al.*, 2017)

Recent evidence indicates that the combination of all three drugs can safely clear almost all mf from the blood of infected people within a few weeks, as opposed to years using the routine two-drug combinations (King *et al.*, 2018; King, Weil and Kazura, 2020), and thus that use of IDA may shorten the required duration of MDA to achieve similar interruption of transmission, in areas where it is feasible.

1.2. Onchocerciasis

Epidemiology

Before the launch of control programmes, an estimated 40 million individuals suffered from onchocerciasis, 99% of whom were living in sub-Saharan Africa (the rest living in small foci in Latin America and Yemen). The African repartition covers pre-Saharan Sahel to Angola and Tanzania. The disease, known as "river blindness" because of its major complication, carries an important morbidity burden, and has been shown to shorten life expectancy (Little *et al.*, 2004). The burden of onchocerciasis is estimated to be around 1.3 million DALYs (disability-adjusted life years). The Global Burden of Disease Study estimated in 2017 that there were 14.6 million people with skin disease and 1.15 million people with vision loss due to *O. volvulus* infections worldwide (World Health Organization, 2021b). Control programmes led to interruption of transmission in four Latin-American countries (Colombia, Ecuador, Mexico, and Guatemala).

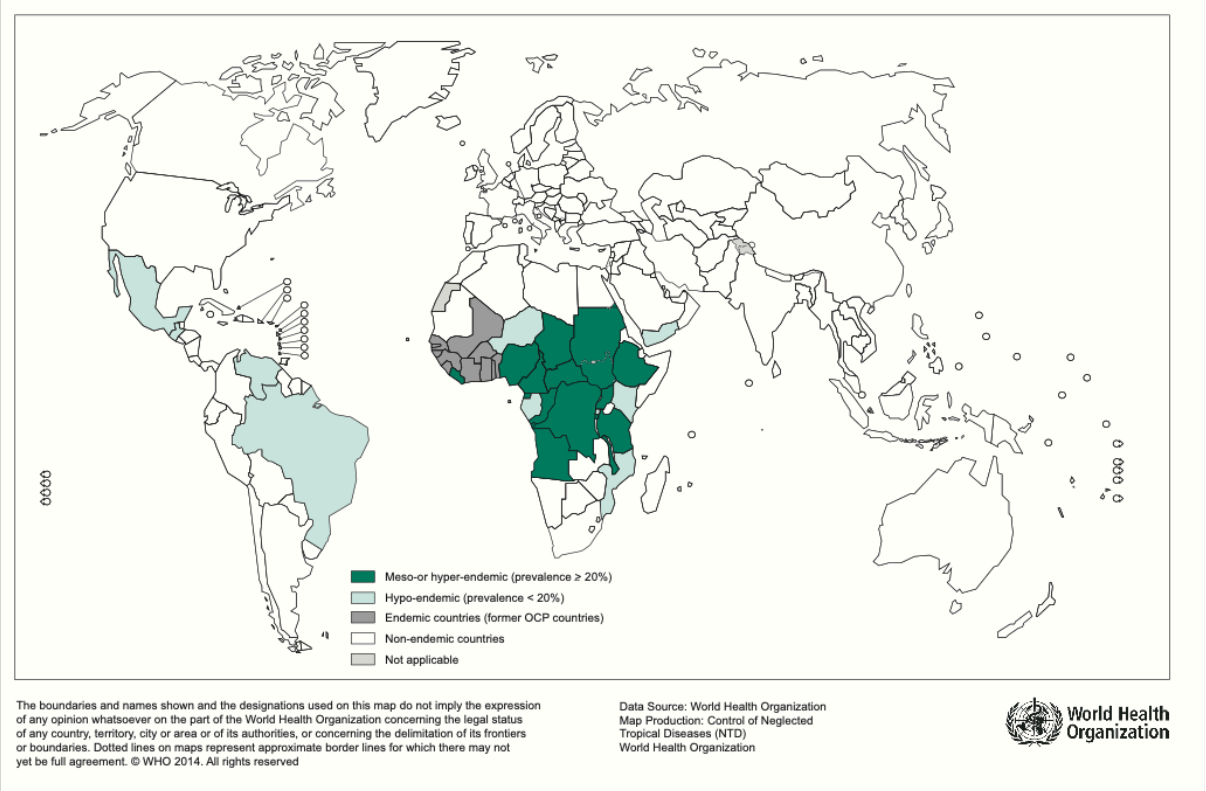

Figure 4. World-wide repartition of onchocerciasis endemic areas as of 2016

Pathogenesis

The causative agent, *Onchocerca volvulus*, is transmitted by black flies of the *Simulium* genus. Species belonging to the *S. damnosum* complex are the only vectors in West and Central Africa. In East Africa and some foci in the Democratic Republic of Congo, species belonging to the *S. neavei* complex can also transmit *O. volvulus*. As female black flies lay their eggs on rocks and vegetal supports present in fast-flowing rivers (larvae need oxygenated water), and as they can disperse from these breeding sites over 20-30 km, black flies' repartition tightly conditions the disease's area of endemicity. *Onchocerca* comes from the Greek words *onchos* (= hook or barb of an arrow) and *kerkos* (= tail) and thus means "hook-tailed", perhaps in reference to the copulatory spicules of the male adult worm[1]. Adult female worms live in subcutaneous fibrous palpable nodules, or in deeper nodules. Male worms are found in nodules but also migrate from nodule to nodule to inseminate the females. The latter can be 40 cm long and have a mean reproductive lifespan of 10-15 years.

[1] https://www.merriam-webster.com/dictionary/onchocerciasis

They produce unsheathed embryos (microfilariae), that spend their lifespan of 1-2 years in the dermis and in the ocular tissues where they generate damage from reactive inflammation.

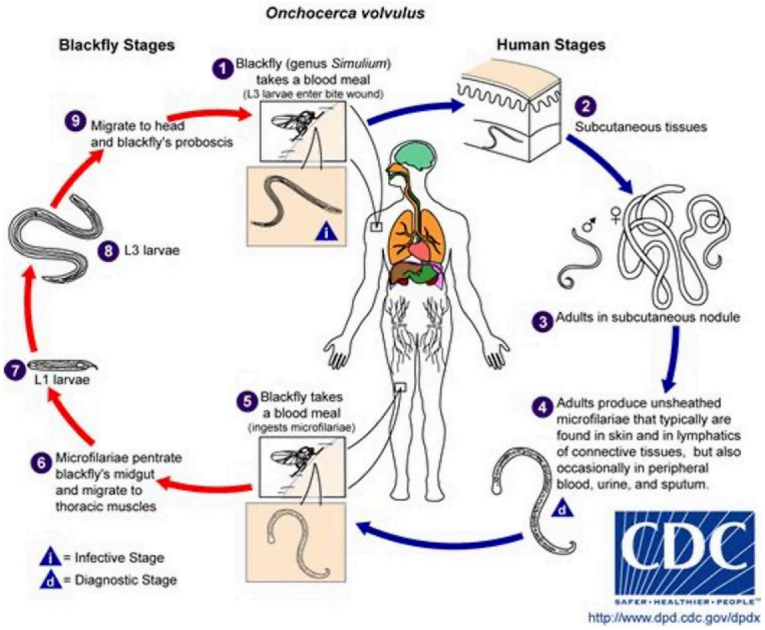

Figure 5. Life cycle of *Onchocerca volvulus* within its intermediary and definitive hosts

Clinical features

Asymptomatic carriers are frequent.

Clinical manifestations concern three main spheres (Figure 6):

Cutaneous manifestations (onchodermatitis): isolated intense pruritus, scratch lesions, prurigo, acute papular onchodermatitis (APOD, "gale filarienne") predominantly on the lumbar region, buttocks and thighs, evolving into chronic papular and lichenified onchodermatitis (CPOD and LOD), and skin atrophy. In elderly subjects, depigmentation of the shins forms the "onchocercal pseudovitiligo" or "leopard skin".

Onchocercomas or onchocercal nodules: in average, 1 to 3 per subject (sometimes up to 15), corresponding to the fibrous encapsulation of adult filariae. They are painless, hard or supple, fibrous, rolling under the finger and can be seen on bony prominences. Their most frequent locations are the trochanters, the iliac crests, the chest wall and sometimes the skull. In Latin America nodules are more often located on the skull and the shoulders and onchocerciasis is often called "Robles' disease".

Ocular manifestations: they are more frequent in savanna areas than in forest areas, and develop after 10 to 15 years of infection. The lesions, due to the immune reactions against the mf, are initially reversible but can lead to definitive blindness. Choroido-retinal lesions can induce night blindness and lesions of the optic nerve leading to visual field constriction. Anterior segment damage initially elicits punctate keratitis, progressing to sclerosing keratitis. Posterior segment involvement takes the form of atrophic and pigmentary choroido-retinitis.

Several atypic manifestations of onchocerciasis are worth to be mentioned:

- In Yemen, "sowda" describes the unilateral hyperreactive dermal involvement of a limb (Connor *et al.*, 1983).
- In expatriates, or visitors coming from non-endemic areas and exposed for the first time in adulthood, onchocerciasis can give a picture historically called "gros bras Camerounais" with swelling of a limb (usually an arm) with red and very pruritic papules, myalgias, and lymphadenopathy (Nozais *et al.*, 1997).
- Onchocerciasis-associated epilepsy have been first described in 1938 in Mexico (Casis Sacre, 1938). Recent studies, have confirmed this association in Africa (Chesnais *et al.*, 2018; Boullé *et al.*, 2019; Colebunders *et al.*, 2021).
- Onchocerciasis has also been associated with stunting, infantile dwarfism and "nodding syndrome" (growth retardation, brain atrophy and characteristic epileptic nodding episodes) (Dowell *et al.*, 2013).

Last but not least, it has been demonstrated that onchocerciasis with high microfilarial densities is associated with shortened life-expectancy (Little *et al.*, 2004).

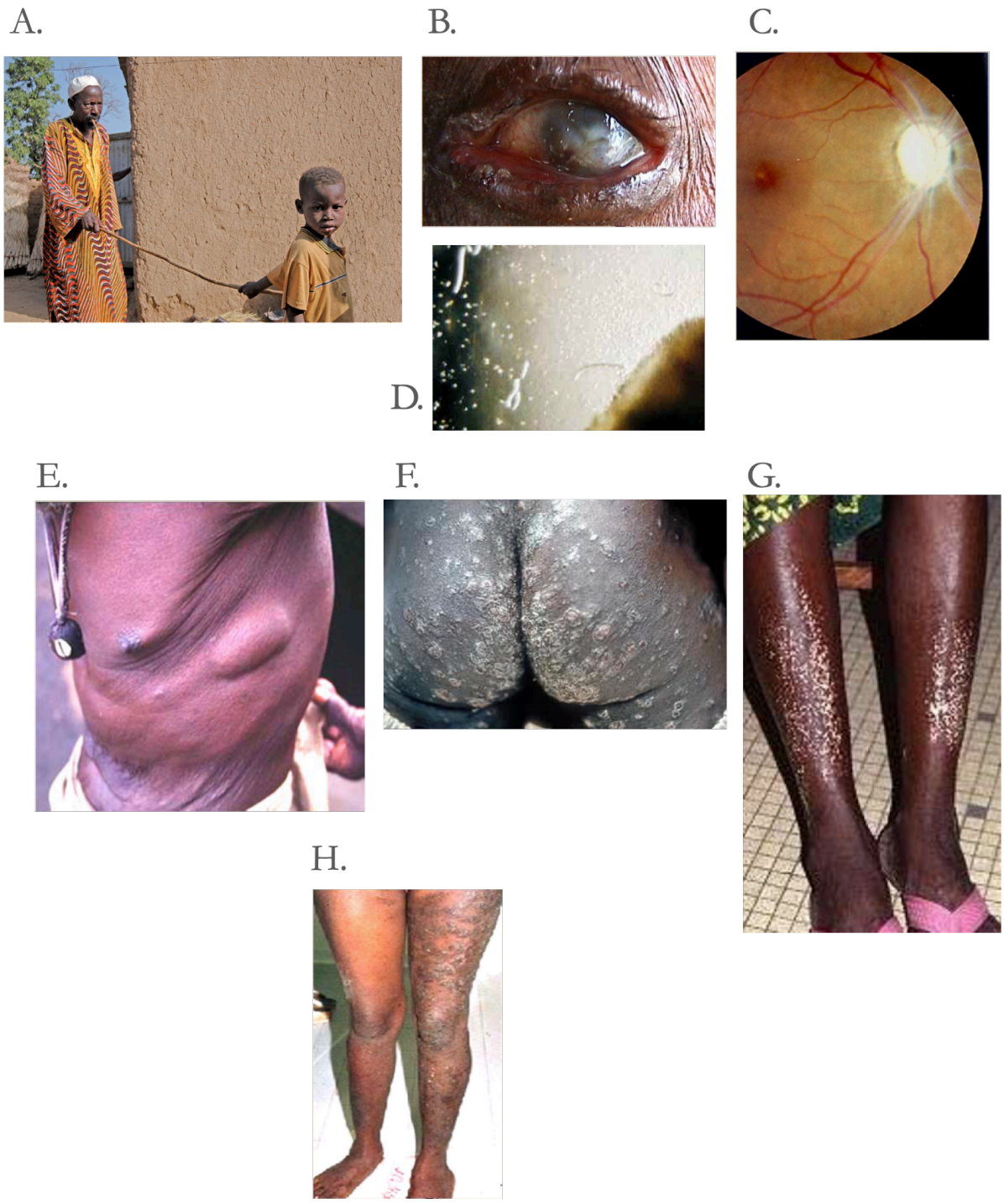

Figure 6. Clinical manifestations of onchocerciasis

A. Blind man guided by a child. B. Sclerosing keratitis. C. Optic nerve atrophy. D. Microfilariae in the anterior chamber of the eye seen at the slit lamp examination. E. Large nodule (onchocercoma) on the chest wall. F. Acute papular onchodermatitis with scratch lesions due to fierce pruritus. G. Typical bilateral depigmentation of the shins ("leopard skin"). H. Sowda.

Diagnosis

Clinical diagnosis can be made when specific manifestations occur in a subject coming or returning from an endemic area. In particular, nodules, depigmentation of the shins and the presence of microfilariae in the anterior chamber of the eye are all pathognomonic or very indicative signs.

Direct:

- **Gold standard**: examination of small skin biopsies (**skin snips**, 1-2 mm in diameter) taken using corneo-scleral punch from iliac crests and incubated for 24 hours in normal saline before counting mf in the incubation medium. Drawbacks: false negative results in case of low microfilaridermia; false positive results in case of concomitant high *L. loa* microfilarial density (MFD). The latter phenomenon could be due to the passage of *L. loa* mf from the capillaries to the dermis, or to the "trapping" within the snip of *L. loa* mf present in the dermal capillaries (mf are much larger than blood cells and while the latter are swept from the snip when the punch is closed – hence the bloodless specimen – the mf have a higher inertia and could stay in the dermal specimen). As *L. loa* and *O. volvulus* have a similar size, and as examination is made without staining (which would reveal the sheath in case of *L. loa* mf), *L. loa* mf can be wrongly identified as *O. volvulus* during reading (Niamsi-Emalio *et al.*, 2021).
- Slit lamp visualization of mf in the anterior chamber of the eye.

Indirect:

- Pan-filarial serology: does not allow for species diagnosis (cross-reactivity of *Dirofilaria immitis, Dipetalonema viteae, Wuchereria bancrofti, Onchocerca volvulus, Loa loa, Mansonella perstans*).
- Testing for specific antibodies directed against the Ov16 (*Onchocerca volvulus*) specific antigen. This can be done using RDT (Alere IgG4 Ov16) or ELISA (Steel *et al.*, 2015). Sensitivity and specificity are still being evaluated in the field.
- PCR are not widely available, and mostly used in research settings.
- Elevated hypereosinophilia.
- Historically, an oral test dose of 50 mg DEC "Mazzotti test" causing a typical cutaneous reaction, and sometimes severe general reactions, was used. This test is dangerous and no longer used.

In practice, in travel medicine clinics in France: in front of typical manifestations in travelers returning from endemic areas or migrant originating from endemic areas:

1. Skin snip + slit lamp examination
2. If negative: Pan-filarial serology +/- IgG4 Ov16 RDT upon availability
3. Diurnal TBS (10:00 am – 2:00 pm for *L. loa* MFD determination if area is co-endemic)
4. If *L. loa* MFD >10,000 mf/mL: consider biopsy coloration/PCR to confirm that mf in the incubation medium were *O. volvulus* mf and not *L. loa* mf.

Treatment

Sensitivity to antimicrobial drugs:

- **IVM**: microfilaricidal, causing mf paralysis, at the posology of 150-200 µg/kg, resulting in lowering of mf densities for up to 2-3 months. In recently infected adults with swelling of a limb, a 3-4 days course of corticosteroids may be warranted to avoid a painful exacerbation of the edema. IVM is also embryostatic (blocking the release of new mf by the female worms during 3-4 months). It is not macrofilaricidal (it does not kill the adult worms rapidly) (Basáñez *et al.*, 2008), but repeated treatment reduce the adult worms' lifespan (Walker *et al.*, 2017).
- **DOX**: macrofilaricidal. Through killing the symbiotic *Wolbachia* allows the destruction of adult worms. No effect on the mf.
- **Moxidectin**: Under evaluation. Labeled for adults (Opoku *et al.*, 2018).
- **DEC**: no longer used in this indication, due to risk of eye damage among other side effects (fierce pruritus, fever, requiring co-prescription of antihistaminic or corticosteroids). Strongly microfilaricidal but no action on adult worms.
- **ALB**: poor efficacy, not used in this indication.

Outside endemic areas, when diagnostic is confirmed, optimal regimen currently consists of **6 weeks DOX (100 mg bid)**. As the mf are the pathogenic stage of the parasite, a single dose of IVM (200 µg/kg) should be proposed before or after the course of DOX (if *L. loa* MFD <30,000 mf/ml).

In case of DOX contraindication, alternative strategy is suspensory IVM (200 µg/kg) repeated every 3 months.

Subcutaneous nodules can be removed surgically to lower the adult worm burden (that produce up to a billion mf/year/female worm).

Programmatic considerations

Onchocerciasis is targeted for global **eradication**, as the parasite is strictly human. Similarly to the strategy described above for LF eradication, one of the cornerstones of the strategy is MDA. Vector control strategies have also been used, including use of larvicides, which we will not detail here.
Onchocerciasis control has been carried out under the aegis of two major programmes: the Onchocerciasis Control Programme in West Africa (OCP) from 1974 to 2002, and the African Programme for Onchocerciasis Control (APOC) for all countries located outside the OCP area from 1995 to 2015. From 2015 ESPEN (Expanded Special Project for Elimination of NTDs) has taken over in an effort to reunite and concentrate the efforts to end the global NTDs burden, including that caused by onchocerciasis and lymphatic filariasis. Great achievements have been made by these control programmes (Figure 7), which have led to the elimination of the disease as a public health problem in most endemic areas and sometimes to the elimination of the infection (from the whole national territory for Columbia, Ecuador, Guatemala and Mexico, Guatemala, or some foci in Western Africa (Diawara *et al.*, 2009; Traore *et al.*, 2012). For MDA, drugs that can be taken as single dose are required for feasibility reasons. Therefore, the MDA strategy involves annual (or in some areas bi-annual) distribution of ivermectin, for which the drug is being provided for free since 1987 through the manufacturer's donation program (Merck & Co., Inc. and its Mectizan® Donation Program, respectively). To reduce costs and reach further goals in therapeutic coverage, a community-based approach has been developed, called Community Directed Treatment with Ivermectin (CDTI). Unfortunately, APOC has soon been slowed down in its roll-out because of the problems raised by loiasis co-endemicity (Figure 8), and the serious adverse events that were seen in this context (*see: Loiasis, treatment p.53*) thereby compromising, elimination of onchocerciasis in these areas.

In order to move forward in Central Africa, at the programmatic level, the level of onchocerciasis endemicity has been mapped using the Rapid Epidemiological Assessment (REA) method based on the prevalence of nodules in adults aged >20 years, and the Rapid Epidemiological Mapping of Onchocerciasis (REMO) strategy to select the villages to be surveyed and extrapolate the REA results to the whole foci (Noma *et al.*, 2002). This allows a correspondence of nodule prevalence

with the three endemicity levels defining levels of clinical burden for populations (Prost, Hervouet and Thylefors, 1979):

- >40%, corresponding to hyperendemic areas (microfilaridermia ≥ 60%)
- 20-40%, corresponding to mesoendemic areas (microfilaridermia 35-60%)
- <20%, corresponding to hypoendemic areas (microfilaridermia <35%)

When APOC was launched in 1995, the objective of the programme was to eliminate onchocerciasis as a public health problem, and thus to restrict the CDTI to those areas where onchocerciasis was hyper- or mesoendemic. In case of coendemicity with loiasis, APOC and the MDP recommended to put in place a specific surveillance system for early identification and management of severe adverse events (SAEs). When it appeared that repeated CTDI could achieve elimination of onchocerciasis, treatment of onchocerciasis hypoendemic areas was considered, to accelerate the elimination of the infection (and not only of its clinical manifestations). In hypoendemic areas of Central Africa where loiasis is coendemic, the risk of SAEs outweighs the benefit of treatment and alternative treatment strategies (ATS) are required (Boussinesq, Fobi and Kuesel, 2018). Several ATS are being developed or evaluated for onchocerciasis, but none has been endorsed by the WHO yet. Among possible interventions, we can describe the "Loa-first TNT strategy" (Test and- or not Treat), where screening of *L. loa* hypermicrofilaremic subjects using the LoaScope portable diagnostic tool (*see: Loiasis, diagnostic p53*) enables to identify hypermicrofilaremic individuals (MFD>20,000 mf/mL) and exclude them from ivermectin treatment, while the rest of the community can be safely treated (Kamgno *et al.*, 2017; Lenk *et al.*, 2020). An "Oncho-first TNT" strategy would consist of the following sequence: 1) search for *O. volvulus* infection, 2) in those positive, determine *L. loa* MFD by LoaScope, 3) treat or not treat with ivermectin and/or a macrofilaricidal course of doxycycline. The main obstacle to its implementation is the method to be applied to diagnose onchocerciasis. Currently, it relies on relatively invasive skin snips, requiring trained technicians, and whose use for hypoendemic areas at such a large scale is ethically questionable. The alternative is IgG4 Ov16 RDT mentioned above, but, like all serologic methods, it cannot distinguish an active and a past infection, and issues regarding its sensitivity and specificity still exist. Treatment with doxycycline requires 5-week bi-daily treatment and pregnancy testing for women, and this is not deemed feasible at a large scale except if the proportion of subjects infected with *O. volvulus* in the community is low (say, <10%). An ideal ATS would consist of administration of a macrofilaricidal, single-dose regimen, without tolerance issue (involving the absence of *L. Loa microfilaricidal* activity). Flubendazole carried great hope in this view but its development has been

interrupted due to probable toxicity. Other potential macrofilaricidal drugs have been identified by the A-WOL (anti-*Wolbachia*) consortium (AWOL, 2021).

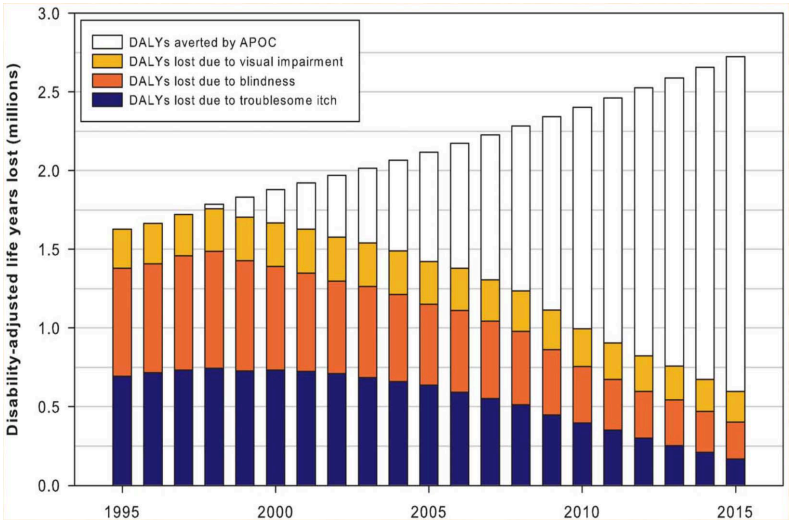

Figure 7. Disability Adjusted Life Years (DALYs) averted by the onchocerciasis control program until 2015

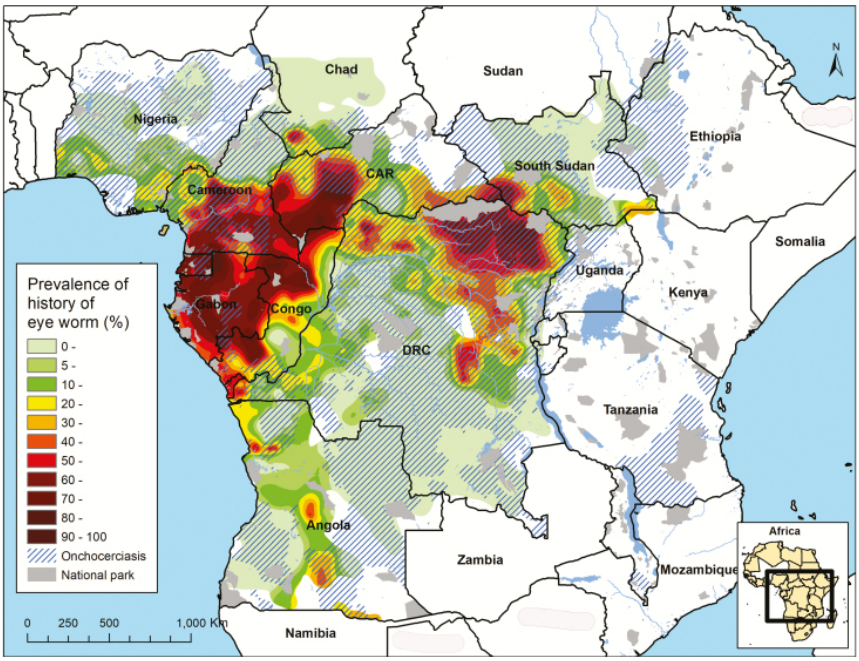

Figure 8. Map of the estimated overlap between the prevalence of palpable onchocercal nodules and the prevalence of eyeworm (loiasis) in Central Africa

Reproduced from (Vinkeles Melchers *et al.*, 2020)

1.3. Loiasis

Epidemiology

The geographical distribution of loiasis is limited to Central Africa. Two high prevalence areas can be described: a block comprising the southern and eastern part of Cameroon, western Central African Republic, Equatorial Guinea, Gabon and the western part of the Republic of Congo, and another comprising the northern and north-eastern part of the Democratic Republic of Congo and southern Sudan. Mapping of loiasis prevalence has been established by the APOC, using a Rapid Assessment Procedure for Loiasis (RAPLOA) method, based on questionnaires on the history of subconjunctival passage of the worm (Figure 9) (Zouré *et al.*, 2011). An estimated 14 million people live in highly endemic foci, where the prevalence of infection is about 60% and the prevalence of subconjunctival passage of the eye is about 40%. An additional 15.2 million people are estimated to live in endemic areas where 20-40% of people report eyeworm history. It is estimated that more than ten million people are infected by *Loa loa* (Vinkeles Melchers *et al.*, 2021).

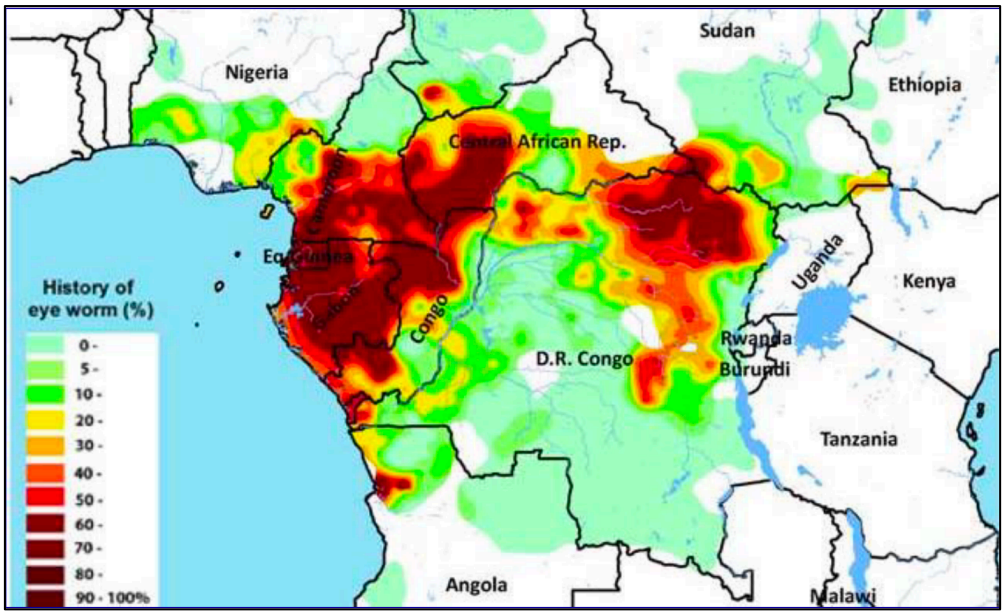

Figure 9. RAPLOA mapping of *Loa loa* endemicity in Central Africa

Reproduced from (Zouré *et al.*, 2011)

Pathogenesis

The parasite *L. loa*, is transmitted by tabanids (red flies) of the *Chrysops* genus, and in particular *C. silacea* et *C. dimidiata*. Adult worms live in subcutaneous tissues and intermuscular fascia for up to

20 years and can episodically migrate under the eye conjunctiva. Females are 5-7 cm long and males about 2 cm long. They produce very high numbers of embryos (mf) as compared to the lymphatic filariae and *O. volvulus*: up to 10-12,000 mf/day/worm, with host's MFD reaching up to 300,000 mf/ml blood. The MFD levels are steady in time and at least partially genetically determined. Mf are found in the peripheral blood with a diurnal periodicity (peak densities between 10:00 am and 2:00 pm), reflecting their coevolution with *Chrysops* hematophagous females that bite during the day and are attracted to the smoke of wood fires. The simian *L. loa* strain, on contrary, exhibits a nocturnal periodicity and is transmitted by species of *Chrysops* that bite the monkeys by night. When ingested by *Chrysops*, mf evolves into infective L2 and then L3 larvae within 10-12 days. Then, at the occasion of a new blood meal, the infective L3s actively penetrate the skin, and molts two times (L3-L4 and L4-adult) to become an adult worm.

Importantly, *L. loa* do not have symbiotic *Wolbachia*, unlike *O. volvulus* or *W. bancrofti*.

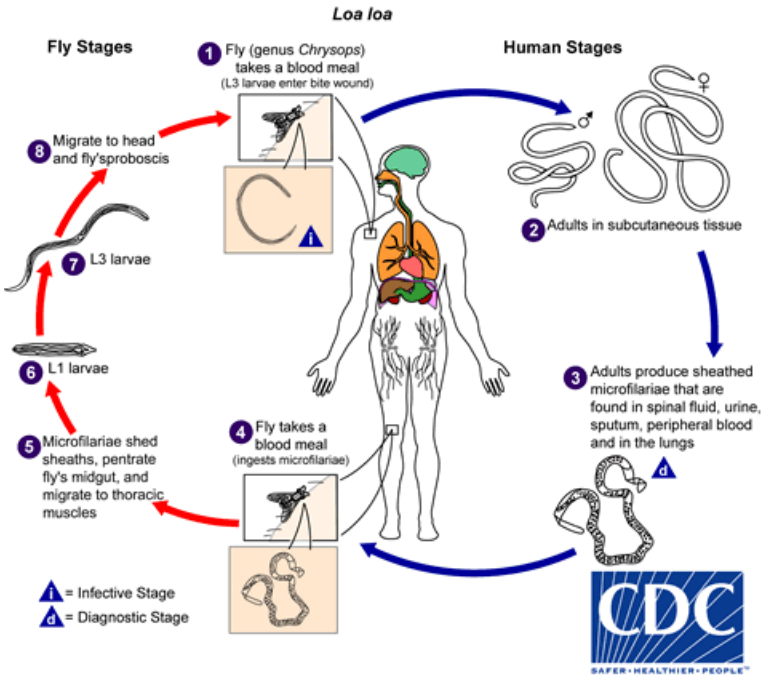

Figure 10. Life cycle of *Loa loa*

Clinical features

In most cases, infected individuals are asymptomatic or suffer from benign symptoms. Loiasis has long be considered to be a benign condition. Nevertheless, its burden is not negligible as it is one of the first causes of consultation in endemic areas. Symptoms can appear as early as a few months

following infection and as long as 20 years later. The characteristic symptoms of the disease are the following (Figure 11):

- Frequent and intense pruritus
- Calabar swellings (named after a town in south-east Nigeria) which are fleeting allergic oedema (lasting a few hours or days) with a feeling of tension and located mainly in the upper limbs (arm, elbow, wrist, hand), face or thorax. It is thought to be immuno-allergic in nature. They are more frequent in expatriates than in people living in endemic areas from childhood.
- "Eyeworm": common transient migration of the adult worm under the conjunctiva or eyelid skin, during which filaria extraction is feasible. It is accompanied by photophobia, conjunctival injection, lacrimation, and foreign body sensation.
- Reptation of the adult worm under the skin (~1 cm/min), frequent after treatment with DEC, that causes adult worms to migrate to the surface of the skin
- Significant and persistent hypereosinophilia

In addition to these classically recognized manifestations, a myriad of symptoms can occur, all of which have been extensively gathered in a recent review (Buell *et al.*, 2019), including rare but serious complications:

- Renal damage (proteinuria, hematuria, nephrotic syndrome, glomerulopathies)
- Spontaneous neurological manifestations (poorly documented owing to differential diagnosis difficulty in remote settings)
- Loeffler's eosinophilic fibroblastic endocarditis due to persistent hypereosinophilia
- Ocular complications (e.g., retinal hemorrhages)
- Arthritis (effusions with live mf in the synovial fluid)

More importantly, an excess mortality in highly parasitized individuals has been evidenced by a cohort study in an endemic area, where an estimated 1:10 deaths was attributed to *L. loa* infection (Chesnais *et al.*, 2017) (Figure 12).

Several infection patterns seem to coexist: hypermicrofilaraemic individuals with low eosinophil counts and frequent clinical manifestations, amicrofilaraemic individuals with very elevated eosinophil levels (occult loiasis).

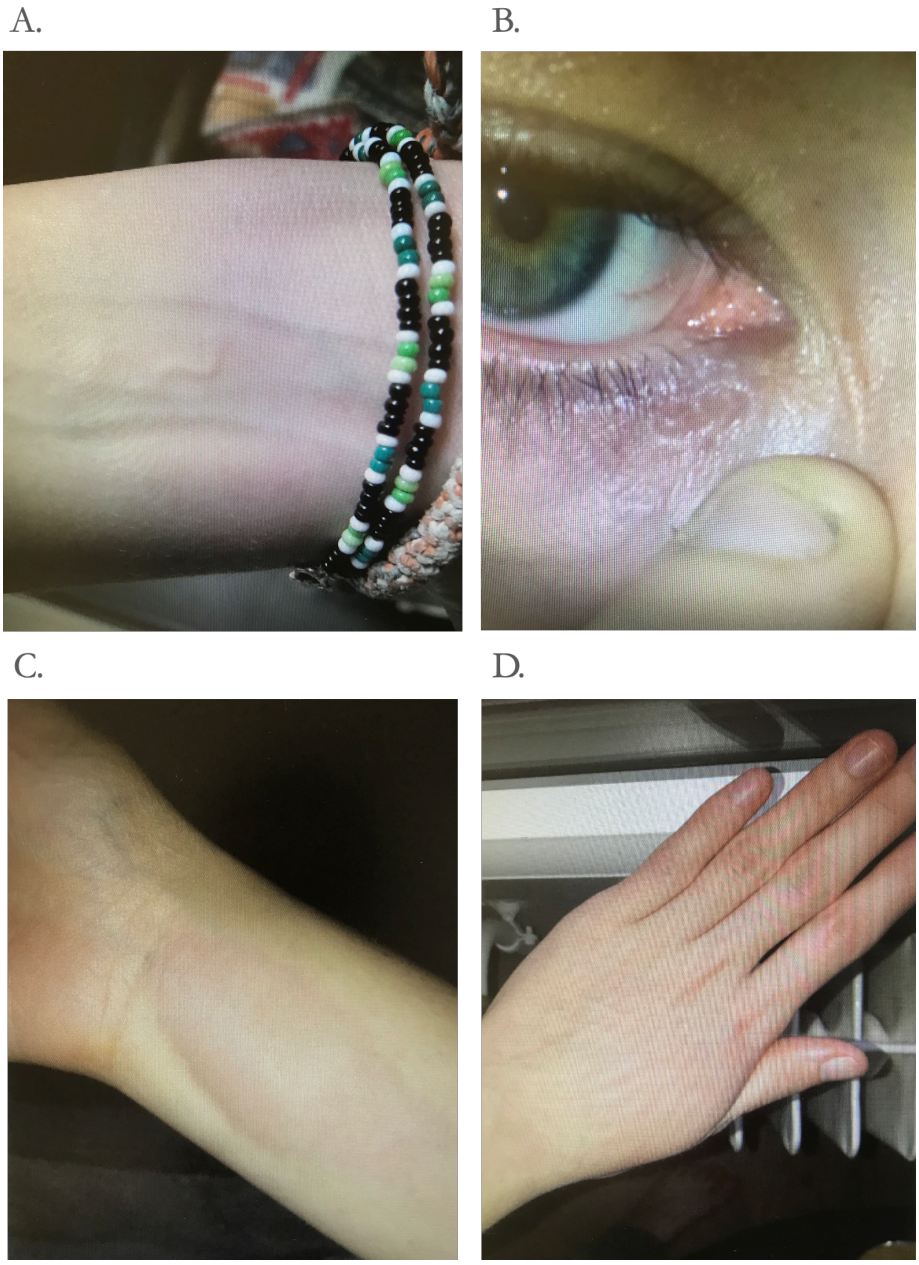

Figure 11. Calabar swelling, eyeworm migration, and spontaneous migration of adult worms in subcutaneous tissues in a traveler consulting at the Montpellier University Hospital in 2021, one year after returning from a 10 month-long stay in forest areas in the Republic of Congo.

Courtesy: Agathe Artiaga

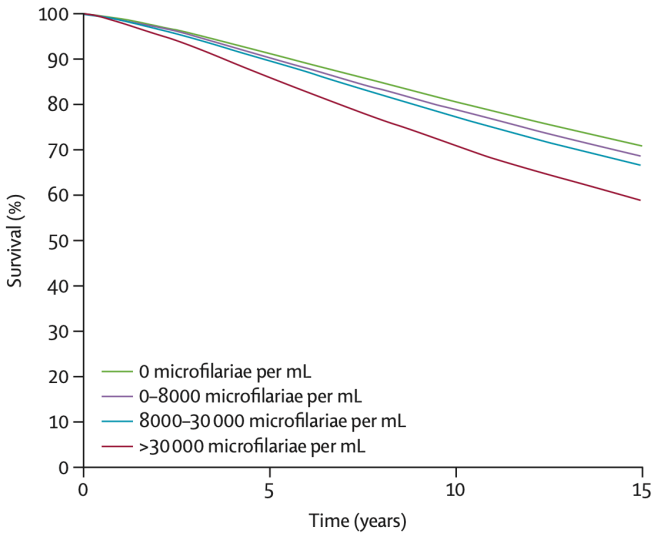

Figure 12. Adjusted predicted survival curves according to the level of *Loa loa* microfilarial density

Reproduced from: (Chesnais et al., 2017)

Diagnostic

First and foremost, clinical in front of typical manifestation (Calabar swelling and eyeworm) and epidemiological arguments.

Direct:

- **Gold standard: calibrated thick blood smear** (TBS) obtained between 10:00 am and 16:00 pm, stained with Giemsa stain. Drawback: false negative result in case of low MFD, or occult loiasis, i.e. infection without circulating mf (frequent).
- LoaScope: visualization and recognition of live microfilariae in a sample of blood collected in a glass capillary using a smartphone camera. Good performance as compared to TBS, with the same major drawback (D'Ambrosio *et al.*, 2015).

Indirect:

- Pan-filarial serology (no species diagnosis allowed), indicated in case subjects have clinical manifestations without circulating mf evidenced.
- Rapid diagnostic test (RDT) identifying antibodies directed against the specific recombinant antigen Ll-SXP-1 (not yet commercially available) (Pedram *et al.*, 2017; Gobbi *et al.*, 2020)

- PCR techniques (qPCR and LAMP) have been developed to detect *L. loa* DNA in peripheral blood, and are used in research settings (Fink, Kamgno and Nutman, 2011; Drame *et al.*, 2014).
- Very high hypereosinophilia (often >2G/L)

In practice, in travel medicine clinics:

1. **TBS** between 10:00 am and 4:00 pm
2. Pan-filarial Serology (when available, replace by specific RDT)

→ Eyeworm or positive TBS: confirmed diagnostic

→ Serology/RDT+/ TBS -: occult loiasis, consider as active infection if return from endemic area <20 years

Treatment

Sensitivity to antimicrobial drugs:

- **DEC**: macrofilaricidal, difficult to use owing to:
  - Frequent side-effects (Carme, Danis and Gentilini, 1982)
  - Contraindication if MFD >2,000 mf/mL, due to a risk of fatal encephalopathy (Downie, 1966; Fain, 1978; Carme *et al.*, 1991)
  - Administration following a slowly increasing dosage schedule (Gentilini and Carme, 1981), associated with antihistaminic or corticosteroid medication.
  - Repetition of courses may be necessary (Klion, Ottesen and Nutman, 1994; Churchill *et al.*, 1996).
- **IVM**: single dose, 150-200 µg/kg. Microfilaricidal, conferring prolonged drop of the MFD for the next year. Although IVM is reputed to have low or no activity on adult worms, a remnant action is plausible -through an embryostatic or a macrofilaricidal mechanism, as one would otherwise expect a more rapid rise in MFD after treatment (Gardon *et al.*, 1997; Pion *et al.*, 2019)
  - Risk of marked adverse event (SAE) when MFD > 8,000 mf/mL and risk of neurological SAE when MFD > 30,000 mf/mL (Gardon *et al.*, 1997). Neurological SAEs are all described in patients with MFD>50,000 mf/mL (Ducorps *et al.*, 1995; Chippaux *et al.*, 1996; Gardon *et al.*, 1997; Boussinesq *et al.*, 2003; Twum-Danso, 2003; Twum-Danso and Meredith, 2003)

- **ALB**: microfilaricidal, 21 days 200 mg bid (Klion *et al.*, 1993)
  - Two exceptional cases of encephalopathy following ALB administration in patients with high MFD have been described recently (Volpicelli *et al.*, 2020; Métais, Michalak and Rousseau, 2021)

Therapeutic regimens (Boussinesq, 2012) depending on individual microfilarial density generally used in French travel medicine clinics:

MFD (mf/mL)	Drug	Duration	Posology	Notes
0	DEC	3-4 w	Start 50 mg qd, double qd until target posology of 400 mg qd is reached	Daily dose if divided in three administration per day In hospital
≤ 2000	DEC	3-4 w	Start 3-6 mg qd, double qd until target posology of 400 mg qd is reached	Use of corticosteroids and antihistamines in case of side effects Repeated treatment may be required
	ALB	3-4 w	200 mg bid	If DEC failure (Klion, Horton and Nutman, 1999)
2001 – 8000 Risk of post-DEC neurological AE	IVM	Single dose	150-200 µg/kg	Target: lower MFD below 2,000 mf/mL, then refer to above. Repeat every 1-3 months if necessary
8001 – 30 000 Risk of post IVM non-neurological AE	IVM	Single dose	150-200 µg/kg	In hospital Target: lower MF below 2,000 mf/mL, then refer to above.
	or ALB	3 w	200 mg bid	
> 30 000 Risk of post IVM neurological AE	ALB	3 w	200 mg bid	Difficult situation. Protocol to be refined.
	or apheresis			Expensive and difficult to advise in case of mild symptomatology (Zhao *et al.*, 2017)

In the USA, the CDC considers that the treatment of choice is DEC, and that albendazole can be used in patients who are not cured with multiple cures of DEC. They recommend that people with heavy infections be treated by experienced specialists, and recall that sometimes treatment is not recommended. Some authors, recommend that patients with MFD<2,000 mf/mL receive DEC, and that they receive ALB otherwise.

Preventive treatment: for long stays in endemic areas DEC 300 mg once a week (Nutman *et al.*, 1988).

2. Challenges

As we just overviewed, human filariases share a common mode of transmission and intersecting endemic areas. Among them, lymphatic filariasis and onchocerciasis are listed as public health priorities by the WHO, because of the burden they place on the health and economy of low- and middle-income countries, and are thereby included in the list of neglected tropical diseases. Control and later planetary eradication programmes have been settled up to tackle them. Even though the clinical features of filariases are rather different, it is not possible to consider each of them separately as their management is tightly intertwined. Loiasis, even while being considered a benign condition, has long hampered mass drug administration programs, first because of encephalopathies following DEC administration (Downie, 1966; Carme *et al.*, 1991)(Fain, 1978; Carme *et al.*, 1991) and, later, ivermectin administration (Twum-Danso, 2003; Twum-Danso and Meredith, 2003). Yet, DEC and IVM are key first-line treatments in MDA programmes targeting lymphatic filariasis and onchocerciasis, respectively. Recent studies have also shown that loiasis is probably not such a benign condition as it was previously thought, with a significant excess of mortality in endemic areas. These findings may encourage reconsideration of the benefit of loiasis treatment *per se* in these areas. Until now, the individual management of loiasis is an issue faced by travel medicine clinics for travelers or migrants returning from endemic areas. Recent events, such as serious side effects following treatment of hypermicrofilaraemic loiasis with albendazole, should encourage reflection on individual loiasis management strategies, which are currently poorly codified given the limited data available. When such serious adverse effects occur, their management is not codified and they are a major obstacle to the extension of the CDTI for onchocerciasis, with the result that hypoendemic areas in Central Africa are not covered when they are co-endemic for loiasis. The first step in improving the management of such serious adverse events is to have a standardized definition for imputability to ivermectin, particularly in a context where many differential diagnoses may coexist. As the cases are reported during surveillance, and most often occur in remote areas, intensity of *L. loa* infection before treatment is obviously not available individually, although it is the major and until now almost unique known determinant of risk. In order to review the cases and to study whether there is a signal showing benefit of some management modalities, it is therefore essential to better define them.

3. Objectives of the thesis

The overall objective of this work is to propose a modest contribution to improve the understanding of the challenges posed by the occurrence of serious adverse events related to the pharmacological treatment of loiasis, both from an individual and a collective point of view. Firstly, we will study the importance of individual factors in order to better define the thresholds at which they can occur, and therefore possibly lead to better individual management in the therapeutic recommendations of travel medicine:

- ⇨ **Chapter 3. Revisit the thresholds for the risk of serious adverse event following ivermectin administration in individuals with *L. loa* microfilaraemia**

In a second step, we will investigate the possibility of inferring pre-treatment microfilarial burdens from monitoring data collected after treatment to provide evidence-based rationale for the WHO definition of *L. loa* related encephalopathy:

- ⇨ **Chapter 4. Retrieving levels of *L. loa* pre-treatment microfilarial densities from post-treatment measurements**

3 Article I

Revisiting risk thresholds for serious adverse events after ivermectin administration in *Loa loa* infected individuals

Revisiting risk thresholds for serious adverse events after ivermectin administration in *Loa loa* infected individuals

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1. Abstract

Introduction: Loiasis if often deemed to be a benign condition, but individuals with high *Loa loa* microfilarial densities (MFD) are at risk of serious adverse events (SAEs) including encephalopathy following ivermectin (IVM) administration. The risk of marked or serious adverse event is usually considered when MFD of infected individuals exceed 8000 mf/mL or 30,000 mf/mL, respectively. There are no international guidelines on the treatment of loiasis, resulting in a variety of practices worldwide for the treatment of infected individuals outside endemic areas. Our objective was to determine the probabilities of SAEs after IVM administration at the published thresholds, and to refine those thresholds using individual characteristics such as age and sex.

Patients and methods: We used data from two clinical trials conducted in Cameroon where *L. loa* MFD were determined before ivermectin administration. The first was held in 1995–1996 in the Lekie department, and enrolled 5550 patients aged >15 years in 106 villages. The second took place in 2005 in the Lom-et-Djerem and Haut-Nyong departments and recruited 4956 ivermectin-naive subjects aged ≥13 years in 74 villages. The risk of SAE was modeled as a logistic function of age, sex, and MFD transformed as a fractional polynomial of first order.

Results: SAEs probabilities at usual thresholds were found to be $<10^4$ for MFD<2000 mf/mL, > 1‰ for MFD >8000 mf/mL, >1% for MFD>20,000 mf/mL, and >2.5% for MFD>30,000 mf/mL. We showed that specific categories may be at a higher risk of SAE than expected, when considering individual characteristics such as age and sex. Specifically, in order not to exceed 2.5% risk, the corresponding thresholds would be 27,000 mf/mL for women in the 31-40 age group; 24,000 mf/mL for male in the 21-30 age group; 17,000 mf/mL for male in the 31-40 age group; and 22,000 mf/mL for male in the 61-70 age group.

Conclusions: Our study suggests that IVM should be used with caution for males or individuals in specific age categories with a high *L. loa* MFD. For them, lowering the thresholds previously used should be considered. Alternative treatment strategies are needed for the individual treatment of subjects harboring high *L. loa* MFD. The increased risk in males requires further investigation to understand the pathophysiological phenomena involved that are crucial to prevent and manage SAEs.

2. Introduction

Loiasis is a filariasis caused by *Loa loa*, a filarial species whose transmission is restricted to Central Africa. In this region, it has been hampering the mass drug administration programs of ivermectin targeted to eliminate onchocerciasis and lymphatic filariasis as subjects harboring high *L. loa* microfilarial densities in peripheral blood can develop serious adverse events (SAEs) following ivermectin administration, including potentially fatal encephalopathies [1]. The disease is well known for two hallmark signs the so-called "Calabar edema" (transient subcutaneous swellings usually affecting the face or upper limbs) and "eyeworm" (migration of an adult worm under the eye conjunctiva), but is genuinely polymorphic [2].

There are no international nor national official guidelines for the treatment of loiasis. Several recent paradigm shifts should lead to reconsidering the benefit and/or modalities of treatment at the individual scale. The treatment of loiasis has long been considered from the point of view of international control programmes, for patients requiring antiparasitic treatment for another indication (in particular ivermectin for onchocerciasis), or eventually in the event that clinical manifestations were very troublesome (e.g., Calabar's oedema, or significant blood hypereosinophilia, likely to have organ repercussions. Indeed, although some of its complications (including severe renal conditions [3,4]) have been known for a long time it was long deemed a benign condition, but recent studies have demonstrated the morbidity and mortality of loiasis [5], encouraging that it be considered as a pathological condition *per se* and treated as such).

Currently, several antiparasitic drugs may be part of the treatment regimen against loiasis. Radical treatment classically requires the administration diethylcarbamazine (DEC), with several courses being often necessary to ensure cure [6,7], through its macrofilaricidal activity. Side-effects of DEC are frequent, affecting almost half of the patients treated for loiasis [8]. It was rapidly documented that it could lead to serious adverse effects including extra-membranous glomerulonephritis, pleural effusion [8], and potentially lethal encephalopathies when administered to patients with microfilaraemia [9–11]. Another problem that can arise is availability of the drug, as countries outside endemic areas do not always have access to this drug for imported cases. This was recently pointed out by Gobbi *et al*, who surveyed TropNet Clinics (European Network for Tropical Medicine and Travel Health) and found that DEC was unavailable in 48% of them (33/69) and required several days to be available in 11 others. Ivermectin (IVM) has been suggested as an alternative treatment although it is reputed to lack activity on macrofilariae, but achieves a significant clearance of the microfilarial density [12,13]. If the initial safety studies were promising [14–17], it also turned out to provoke serious adverse events described during MDA campaigns in co-endemic areas [18–21] including fatal encephalopathies [22,23].

Eventually, albendazole (ALB) has been evaluated in clinical trials with low efficacy of low-dose/short regiments [24,25], retrieved with higher dosages. The common strategy includes 21 days 200 mg b.d. leads to a progressive and persistent decrease in microfilariaemia by 60% in 6 months suggesting an action on the macrofilariae fecundity and/or survival [26]. Longer courses at higher doses have been tested (e.g., 400 mg b.d. 28 days) followed by single dose ivermectin with high MFD suppression rate of 94% after 6 months [27]. It is currently being used in case of relapse despite several courses of DEC or in patients with high microfilarial densities prohibiting the use

of DEC or IVM [26]. Nevertheless, two cases of encephalopathy following the administration of albendazole, one of which was fatal, for the treatment of patients with high *L. loa* microfilaremia have been published recently, suggesting that this molecule may also be the cause of serious adverse effects [28,29]. This should be taken into consideration when choosing the treatment. Another member of the benzimidazole therapeutic class, mebendazole is seldom used, especially in Spain, and one meningoencephalitis secondary to treatment has been documented [30]. Apart from antiparasitic treatments, apheresis has been used to lower blood microfilaremia in patients with high loads as soon as 1969 but is rarely used [31].

Recent large series reporting treatment assigned to patients with imported loiasis in France [32–34], Italy [35], England [36], and Spain [37] reflect the striking heterogeneity of drug use between countries [38] and even between specialized travel medicine clinics belonging to a same European Network [39].

The commonly applied strategy in France and other European countries is mainly based on a graded strategy based on the microfilaraemia expressed in mf/mL as proposed by Boussinesq *et al* [40,41]:

(i) amicrofilaremic: DEC at progressively increasing dose in three doses per day (15mg q.d., double each day until reaching 8-10/mg/kg q.d., over 3-4 weeks)

(ii) ≤2000 mf/mL: DEC (starting 3-6mg q.d, double each day until reaching 400 mg q.d., over 3-4 weeks [42]);

(iii) 2,001-8,000 mf/mL: IVM 150 μg/kg every 1-3 months then DEC;

(iv) 8,001-30,000 mf/mL: IVM 150 μg/kg under hospital surveillance OR albendazole 200 mg b.d. during 21 days;

(v) >30,000 mf/mL: ALB (although efficacy data on such high microfilarial densities lack) OR apheresis.

To our knowledge, in the USA, authors suggest treating with DEC if <2,500 mf/mL, and otherwise advised that the treatment is conducted by experienced specialist, with albendazole for instance, or that the indication to treat is reconsidered [43,44].

Our aim was thus to determine and discuss the risk probabilities of adverse effects following IVM administration based on the thresholds commonly accepted in the literature and to refine them with regard to the individual characteristics available in an individual medicine approach, and review the published neurological adverse events for which pre-treatment microfilarial densities are available.

3. Patients and methods

Study population

We use data from two clinical trials in Cameroon where *L. loa* microfilaremia were performed before ivermectin administration. The first was held in 1995–1996 in the Lekie department (in the Centre Region), to determine the incidence of post-ivermectin serious adverse events (SAEs) in a loiasis-endemic area, and the *L. loa* microfilarial density threshold above which SAEs can occur. The trial enrolled 17,877 subjects in 106 villages, of whom 14,676 were IVM-naive. Among them, 6415 were aged ≥15 years. For technical reasons, 865 blood smears could not be examined leaving 5,550 adult patients with *L. loa* microfilarial density examination. The second was held in 2005 in the Lom-et-Djerem and Haut-Nyong departments (in the East Region) to evaluate whether *Plasmodium sp.* was a risk cofactor for *L. loa*-related post-ivermectin SAEs. It enrolled 4,956 ivermectin-naive subjects aged ≥13 years in 74 villages. Both studies were approved by the Cameroon National Ethics Committee for Research in Human Health. A written informed consent was signed by all voluntary participants in the 2005 study. For the Lekie study supported by the WHO-TDR in 1995-1996, the Ministry of Public Health of Cameroon considered that the study area needed to be treated with ivermectin, and that therefore no consent form had to be signed by the participants.

Parasitological examination

In both trials a calibrated (50 μL) thick blood smear (TBS) from a finger prick obtained between 10:00 AM and 4:00 PM was performed to measure the *L. loa* microfilarial density. Within 48 h, the slides were dehaemoglobinized and stained with Giemsa, then were stored and examined for microfilariae after 1–2 weeks. The TBS were read by experienced microscopists and individual MFDs expressed in mf/mL of blood.

Treatment and monitoring of serious adverse events

In both trials, ivermectin was given orally to eligible individuals at a standard dose of 150 μg/kg as part of the Community Directed Treatment with Ivermectin campaign targeting onchocerciasis, respecting the usual contraindications. Active surveillance procedures were set up to detect the occurrence of adverse event during the 7 days following treatment.

Classification of adverse events

Adverse events are classified as: (i) *mild/marked* if patients complains of reactions without functional impairment/with limited functional impairment requiring partial assistance for several days, both referred to as AEs; (ii) *serious non-neurological* if patients have functional impairment with the need for full-time assistance for at least one week without neurological sign; and *serious neurological* if they develop disorders of consciousness and objective neurological signs and are admitted to the hospital for appropriate management, both referred to as SAEs. These definitions correspond to gradation of adverse events linked to ivermectin, which has been adapted by Merck & Co. Inc. from the definitions of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and agreed on by the Mectizan ® Expert Committee under the aegis of the Special Programme for Research and Training in Tropical Diseases of the World Health Organization.

Statistical analyses

According to a previous study, the occurrence of an SAE can be best modelled using a fractional polynomial (FP) of order 1 transformation of the *L. loa* MFD. We constructed bivariate models using age, sex, and pre-treatment *L. loa* as covariables. The initial model used a fractional polynomial (FP) of order 2 transformation of the age, that had only slightly lower Akaike Information Criterion when compared to the categorical transformation of age (≤20, 21-30, 31-40, 41-50, 51-60, 61-70, >70) guided by the shape of the polynomial relationship of age with the occurrence of SAEs. In order to provide more understandable estimates, this latter transformation was chosen. Logistic models with SAEs as the dependent variable and *L. loa* MFD, age, and sex were compared. The previously accepted risk probabilities of SAEs at the usual *L. loa* MFD cut-offs were retrieved using a logistic model including only the *L. loa* MFD. The risk probability of SAEs at those same cut-offs, accounting for age and sex that were both significant in the logistic model, were then calculated to identify risk categories.

All analyses were performed using Stata 17.0 © (StataCorp, College Station, Texas, TX, USA).

4. Results

Description of the study population

A total of 10,506 individuals were enrolled in the studies conducted in the Center and East regions in Cameroon. Thirty-eight SAEs occurred including 2 neurological SAEs. Those who presented SAEs, were more likely to be males (79.0%, p<0.001), and had more elevated *L. loa* MFD (range: 5620 – 182,400 mf/mL) (**Table 1**).

Table 1. Description of the study population

	All individuals (N=10,506)	Individuals who presented SAEs (n=38)	p-value
Age (median, IQR)	31 (19-50)	36 (30-48)	0.0240
13-20	3,147 (30.0)	2 (5.3)	<0.001
21-30	1,984 (18.9)	9 (23.7)	
31-40	1,523 (14.5)	13 (34.2)	
41-50	1,428 (13.6)	6 (15.8)	
51-60	1,264 (12.0)	1 (2.6)	
61-70	839 (8.0)	6 (15.8)	
>70	321 (3.1)	1 (2.6)	
Sex			<0.001
Female	5,367 (51.1)	8 (21.1)	
Male	5,109 (48.9)	30 (79.0)	
L. loa MFD			<0.001
0	7,534 (72.0)	0 (0)	
1-2,000	1,425 (13.6)	0 (0)	
2,001-8,000	703 (6.7)	1 (2.6)	
8,001-30,000	597 (5.7)	2 (5.3)	
30,001-50,000	126 (1.2)	7 (18.4)	
>50,000	83 (0.8)	28 (73.7)	

SAE: serious adverse event; IQR: interquartile range; MFD: microfilarial density.

p-values were obtained using the Mann-Whitney (age), or chi-2 test.

Predicted probabilities of SAEs according to the microfilaremia

The probability of developing a serious adverse event in relation to the MFD of an individual has been described as $P_{SAE} = \frac{e^{[-9.74+2.54\times ln(\frac{Loa+2.22216796875}{100000})+3.658185875]}}{1+e^{[-9.74+2.54\times ln(\frac{Loa+2.22216796875}{100000})+3.658185875]}}$ [45]. Using the common thresholds identified in the literature this led to SAE risk probabilities below 10^4 for MFD below 2000 mf/mL, above 1‰ starting at 8000 mf/mL, 1% starting at 20,000 mf/mL, 2.5% starting at 30,000 mf/mL (**Table 2**).

Table 2. Predicted probabilities of post-ivermectin serious adverse events at various *L. loa* microfilarial densities cutoffs

L. loa MFD (mf/mL)	Probability of post-IVM SAE	95%CI	
0	$<10^{-11}$	[0-$<10^{-11}$]	
2000	$<10^{-4}$	[0-$<10^{-4}$]	
5000	0.03%	[0; 0.08%]	
8000	0.10%	[0; 0.22%]	
10,000	0.18%	[0; 0.37%]	
20,000	1.01%	[0.32; 1.71%]	
30,000	2.76%	[1.39; 4.13 %]	
50,000	9.31%	[6.16; 12.45%]	
100,000	36.99%	[25.21; 48.76%]	

Green indicates probabilities of SAE below 0.005%, yellow indicates probabilities greater than 0.1% (8,000 mf/mL), orange indicates probabilities greater than 1% (20,000 mf/mL), red indicates probabilities greater than 2.5% (30,000 mf/mL).

MFD: microfilarial density

Predicted probabilities of SAEs according to the microfilaremia and individual characteristics

Probabilities of developing a SAE for those thresholds were computed using a multivariate model with *L loa* MFD, age, and sex as covariates. Results are presented in **Table 3** and **Figure 1**.

For specific categories, the rounded threshold to fall to a predicted risk of exceeding 2.5% (corresponding to the predicted overall risk when MFD exceeds 30,000 mf/mL) was lower than 30,000 mf/mL. Specifically, this threshold was 27,000 mf/mL for women in the 31-40 age group;

24,000 mf/mL for male in the 21-30 age group; 17,000 mf/mL for male in the 31-40 age group; and 22,000 mf/mL for male in the 61-70 age group.

Table 3. Predicted probabilities of SAEs depending on sex, pre-treatment *L. loa* microfilaremia and age.

a) Females

L. loa MFD (mf/mL)	Age category (years)						
	≤20	21-30	31-40	41-50	51-60	61-70	>70
0	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
2000	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
5000	0.00%	0.01%	0.03%	0.01%	0.00%	0.02%	0.01%
8000	0.01%	0.04%	0.10%	0.03%	0.00%	0.05%	0.02%
10,000	0.03%	0.08%	0.19%	0.05%	0.01%	0.09%	0.04%
20,000	0.16%	0.48%	1.15%	0.32%	0.04%	0.58%	0.26%
30,000	0.46%	1.38%	3.27%*	0.91%	0.13%	1.67%	0.75%
50,000	1.74%	5.10%*	11.52%*	3.43%	0.49%	6.15%	2.84%
100,000	9.95%	25.07%*	44.78%*	18.11%*	3.00%	29.00%*	15.38%

b) Males

L. loa MFD (mf/mL)	Age category (years)						
	≤20	21-30	31-40	41-50	51-60	61-70	>70
0	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
2000	0.00%	0.00%	0.01%	0.00%	0.00%	0.00%	0.00%
5000	0.01%	0.04%	0.09%	0.03%	0.00%	0.05%	0.02%
8000	0.04%	0.13%	0.32%	0.09%	0.01%	0.16%	0.07%
10,000	0.08%	0.24%	0.57%	0.16%	0.02%	0.29%	0.13%
20,000	0.49%	1.46%	3.46%*	0.97%	0.14%	1.77%	0.80%
30,000	1.40%	4.13%*	9.45%*	2.77%	0.40%	4.99%	2.29%
50,000	5.19%	14.22%*	28.66%*	9.87%*	1.51%	16.83%*	8.26%
100,000	25.43%	50.81%*	71.45%*	40.56%*	8.71%	55.76%*	35.94%

Green indicates probabilities of SEA below 0.005% (corresponding to the threshold of 2000 mf/mL in univariate analysis) yellow indicates probabilities greater than 0.1% (corresponding to the threshold of 8000 mf/mL in univariate analysis), orange indicates probabilities greater than 1% (corresponding to the threshold of 20,000 mf/mL in univariate analysis), red indicates probabilities greater than 2.5% (corresponding to the threshold of 30,000 mf/mL in univariate analysis).

* indicates p-value<.05

MFD: microfilarial density

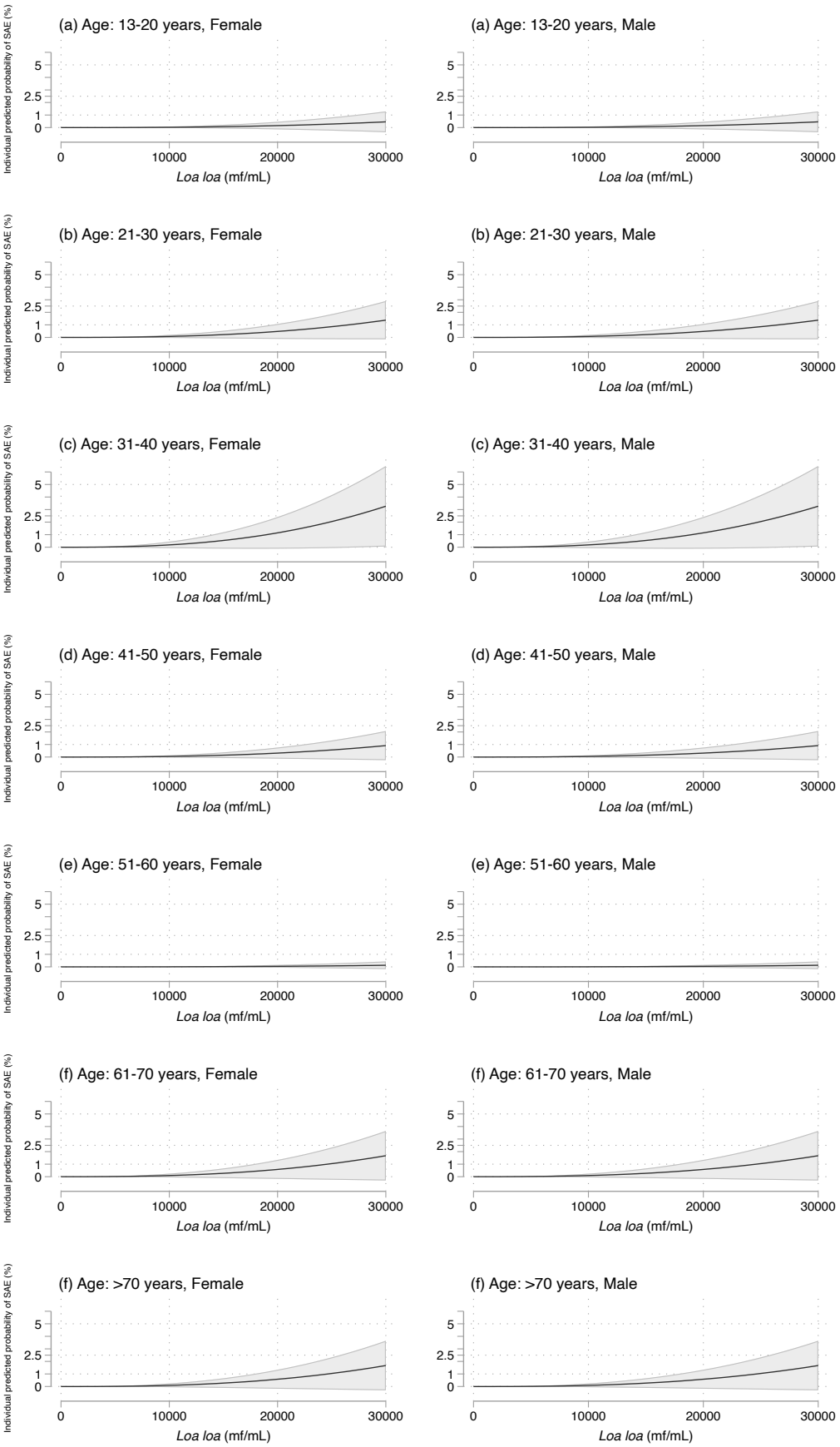

Figure 1. Predicted probabilities of developing SAEs according to age and sex.

5. Discussion

Our results indicate that the commonly accepted thresholds for individual treatment guidance correspond to mean risks of SAEs above 1‰ for 8000 mf/mL and above 2.5% for 30,000 mf/mL. We also showed that specific categories may be at a much higher or sometimes lower risk of SAE than expected, when considering individual characteristics such as age and sex. Considering this, we would advise that the threshold for ivermectin use in *L. loa* microfilaremic patients is lowered down to 20,000 mf/mL for adult men, or women in the 30-40 age group. Men in their 30-40 being at even higher risk, ivermectin therapy may not seem reasonable above 15,000 mf/mL. Individuals harboring MFD above those thresholds should probably be considered for apheresis or receive albendazole. Given the lack of hindsight into safety of albendazole at higher dosages in loiasis (400 mg b.d. for 28 days, as done in some centers), and the recent concerns raised by two adverse events in patients treated with albendazole [28,29], it is advisable to keep with the protocol used in the trial by Klion *et al*, e.g. 200 mg b.d. during 21 days, and repeat if necessary. Apheresis, when available should be considered when the microfilarial burden exceeds the thresholds mentioned above.

The most severe form of life-threatening events are encephalopathies, with occurrence of a febrile coma usually 3-5 days, and sometimes delayed up to 7 days after ivermectin administration. The two patients who experienced neurological SAEs included in this study harbored respectively 50,520 and 152,940 mf/mL and eventually recovered. Six other cases of neurological SAE following ivermectin administration with known *L. loa* microfilaremia have been published, all of whom had higher than 100,000 mf/mL, and more specifically 162,920 mf/mL [21]139,000 mf/mL ;109,000 mf/mL;199,000 mf/mL;217,000 mf/mL [20]; and 120,000 mf/mL [46]. Six out of 8 total neurological SAEs were males, and 6/8 were aged between 20 and 40 years, the two others being 18 years old and 59 years old.

As part of the Mectizan® Donation Program surveillance 65 probable or possible *L. loa* encephalopathy temporally related to treatment with ivermectin with unknown MFD were described during the mass treatment campaigns from 1989 to 2001 [47], although it is likely that this feature is underestimated due to absence of systematic follow-up and owing to the remote location of many villages. Among those cases for whom outcome was known 8/34 (23.5%) died (including 3 with infected decubitus bedsores prior to death), and 4/34 (12%) had neurologic sequalae. It has been debated to whether or not those encephalopathies were solely attributable to infestation with *L. loa*. Pharmacovigilance studies highlighted that neurological SAEs may happen after ivermectin administration for scabies, acarodermatitis, strongyloidiasis, outside of *L. loa*-

endemic areas [48,49] putting the light on various mechanisms that may be involved. In cases outside of *L. loa* infestation, those mechanisms are believed to be mostly toxic, through concomitant use of drugs inhibiting CY3A4 or owing to host susceptibility similarly to what is better known in veterinary medicine, with some species (collies) with p-glycoprotein deficiency (*ABCB1/mdr-1* gene) being at risk for neurological side effects. Recently, one case in 13 years old-boy who had received a standard single dose of ivermectin for scabies was described, and lead to the finding that he was a compound heterozygote for two nonsense mutations [50]. Nevertheless, the distribution of SAE almost exclusively in *L. loa* endemic zones, and the wide use of ivermectin is not in favor of this being the underlying mechanism, which was corroborated by a pilot study that did not find loss-of-function mutations in mdr-1 in 4 individuals who had experienced a SAE, but nonetheless found that half of them had mdr-1 polymorphisms [51]. It is also important to note that few cases of spontaneous filarial encephalopathies have been described, before the registration of DEC or in untreated patients but this diagnostic is supposedly very rare [4].

Although neurological side effects are rare, they are the main concern when implementing loiasis treatment, and it is believed that there is a continuum between mild, marked (with functional impairment), serious non neurological and serious neurological adverse events [52], reflecting the importance of understanding the underlying mechanisms in order to develop prevention or alternative strategies. The *primum movens* is thought to be the destruction of microfilariae in tissues leading to organ damage. The mechanisms underlying severe adverse reaction to DEC or IVM remain unelucidated, partly owing to the lack of pathology data. A historical necropsy found lesions associated with vascular stasis, thrombosis, granulomas around degenerating blood vessels packed with microfilariae in the brain parenchyma in both the grey and white matter after DEC treatment [53]. More recently, a study by Wanji and colleagues used an animal model of hypermicrofilaremic splenectomized baboons, who experienced clinical manifestations very similar to that of humans following ivermectin administration. Post-mortem examination revealed hemorrhages in various organs including the brain, lungs, heart, degenerating microfilariae in small vessels associated with fibrin deposition and extravascular erythrocytes, and eosinophilic infiltration in tissues. Although the small sample size did not allow for multivariate analysis, there was an increase in the number of MFD in the brain and kidneys as compared to untreated controls, that was further increased in the two individuals who had steroid co-administration but had higher initial MFD, and decreased in those who had aspirin coadministration [54]. The presence of live microfilariae in the cerebro-spinal fluid (CSF) has been described after DEC treatment [10], but a study where a sample of 10

patients with MFD>30,000 mf/mL had lumbar punction prior to the treatment confirmed that CSF was mf-free before treatment and that live microfilariae were seen after treatment initiation, in CSF as well as in urine samples along with hematuria [21]. Those findings, along with the frequent presence of sub-conjunctival hemorrhages associated with SAEs [55,56] and of retinal fundus haemorrhages are associated with Mf evocative of malaria-related micro-emboli [15] are in favor of vascular damages. Those vascular damages may be secondary to inflammation, immune-complex mediated.

Ivermectin is better tolerated than DEC [57], but hematologic and immunologic profiles of patients post single dose of DEC or IVM with adverse events suggest that post treatment reactions share a common pathophysiology, with a raise in the eosinophil counts following treatment [58]. Interestingly, different patterns of host-parasite relationships seem to exist with patients exhibiting major hypereosinophilia, filarial antibody titers and IL-5 levels with no circulating microfilariae on the contrary patients with very high MFD burden and lower eosinophil counts, [59–61] suggesting different immune response profiles. Those immunological modifications are resolutive post-treatment [62]. These observations motivated the recent conduct of a pilot clinical trial of an anti-IL5 monoclonal antibody (reslizumab) to test whether it lowered the frequency of secondary events following DEC, but eventually did not prove any benefice with this regard.

One of the questions that our study raises is the higher risk of SAEs in males, as compared with females in the same age category and with similar MFD. It may relate to unmeasured extrinsic confounders (for instance alcohol intake) or be linked to intrinsic differences and provide a clue to deciphering the mechanisms of toxicity. The influence of sex hormones and steroids hormone, which have in addition a circadian circle deserves to be investigated. Although elevation in hormone levels between *L. loa* microfilaremic girls as compared to controls have been observed [63], no link to side effect have been studied. The influence of sex on the eosinophil response to leishmaniosis, another parasitic disease has been questioned in a very preliminary manner [64]. Sex differences in the IL5 response also exist, better studied in the field of allergy or asthma [62]. This influence could be consistent with the finding of a much lower number of adverse events in children compared to adults.

Other possibilities have been explored such as the influence of coinfections (*Mansonella perstans* [45], *Plasmodium sp.* [65]).

Our study provides refined estimates of individual risk to guide individual treatment of microfilaremic individuals, both for imported loiasis or for the management of the disease in endemic areas if its clinical impact is confirmed by ongoing studies, and where single dose treatment

may reveal more feasible than bi-daily three-week long regimen. Our data does not allow to reconsider the threshold for DEC use which is commonly accepted to be below 2000 mf/mL. We did not use *M. perstans* microfilarial load as a covariate as it was found to be only marginally significant in the precedent publication and as our objective was to provide easily applicable data to guide the treatment of *L. loa* independently outside of the endemic area. The main limitations are the lack of data on confounding factors that could partially explain the gender-related excess risk, which is nevertheless consistent with previously published data. The overall strategy for prevention and management of those SAEs remains poorly studied, and is hampered by the lack of knowledge about the pathophysiological mechanisms. Up to date, although used quite frequently, corticosteroid therapy is not recommended as it can precipitate decubitus complications depending on the local context which can themselves precipitate death in comatose patients. Its use in settings where nursing can be provided adequately needs to be studied. Preliminary animal data has been obtained on the use of antithrombotic medication with aspirin, but this should be studied in depth before considering translation to human medicine in view of the benefit-risk balance giving the findings of tissue hemorrhages and vascular damages. Other adjuvant such as preventive anticoagulation should be studied. Albendazole was not the most widely used therapeutic in published series, and recent cases highlight that surveillance of its administration in heavily loaded individuals should be strictly watched, until an antiparasitic with an ideal safety and efficacy profile is available.

6. Conclusions

Our study suggests that IVM should be used with caution for males or individuals in specific age categories with a high *L. loa* MFD. For those individuals, lowering the thresholds previously used should be considered. The mechanism underpinning the increased risk in males needs to be clarified as it could provide crucial elements for the prevention or management of SAEs.

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4 Article II

Retrieving levels of pretreatment *Loa loa* microfilarial densities from microfilarial densities measured after ivermectin administration

Retrieving levels of pre-treatment *Loa loa* microfilarial densities from microfilarial densities measured after ivermectin administration

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1. Abstract

Introduction: Following the demonstration that ivermectin can interrupt the transmission of *Onchocerca volvulus,* it is now targeted by the WHO for eradication by 2030. This requires the treatment of all endemic areas including hypoendemic areas for onchocerciasis where loiasis is co-endemic. Yet, individuals with high microfilarial densities (MFD) are at risk of serious adverse events (SAEs), including encephalopathy, following ivermectin (IVM) administration. Better assessing the attributability of ivermectin in the occurrence of SAEs would enable to better manage the case, to refine the estimates of incidence of *L. loa* encephalopathy. Therefore, our objective was

to assess the extent to which the pre-treatment MFD can be inferred from the MFD measured after treatment.

Methods: We used data from seven clinical or community trials conducted in Cameroon during which *L. loa* MFD were measured before and at various timepoints following ivermectin administration. The classification performance of post-treatment MFD to accurately identify classes of pre-treatment MFD was assessed. Bootstrap procedures were used to compute the sensitivity, specificity, and positive and negative predictive values of different post-IVM MFD cutoffs for classifying individuals according to the commonly used pre-treatment thresholds.

Results: Our results indicate that an individual with MFD >3500 mf/mL at day 3-4 (D3-4) has a 69% probability of having pre-treatment MFD>20,000 mf/mL. At D5-10, a MFD>3500 mf/mL corresponds to 72% chance of having pre-treatment MFD >20,000 mf/mL. This probability is raised to 79% if MFD>4500 mf/mL. On the other hand, an individual with MFD<2500 mf/mL at D3-4 or D5-10 has a probability of 92 or 93% of having a pre-treatment MFD<20,000 mf/mL. Further more, if an individual harbors MFD<1500 mf/mL at day 3-4 (D3-4) or D5-10 he has 78% or 90% chances, respectively, of having pre-treatment MFD<8000 mf/mL.

Conclusions: We show that the MFD threshold of 1000 mf/mL within one month after treatment used to impute the occurrence of a SAE to IVM in the month following drug administration is probably too low. As ivermectin treatment might expand in the future to onchocerciasis hypoendemic areas where loiasis is coendemic, it is key to classify SAE cases as probable or possible using robust criteria. In this study, we propose abacuses that can be used to assess this imputability in mass or individual treatments.

2. Introduction

Mass drug administration (MDA) of ivermectin (Mectizan®, donated by Merck and Co. Inc.) is at the very core of the onchocerciasis elimination programmes conducted in Africa by the African Programme for Onchocerciasis Control (APOC) between 1995 and 2015, and the Expanded Special Project for Elimination of Neglected tropical diseases (ESPEN) since 2015. APOC's initial objective was to eliminate onchocerciasis as a public health problem, and community-directed

treatment with ivermectin (CDTI) was thus restricted to areas where surveys had shown that onchocerciasis was meso- or hyperendemic. Following the demonstration that ivermectin can interrupt the transmission of *Onchocerca volvulus* (the parasite causing human onchocerciasis) [1,2], the target switched now to the eradication of onchocerciasis by 2030, requiring the treatment of hypoendemic areas, i.e. where the prevalence of onchocercal nodules in adult men is ≤20% [3,4], where an estimated 17 million people will live in 2025 [5].

Serious adverse events (SAE) following MDA of ivermectin have been described since 1991 [6,7] whilst data gathered in community trials had not raised any safety concern [8–12]. SAEs were found to be due to infection with another filarial species, *Loa loa*, and are closely related to the density of *L. loa* microfilariae (mf, larval stage of the parasite) in the blood of infected individuals [13]. In areas where onchocerciasis is meso- or hyperendemic, CDTI should be accompanied by specific surveillances procedures to identify and manage SAE cases early. In hypoendemic areas, CDTI cannot be organized because the risk of SAE outweighs the benefit of treatment. In such areas, alternative treatment strategies (ATS) are being investigated such as initial test and not treat (TNT) strategy using a point of care diagnostic tool to measure *L. loa* microfilarial densities (MFD), the LoaScope [14–16]. However, despite allowing for repeated rounds without retesting, TNT is undoubtedly more costly per year of treatment than MDA. Those expenses, although estimated to be affordable given the economic benefits of onchocerciasis eradication [17] are feared to be prohibiting [4] and the strategy is therefore not yet endorsed by the WHO. Post-ivermectin *Loa*-related SAEs constitute a major impediment to the eradication of onchocerciasis because they prevent CDTI in hypoendemic areas.

Adverse events have been classified as (i) mild with no functional impairment, (ii) marked with functional impairment lasting less than 7 days and (iii) serious with or without neurological involvement. Among them, encephalopathies are the most feared events, with an estimated incidence of 1.1 per 10,000 treatments as in the clinical trial by Gardon *et al* [13]. Benign manifestations are usually observed within the 48 hours following intake, and include pruritus, arthralgias, headache, and first symptoms of concern usually occur 3 to 5 days and up to 7 days post-administration with progressive onset of language and consciousness disorders, incontinence, motor deficit, the ultimate evolution of which would be feverish coma of various stages [18]. All those manifestations are totally aspecific with respect to the etiology involved, accounting for the time that was needed to establish the causal relationship. As mentioned above, the surveillance and

detection of SAEs in CDTI areas where onchocerciasis and loiasis are co-endemic is part of the global strategy and has been described in recommendations made by the Mectizan® Donation Program (MDP) and APOC. It involves visits by trained medical staff in the days following the distribution with the aim to identify and early manage those patients with marked or serious adverse events. Treatment of SAE cases is not standardized and consists first and foremost of supportive care and eliminating other curable causes of neurological conditions (e.g., cerebral malaria). As part of the surveillance, 65 out of the 103 encephalopathies that represented half of the reported events (207) during the campaigns from 1989 to 2001, had been linked to loiasis [19]. As ivermectin is distributed as part of MDA campaigns, no individual pre-treatment data is usually available. Actually, only eight cases of post-ivermectin *Loa*-related SAE with documented pre-treatment *L. loa* MFD have been published. In these 8 cases, MFD ranged from 50,520 mf/mL to 217,000 mf/mL [6,7,13,20]. In the first study aimed at evaluating the incidence of post-ivermectin *Loa*-related SAEs, subjects harboring more than 8100 mf/mL were found to have a 10-fold risk of developing marked adverse events as compared non individuals with 0 mf/mL, and this risk was as high as 1000-fold for subjects harboring *L. loa* MFD >30,000 mf/mL. There is probably a continuum of severity between severe and non-severe adverse events [21].

Ivermectin is a potent microfilaricidal drug again *L. loa*, lowering rapidly the MFD that reaches a steady state after 1 week or so [22,23] (**Figure 1**). Probable *L. loa* encephalopathy has been defined as an encephalopathy occurring ≤7 days after ivermectin treatment in a previously healthy subject whose *L. loa* MFD was >10,000 mf/mL before treatment, or >1000 mf/mL within one month after treatment, or >2700 mf/mL within 6 months post-treatment [24]. However, these thresholds were defined in the early years of CDTI and are not strongly supported by data. Besides probable cases clearly defined, "possible cases" involve non-quantitative *L. loa* MFD estimations. The threshold that arouses more interest for acute care is the post-treatment "early" threshold of 1000 mf/mL as this may guide physicians towards the diagnosis of *L. loa* encephalopathy or urge them to search for an alternate diagnosis. As ivermectin treatment might expand in the future to onchocerciasis hypoendemic areas where loiasis is coendemic, it is key to classify SAE cases as probable or possible using strong criteria. Better assessing the attributability of ivermectin in the occurrence of SAEs would enable to better manage the case, to refine the estimates of incidence of *L. loa* encephalopathy, and map the risk for communities. Therefore, our objective was to assess the extent to which the pre-treatment MFD can be inferred from the MFD measured after treatment.

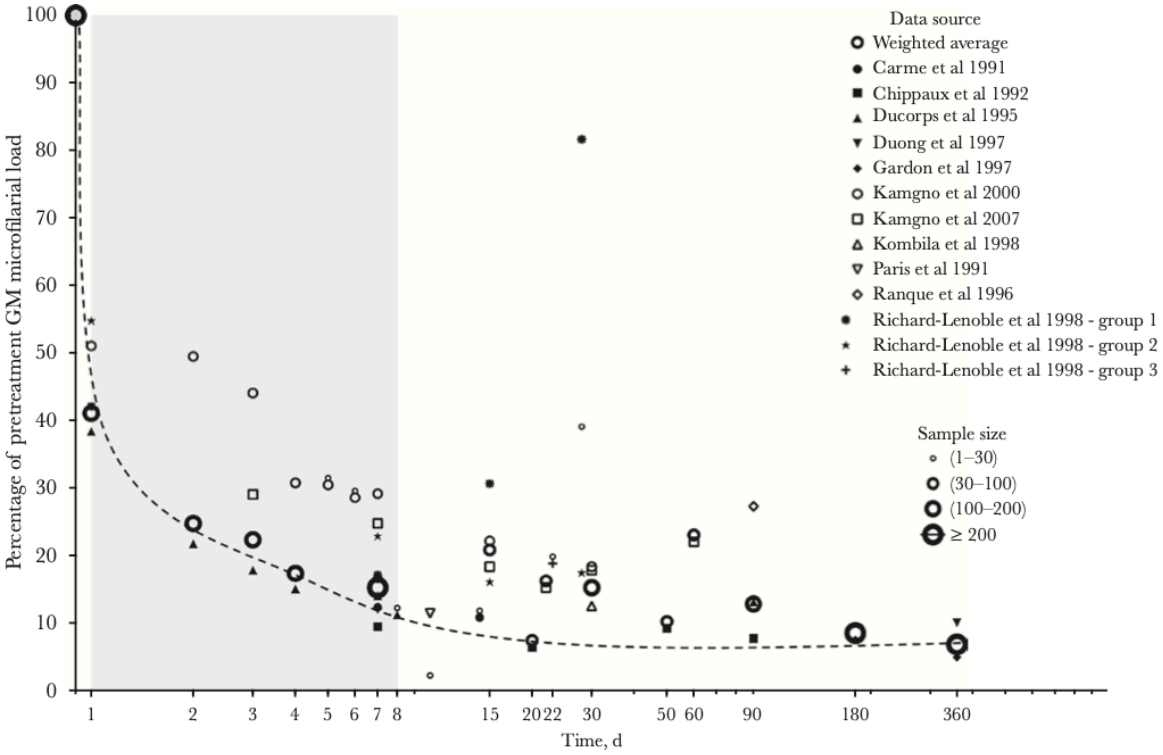

Figure 1. Weighed geometric mean of *Loa loa* microfilarial density after ivermectin treatment.

The dashed line represents the average trend in microfilarial density.

Reproduced from Pion *et al* [23]

3. Patients and methods

Study population

We use data from six clinical or community trials conducted in Cameroon during which *L. loa* MFD were measured before treatment and within 14 days of the administration of a unique standard dose of ivermectin (IVM, 150-200 μg/kg). The studies were identified using the PubMed and ISI Web of Knowledge database and data extracted as previously described in Pion *et al* [23]. Details on the methods can be found in the original publications [6,25–29]. Briefly, the study by Chippaux *et al* [25] enrolled 290 individuals aged ≥5 years in two villages of the Sanaga Valley (southern Cameroon), to evaluate repeated standard doses of ivermectin (200 μg/kg) every 3 months two (n=225, of whom 84 had MFD>0 mf/mL) or three times (n=65, of whom 26 had MFD>0 mf/mL). Thick blood smears (TBS) were drawn prior treatment administration and on days 7 (D7), D21, and D50 after intake. A total of 80 individuals had at least one post-treatment measurement. Ducorps *et al* [6] conducted in 1993-94 a clinical trial in the Central Hospital of Yaoundé, to assess the tolerance of IVM 200 μg/kg in 112 individuals aged 18-60 years with high MFD (inclusion criterion: MFD≥3300mf/mL). TBS were performed before treatment and the 5 following days at least, or later if their status warranted additional surveillance. The community trial conducted by Ranque *et al* [26] took place in the forest village of Ngat in in southern Cameroon in 1993-1995 to assess the impact of yearly IVM administration. As part of the study, 42 and 27 individuals with initially MFD>0 mf/mL had TBS follow-up information available 7 days and 3 months after the first administration, respectively. Kamgno *et al* [27] enrolled 23 adult patients aged 18-70 years, in the Sanaga Valley with 100<MFD<3000 mf/mL to compare the administration of low dose IVM to the standard dose (150 μ/kg). Thirteen patients were included in the standard arm, and TBS were taken before treatment and at D1, D7, D15, and D30. The second clinical trial conducted by Kamgno *et al* [28] in 7 villages of the Central Province of Cameroon enrolled 95 people with 100<MFD<15,000 mf/mL, aged 15-70 years, to receive low-dose (n=55) or standard IVM (n=29). TBS were taken before treatment and 3, 7, 15, 22, 30 and 50 days after. Lastly, Paris *et al* [29] studied the impact of IVM (200 μ/kg) on 7 participants aged with MFD>0 mf/mL among whom 5 had at least one post-treatment measure available.

Validation data comprised measurement made as part of all the above mentioned studies plus the study by Gardon *et al* [22] conducted in 1994-1995 in the Lekie valley (Center Region, Cameroon), where 420 individuals aged ≥ 15 years in 7 MFD strata were included (0,1-100, 101-500, 501-2000, 2001-10,000, 10,001-30,000, >30,000 mf/mL), and TBS drawn 180 days after IVM administration.

Four additional studies were found to have MFD data obtained before and after treatment, but we had no access to individual data [9,10,30,31].

Parasitological examination

As part of the studies, calibrated (30 or 50 μL) TBS from a finger prick obtained between 10:00 AM and 4:00 PM were performed to measure the *L. loa* microfilarial density. Individual MFD are expressed in mf/mL of blood.

Statistical analyses

For the purpose of analysis, prespecified treatments MFD thresholds were considered for the pre-treatment value (*L. loa* MFD_{D0}):

(i) 8000 mf/mL, corresponding to a 10-fold increase in the risk of marked adverse event [13], and used in therapeutic guidance [32]

(ii) 10,000 mf/mL, which is the threshold acknowledged by expert from the MDP in 1995 and included in the 2003 classification of *L. loa*-related adverse events [24].

(iii) 20,000 mf/mL, which is the threshold used with the LoaScope point of care device which measure *L. loa* MFD within 3 minutes after blood sampling

(iv) 30,000 mf/mL, which is the threshold above which IVM is usually contraindicated

(v) 50,000 mf/mL, corresponding to the lower bound of MFD in documented *L. loa*-related cases as mentioned above.

The post-treatment MFD were considered at two different time-points. Considering that clinical manifestations of concern occur usually at or after D3, and that therefore investigation of potential SAEs by may not start earlier, the first time-point was set at day 3-4 post treatment (*L. loa* MFD_{D3-4}). For individuals who had MFD measured at both D3 and D4 we used the arithmetic mean of the values to lower the variability linked to TBS reading. Considering that there is a significant decrease between MFD measured after 3-4 and 7 days, another time point was set around D7, for which any MFD measured between D5 and D10 could contribute, or the arithmetic mean (cf. supra, *L. loa* MFD_{D5-10}). This was done to allow for flexibility given the remote location of certain areas that may be difficult to reach by the medical surveillance staff as part of the CDTI surveillance.

Receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC) were drawn to assess the capacity of *L. loa* MFD_{D3-4} or *L. loa* MFD_{D5-10} measured as a continuous

variable (mf/mL) discriminate between pre-treatment MFD below or above each of the prespecified thresholds. The theoretical best cutoff for each pair (pre-treatment threshold, measurement timepoint) were determined using Youden's index. Intrinsic (sensibility, specificity, accuracy) and extrinsic (positive and negative predictive values) attributes of various surrounding cutoffs were estimated using a classic bootstrap procedure with 1,000 resampling iterations.
We investigated whether individual characteristics (age and sex) could enhance prediction accuracy by fitting multivariate logistic regression model and retrieving the estimated coefficients using a .632 bootstrap procedure before fitting the derived score in a classical bootstrap procedure. As this procedure did not lead to significantly better estimates, which was consistent with the finding by Pion *et al* that MFD reduction rates increased minimally with age and did not differ between sexes, we chose not to keep it, since it is by far more operational on a large scale to use the value of post-treatment MFD alone as a predictor.

Eventually, as MFD reduction is relatively stable after one week or so and for at least 6 months, cutoffs of interest were then used to assess how accurate was the discrimination of the first MFD measured between 2 and 26 weeks after treatment, on a sample of individuals that had not participated in the first part of the study [33] and additional individuals who had a measurement following that of $MFD_{D3\text{-}4}$ or $MFD_{D5\text{-}10}$.
All analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria), and Stata© version 17.0 (StataCorp, College Station, Texas, TX, USA).

4. Results

Description of the study population

A total of 281 individuals with *L. loa* MFD available both before treatment and 3 to 10 days after ivermectin treatment were enrolled in the 6 studies described above. The description of the study population can be found in **Table 1**. The median age was 43 years (range: 5-78) and 45% of participants were women (124/276). The mean *L. loa* MFD_{D0} was high (16,700 mf/mL) with a skewed distribution, and 48 participants had a *L. loa* MFD_{D0} above 30,000 mf/mL. A total of 157 participants had *L. loa* $MFD_{D3\text{-}4}$ available, of whom 39 had *L. loa* MFD measured only on D3, 4 only on D4, and 114 at both. Similarly, 190 participants from all 6 studies had *L. loa* $MFD_{D5\text{-}10}$ available, to which contributed 13, 13, 171, 14, and 5 measures made on D5, D6, D7, D8, and D10.

Table 1. Baseline characteristics of the study population

	N=281
Age (median, IQR) *	43 (32-54)
≤15	12 (4.4)
16-30	47 (17.0)
31-45	94 (34.1)
46-60	88 (31.9)
≥60	35 (12.7)
Sex *	
Female	124 (44.9)
Male	152 (55.1)
L. loa MFD_{D0} (median, IQR)	7,640 (2,266-22,064)
1-2000	67 (23.8)
2001-8000	82 (29.2)
8001-10,000	19 (6.8)
10,001-20,000	36 (12.8)
20,001-30,000	29 (10.3)
30,001-50,000	26 (9.3)
>50,000	22 (7.8)
Cumulated MFD *L. loa* below/above thresholds	
8000	149 (53.0) / 132 (47.0)
10,000	168 (59.8) / 113 (40.2)
20,000	204 (72.6) / 77 (27.4)
30,000	233 (82.9) / 48 (17.1)
50,000	259 (92.2) / 22 (7.8)
Study of origin	
Paris *et al*, 1991 [29]	5 (1.8)
Chippaux *et al*, 1992 [25]	76 (27.1)
Ducorps *et al*, 1995 [6]	112 (39.9)
Ranque *et al*, 1996 [26]	42 (15.0)
Kamgno *et al*, 2000 [27]	13 (4.6)
Kamgno *et al*, 2007 [28]	33 (11.7)

IQR: interquartile range; MFD_{D0}: microfilarial density pre-treatment

* 5 missing values from the study [29]

Evaluation of discrimination performance using ROC curves

Using *L. loa* MFD_{D3-4}, AUC were 0.903 (95% confidence interval [95%CI]: 0.858-0.948), 0.897 (95%CI: 0.849-0.946), 0.866 (95%CI: 0.802-0.929), 0.809 (95%CI: 0.716-0.902), and 0.757 (95%CI: 0.614-0.900) for predicting *L. loa* MFD_{D0} at the thresholds of 8000, 10,000, 20,000, 30,000 and 50,000 mf/mL, respectively. Using *L. loa* MFD_{D5-10}, the values were lowered to 0.892 (95%CI: 0.846-0.939), 0.881 (95%CI: 0.833-0.930), 0.878 (95%CI: 0.818-0.938), 0.860 (95%CI: 0.774-0.946), and 0.888 (95%CI: 0.790-0.986), respectively. Corresponding curves for the 8000 to 30,000 thresholds are presented in **Figure 2**.

Best cutoffs determined from Youden's index are shown in **Table 2**. For the 10,000 mf/mL threshold used in the previously published SAE definition, the optimal cutoff was of 2245 mf/mL when *L. loa* MFD was measured at D3-4 and 1483 mf/mL at D5-10.

Table 2. Best cutoffs determined from Youden's index

L. loa MFD_{D0} Thresholds (mf/mL)	*L. loa* MFD_{D3-4}			*L. loa* MFD_{D5-10}		
	Cutoff (mf/mL)	Se (%)	Sp (%)	Cutoff (mf/mL)	Se (%)	Sp (%)
8000	2230	75	92.8	1563	82.6	81.8
10,000	2245	80.5	90.0	1483	85.7	74.6
20,000	2478	86.3	79.2	2283	78.4	83.6
30,000	4091	69.7	85.5	2283	81.8	78.6
50,000	4166	64.3	79.7	3099.7	84.6	85.3

MFD: microfilarial density; D0: pre-treatment; D3-4: 3 to 4 days after treatment; D5-10: 5 to 10 days after treatment; mf: microfilaria; se: sensitivity; sp: specificity.

Performance of the threshold of 1000 mf/mL to predict *L. loa* MFD_{D0}>10,000 mf/mL

The threshold used in the definition provided by Twum-Danso *et al* [24] exhibited low accuracy of around 72% at both D3-4 or D5-10. In particular, at those timepoints sensitivity (Se) was high (94.9 and 89.5%), as was negative predictive values (NPV, 90.9 and 93.7%) but contrasted with very low specificity (Sp, 50.6 and 72%) and low positive predictive values (PPV, 64.8 and 51.2%).

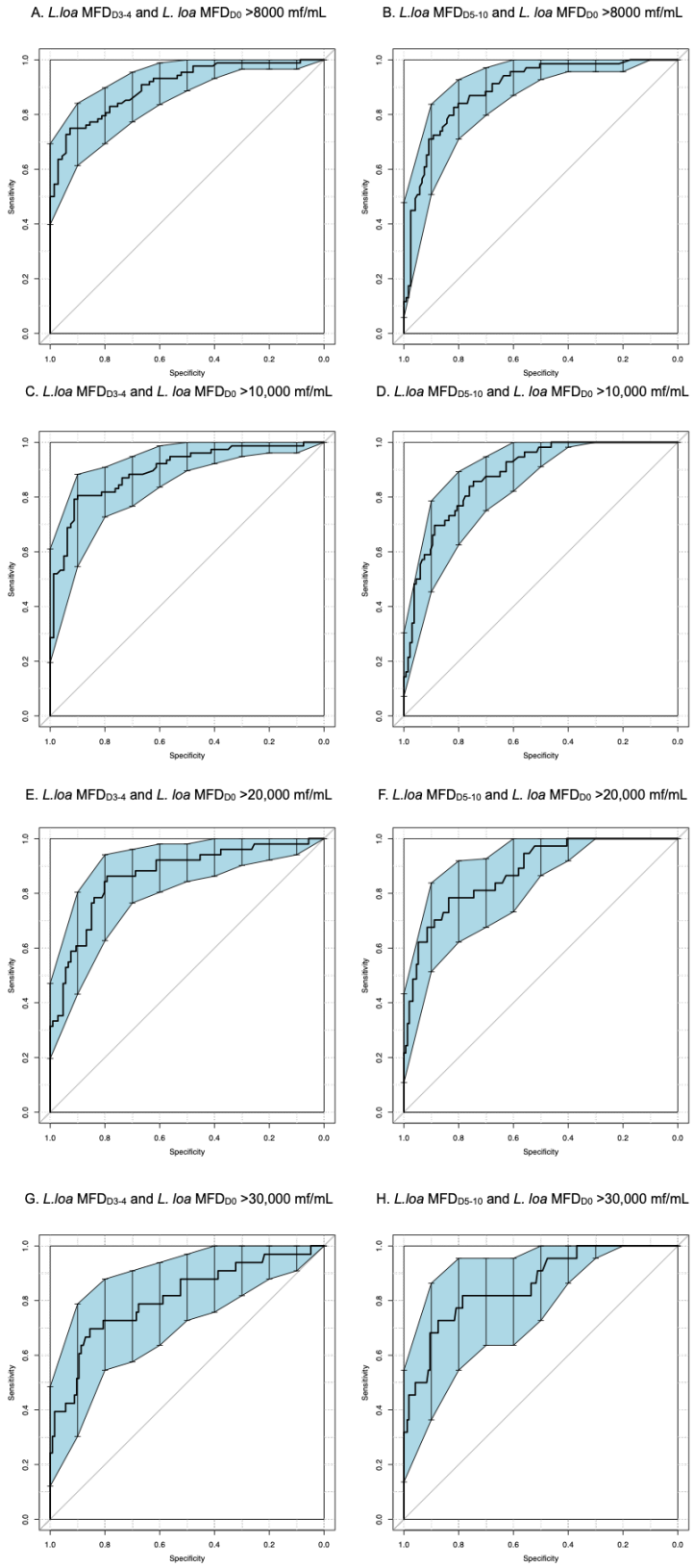

Figure 2. ROC curves for determining *L. loa* MFD$_{D0}$ above 10,000 (A and B), 20,000 mf/mL (C and D), 20,000 mf/mL (E and F) 30,000 mf/mL (G and H) from *L. loa* MFD$_{D3-4}$ (first column) or *L. loa* MFD$_{D5-10}$ (second column).

Performance of various cutoff for predicting pre-treatment *L. loa* MFD categories

Predicting* L. loa *MFD_{D0} over 8000 mf/mL ($T_{8,000}$) or 10,000 mf/mL ($T_{10,000}$)

The accuracy of classification was highest for the cutoffs of 2500 mf/mL for both $T_{8,000}$ and $T_{10,000}$, reaching 80.9% and 84.1%, respectively at D3-4. At D5-10, accuracy was maximal at 2000 mf/mL for $T_{8,000}$ (83.2%) and $T_{10,000}$ (80.5%), although for this latter threshold, the cutoff of 2500 mf/mL was slightly better (82.5%).

If we retain accordingly the cutoff of 2500 mf/mL, for $T_{10,000}$ it corresponds to a Se of 76.5%, a NPV of 80.2%, a Sp of 91.4% and a PPV of 89.5% at D3-4; or to 66.0% Se, 86.3% NPV, 84.1% Sp, and 72.7 PPV at D5-10.

One may want to optimize Se/NPV by lowering the cutoff, closer to the best threshold by Youden's index method. The choice of a cutoff of 1500 mf/mL would then give NVP/PPV of 85.3/75.3% at D3 and 92.6/58.5% at D5-10. A cutoff of 2000 mf/mL would provide NVP/PPV of 81.2/80.5% at D3 and 87.6/65.5% at D5-10.

Predicting* L. loa *MFD_{D0} over 20,000 mf/mL ($T_{20,000}$)

Classification clearly plateaued for thresholds values of *L. loa* MFD_{D0} above 20,000 mf/mL owing to the lesser number of observations available and resulting in asymptomatic parameters very closely related to the prevalence of cases. At $T_{20,000}$, classification was still performing quite well and showed maximum accuracy of 81.5% for the cutoff of 3000 mf/mL at D3-4 and of 87.9% for the cutoff of 3500 mf/mL at D5-10.

The cutoff of 3000 mf/mL corresponded to 75.9% Se, 88.0% NPV, 84.1% Sp, and 69.4% PPV at D3-4 and 67.6% Se, 92.3% NPV, 81.5% Sp, and 65.8% PPV at D5-10. The cutoff of 3500 mf/mL corresponded to 68.1% Se, 84.8% NPV, 85.0% Sp, 68.6% PPV at D3-4 and 62.4% Se, 91.2% NPV, 79.6% Sp, 72.2% PPV at D5-10. Lowering the cutoff, closer to 2000 mf/mL would then provide NVP/PPV of 91.1/56.7% at D3 and 92.3/66.2% at D5-10. The cutoff of 2500 would yield NVP/PPV of 93.9/47.3% at D3 and 92.8/52.6% at D5-10.

In a view of their use as abacuses, comprehensive extrinsic (NPV and PPV) and intrinsic (accuracy, sensitivity, and specificity) qualities of *L. loa* MFD_{D3-4} and MFD_{D5-10} at cutoffs from 500 to 5000 mf/mL to classify *L. loa* MFD_{D0} according to the prespecified thresholds are presented in **Tables 3 to 5** and represented along with their IQR and 95%CI determined by bootstrap in **Figure 3**.

Table 3. Positive and negative predictive value of post-treatment microfilarial densities for predicting pre-treatment microfilarial densities

	Day 3-4 Pre-treatment MFD thresholds					Day 5-10 Pre-treatment MFD thresholds				
Cutoffs	8000	10,000	20,000	30,000	50,000	8000	10,000	20,000	30,000	50,000
Predictive positive value										
500	66.4%	58.1%	38.0%	24.6%	10.5%	55.4%	45.3%	30.1%	17.5%	10.7%
1000	72.6%	64.8%	42.3%	26.5%	11.3%	62.6%	51.2%	33.7%	19.4%	12.0%
1500	**82.1%**	**75.3%**	52.5%	32.5%	13.3%	**70.7%**	**58.5%**	37.6%	21.8%	13.0%
2000	**87.1%**	**80.5%**	56.7%	33.8%	12.9%	**80.4%**	**65.5%**	47.3%	29.3%	17.5%
2500	**94.2%**	**89.5%**	**66.2%**	39.4%	15.2%	**82.6%**	**72.7%**	**52.6%**	33.3%	20.8%
3000	96.6%	91.4%	**69.4%**	42.9%	16.0%	86.8%	79.4%	**65.8%**	42.2%	28.2%
3500	96.3%	90.5%	**68.6%**	46.8%	17.5%	90.6%	84.6%	**72.2%**	47.1%	30.3%
4000	100.0%	95.5%	73.9%	54.8%	21.2%	88.0%	80.0%	72.2%	43.5%	31.5%
4500	100.0%	97.0%	80.8%	58.3%	22.6%	87.0%	83.0%	78.6%	47.6%	34.4%
5000	100.0%	96.8%	83.3%	59.4%	24.1%	85.0%	80.0%	75.0%	55.0%	38.9%
Negative predictive value										
500	96.3%	96.3%	96.3%	96.3%	100.0%	95.8%	97.2%	98.6%	98.6%	100.0%
1000	86.4%	90.9%	93.3%	93.3%	97.8%	91.4%	93.7%	95.7%	96.8%	98.9%
1500	**78.3%**	**85.3%**	94.0%	94.0%	97.1%	**89.6%**	**92.6%**	94.4%	96.3%	98.2%
2000	**74.0%**	**81.2%**	91.1%	91.1%	95.1%	**84.6%**	**87.6%**	93.9%	96.9%	98.5%
2500	**71.6%**	**80.2%**	**92.3%**	92.3%	95.7%	**80.6%**	**86.3%**	**92.8%**	96.4%	98.6%
3000	66.3%	74.0%	**88.0%**	91.0%	95.1%	76.1%	83.0%	**92.3%**	96.1%	98.7%
3500	63.3%	70.4%	**84.8%**	91.4%	95.4%	74.5%	81.8%	**91.2%**	95.5%	98.1%
4000	60.0%	67.6%	82.8%	91.2%	95.7%	71.4%	78.2%	88.5%	93.3%	97.0%
4500	54.9%	62.5%	79.5%	87.9%	94.5%	70.7%	77.9%	88.7%	93.4%	97.1%
5000	54.1%	61.5%	79.1%	87.3%	94.6%	69.5%	76.6%	87.1%	93.5%	97.1%

(continued)

Values indicate median bootstrapped values of predictive positive value and negative predictive value of pre-treatment MFD according to post-treatment MFD measured at day 3-4 or 5-10 after ivermectin administration. For instance, column 1 indicates that if MFD measured 3 to 4 days after IVM treatment is above 500 mf/mL there is a probability of 66.4% that MFD was above 8000 mf/mL before treatment, and that if MFD measured 3 to 4 days after IVM treatment is below 500 mf/mL there is a probability of 96.3% that MFD was below 8000 mf/mL before treatment.

Bold indicates threshold that may be considered except for thresholds of 30,000 mf/mL and 50,000 mf/mL owing to larger uncertainty in estimates.

Table 4. Accuracy of post-treatment microfilarial densities for predicting pre-treatment microfilarial densities.

	Day 3-4 Pre-treatment MFD thresholds					Day 5-10 Pre-treatment MFD thresholds				
Cutoffs	8000	10,000	20,000	30,000	50,000	8000	10,000	20,000	30,000	50,000
Accuracy										
500	71.3%	64.3%	47.8%	36.3%	25.5%	70.5%	64.7%	55.8%	47.9%	44.2%
1000	76.4%	72.0%	56.7%	45.9%	35.7%	76.8%	72.1%	64.2%	57.4%	54.2%
1500	80.3%	79.6%	70.7%	59.2%	49.7%	81.6%	77.9%	70.0%	64.2%	61.6%
2000	80.3%	80.9%	74.5%	63.1%	54.8%	**83.2%**	80.5%	78.9%	75.3%	72.6%
2500	**80.9%**	**84.1%**	**81.5%**	70.1%	61.8%	81.1%	**82.6%**	82.1%	79.5%	77.9%
3000	77.1%	80.3%	**81.5%**	73.9%	67.5%	78.4%	82.1%	86.8%	85.3%	84.7%
3500	73.9%	77.1%	79.6%	77.1%	70.1%	77.4%	82.1%	**87.9%**	87.4%	86.8%
4000	70.7%	75.2%	80.3%	81.5%	75.8%	73.7%	78.4%	86.3%	86.8%	88.4%
4500	63.7%	69.4%	79.6%	82.2%	80.3%	72.6%	78.4%	87.4%	87.9%	89.5%
5000	62.4%	68.2%	79.6%	82.2%	81.5%	71.1%	76.8%	85.8%	89.5%	91.1%

Bold indicates threshold that may be considered except for thresholds of 30,000 mf/mL and 50,000 mf/mL owing to larger uncertainty in estimates.

Table 5. Sensitivity and specificity of post-treatment microfilarial densities for predicting pre-treatment microfilarial density level.

	Day 3-4 Pre-treatment MFD thresholds					Day 5-10 Pre-treatment MFD thresholds				
Cutoffs	8000	10,000	20,000	30,000	50,000	8000	10,000	20,000	30,000	50,000
Sensitivity										
500	98.9%	98.7%	98.1%	97.1%	100.0%	95.7%	96.5%	97.4%	95.7%	100.0%
1000	93.1%	94.9%	94.2%	91.0%	93.3%	88.6%	89.5%	89.2%	87.0%	92.9%
1500	**83.1%**	**87.1%**	92.2%	88.0%	86.7%	**84.0%**	**85.7%**	83.8%	82.1%	85.4%
2000	**76.3%**	**80.6%**	86.2%	78.8%	71.4%	**71.0%**	**71.2%**	78.1%	82.1%	85.4%
2500	**70.5%**	**76.5%**	**86.2%**	78.8%	71.4%	**60.6%**	**66.0%**	73.0%	77.8%	85.4%
3000	61.1%	65.9%	**75.9%**	72.4%	64.3%	47.5%	53.3%	67.6%	72.6%	85.4%
3500	55.4%	59.3%	**68.3%**	72.4%	64.3%	41.5%	47.8%	62.4%	68.0%	76.9%
4000	47.6%	51.5%	60.7%	69.4%	64.3%	31.4%	35.3%	48.5%	50.0%	61.5%
4500	34.9%	38.5%	48.8%	54.2%	50.0%	28.6%	33.9%	48.5%	50.0%	61.5%
5000	32.6%	36.0%	46.8%	51.4%	50.0%	24.3%	28.3%	40.0%	50.0%	61.5%
Specificity										
500	36.1%	31.3%	23.4%	20.2%	18.1%	71.3%	64.3%	47.8%	36.3%	25.5%
1000	55.1%	50.6%	38.7%	33.1%	30.1%	76.4%	72.0%	56.7%	45.9%	35.7%
1500	**76.7%**	**72.4%**	60.2%	51.6%	46.1%	**80.3%**	**79.6%**	70.7%	59.2%	49.7%
2000	**85.7%**	**81.3%**	68.8%	59.1%	53.2%	**80.3%**	**80.9%**	74.5%	63.1%	54.8%
2500	**94.4%**	**91.4%**	**79.3%**	68.0%	61.1%	**80.9%**	**84.1%**	**81.5%**	70.1%	61.8%
3000	97.2%	94.0%	**84.1%**	74.6%	67.6%	77.1%	80.3%	**81.5%**	73.9%	67.5%
3500	97.2%	94.0%	**85.0%**	78.6%	71.0%	73.9%	77.1%	**79.6%**	77.1%	70.1%
4000	100.0%	97.6%	89.8%	84.9%	77.1%	70.7%	75.2%	80.3%	81.5%	75.8%
4500	100.0%	98.8%	94.4%	89.8%	83.5%	63.7%	69.4%	79.6%	82.2%	80.3%
5000	100.0%	98.8%	95.5%	90.7%	84.9%	62.4%	68.2%	79.6%	82.2%	81.5%

Bold indicates threshold that may be considered except for thresholds of 30,000 mf/mL and 50,000 mf/mL owing to larger uncertainty in estimates.

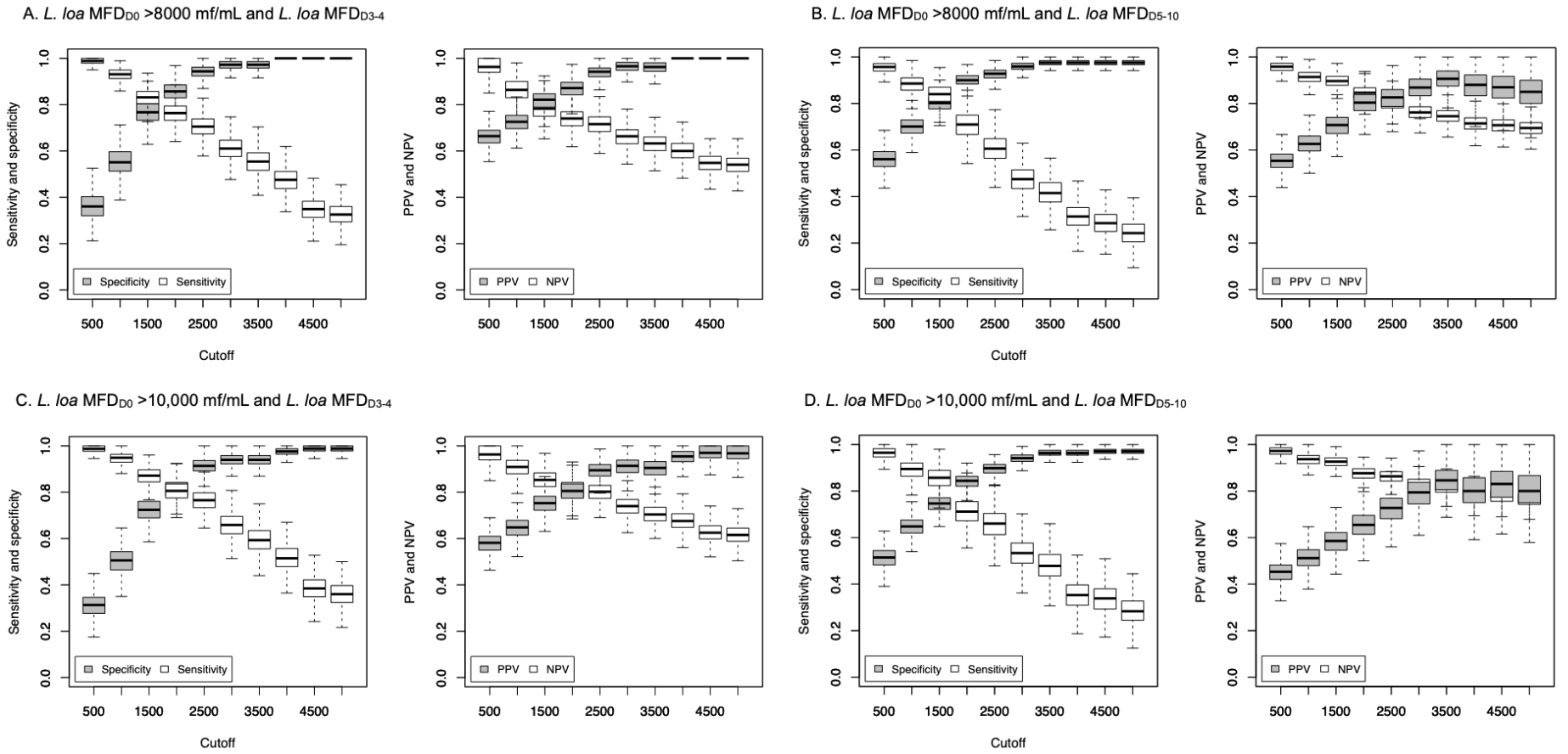

Figure 3. Interquartile ranges of sensitivity, specificity, positive and negative predictive values, according to the cutoffs of *L. loa* microfilarial density measured 3 to 4 or 5 to 10 days after ivermectin administration.

MFD: microfilarial density; PPV: positive predictive value; NPV: negative predictive value; pre: pre-treatment; D3-4: day 3 or 4 after treatment; D5-10: 5 to 10 days after treatment.

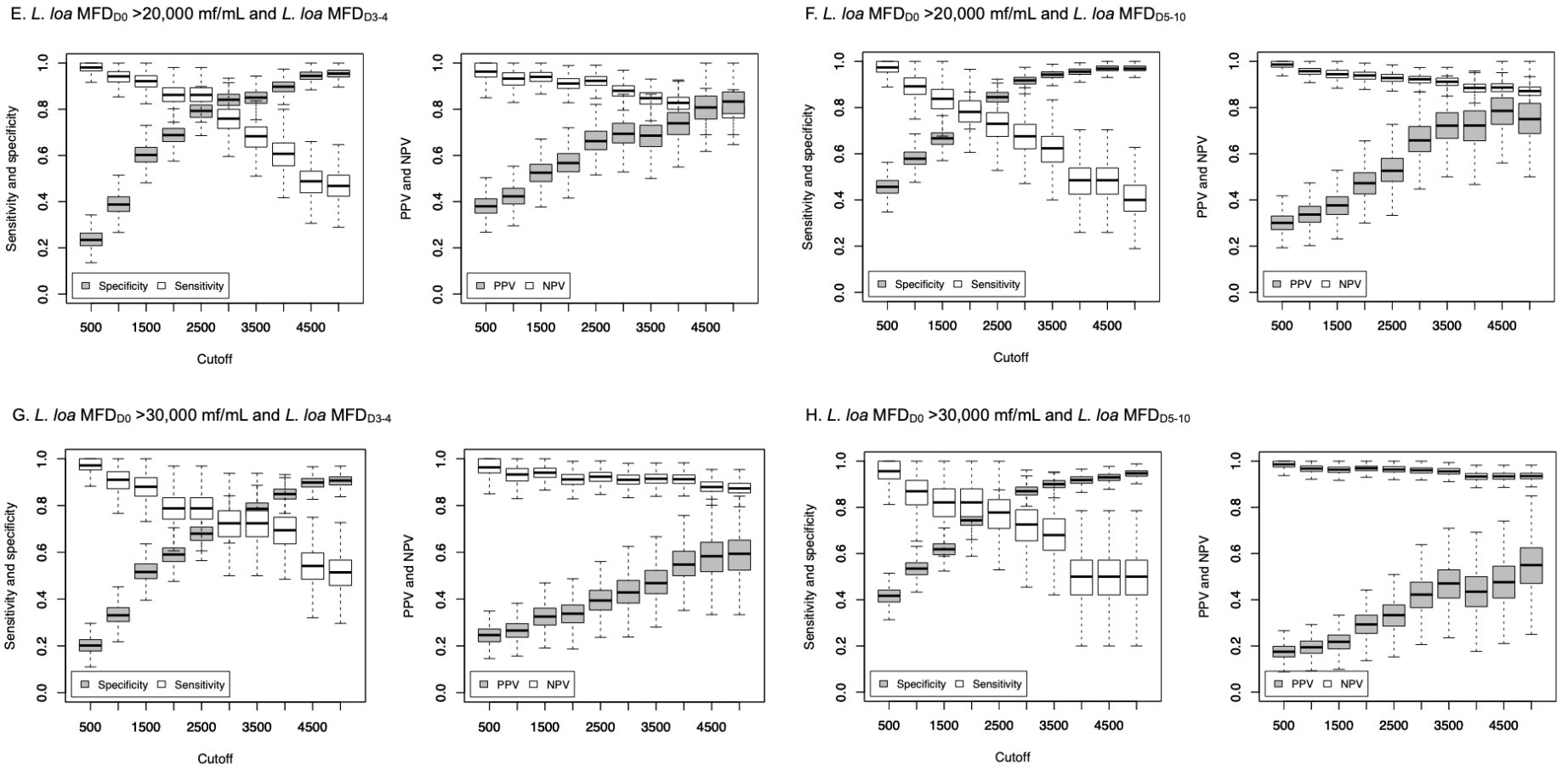

Figure 3. (continued) Interquartile ranges of sensitivity, specificity, positive and negative predictive values, according to the cutoffs of *L. loa* microfilarial density measured 3 to 4 or 5 to 10 days after ivermectin administration.

MFD: microfilarial density; PPV: positive predictive value; NPV: negative predictive value; pre: pre-treatment; D3-4: day 3 or 4 after treatment; D5-10: 5 to 10 days after treatment.

Semi-external validation of the thresholds on MFD obtained 2 to 26 weeks after ivermectin administration

The validation sample was composed of 167 individuals who had another MFD measurement between 5 and 10 days which contributed to the previous analyses, and of 271 other patients that were not part of the original sample. The populations did not differ in terms of age, sex ratio or initial MFD category (1-2000: 32.3% (n=34); 2001-8000: 34.1% (n=57); 8001-10,000: 6.6% (n=11); 10,001-20,000: 9.6% (n=16); 20,001-30,000: 4.2% (n=7); 30,001-50,000: 7.2% (n=12), >50,000 mf/mL:6.0% (n=10)). Discrimination performances were good with accuracy over 80% in most cases (**Table 6**).

Table 6. Observed sensitivity, specificity, positive and negative predictive values when using post-treatment *L. loa* MFD measured 2 to 26 weeks after ivermectin administration at selected cutoffs to predict the pre-treatment MFD category according to various thresholds.

Threshold $MFD_{D0\ (mf/mL)}$	Cutoff MFD_{post}	Se	Sp	PPV	NPV	Accuracy
8000						
	1500	83.0	87.5	74.7	92.0	86.0
	2000	80.0	91.8	81.2	91.2	79.0
	2500	71.1	94.1	84.2	88.0	87.0
10,000						
	1500	85.3	84.2	66.0	94.1	84.5
	2000	81.9	88.2	71.4	93.1	86.5
	2500	75.0	91.6	76.3	91.1	87.2
20,000						
	2500	85.5	86.5	57.0	96.6	86.3
	3000	84.2	88.4	60.4	96.4	87.7
	3500	79.0	89.8	61.9	95.3	87.9
30,000						
	3500	84.2	87.1	49.5	97.4	86.8
	4000	79.0	89.8	53.6	96.6	88.4
	4500	75.4	91.3	56.6	96.1	89.3
	5000	73.7	93.7	63.6	96.0	91.1

Data are % unless otherwise specified.

MFD: microfilarial density; pre: pre-treatment; post: post-treatment; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value

As expected, though performance indicators were elevated for the threshold 30,000 mf/mL, PPV and (1-Sensitivity) were low and high respectively, accounting for the fact that accurate classification was aggregated among values below the threshold, which is better captured by visualization of contingency tables (data not shown), therefore caution should be used when considering this threshold and that of 50,000 mf/mL.

5. Discussion

One of the main challenges when monitoring SAEs occurring during CDTI, as with pharmacovigilance data in general, is to assess the attributability (degree of causality) between the drug received and the event. On a scale as large as that of an international elimination program, it is therefore important to have definitions to guide this investigation of attributability. It is now clearly established that SAEs, and in particular potentially fatal encephalopathies can occur following ivermectin administration to individuals harboring high *L. loa* MFD, in a dose-dependent fashion. However, information on the *L. loa*. MFD of subjects receiving the drug is usually -apart from a few clinical trials- not known until an adverse event occurs, and the case is referred for individual care and undergoes additional biological examination in this context. For this reason, *L. loa* MFD of suspected *L. loa*-related adverse events is generally known several days after ivermectin treatment, after the onset of symptoms. Yet, ivermectin is a very potent microfilaricidal drug, and a single standard dose results in a drastic reduction in *L. loa* MFD, estimated in a recent meta-analysis at, in average, 85% of the initial MFD at D7, with important inter-individual variability [23]. Our study evaluates for the first time the pertinence of the threshold values proposed during a meeting on the post-ivermectin SAEs organized in 1995 by the MDP, which have been used again in the classification of Twum-Danso *et al* in 2003 [24]. Apart from clinical (progressive onset of encephalopathy, without seizures, usually feverish, in a previously healthy individual) and temporality (onset within 7 days of ivermectin administration) criteria, biological data have been included with a threshold of MFD >10,000 mf/mL before treatment defining "probable" cases. In case no pre-treatment *L. loa* MFD was available, the thresholds of 1000 mf/mL measured in the month following treatment or 2700 mf/mL between 1 and 6 months after treatment, were proposed. In this study, we use the data from all published studies with pre- and post-treatment measurement identified and for which individual data was available. Doing so, our results show that while the threshold of 1000 mf/mL is very sensitive, it is probably too low, since there is only

a 64.8% probability that an individual with an MFD >1000 mf/mL measured 3 to 4 days after treatment had a pre-treatment MFD >10,000 mf/mL, and this probability is further lowered to 51.2% if MFD is measured 5 to 10 days after treatment. Furthermore, the consistency of using 10,000 mf/mL as a pre-treatment threshold for defining *L. loa*-encephalopathy may be questioned. Actually, the original publication acknowledged that there were various definitions of "high" microfilarial density. Raising the threshold would be coherent when considering that the 20 "probable" cases reported by Twum-Danso *et al* had a mean post-treatment (<1 month) MFD arithmetic mean value of 4000 mf/mL suggesting that pre-treatment levels were probably much higher than 10,000 mf/mL. Indeed, their D0 MFD might have been closer to 30,000 mf/mL if one uses the 85% relative reduction at D7 shown by Pion *et al* or even closer to 100,000 mf/mL if one uses the 96% reduction in pre-treatment levels after 1 month evidenced by Kombila *et al* [30]. In the end, their MFDs would therefore probably be close from those of individuals with serious neurological adverse events for whom pre-treatment data was available and which were of 50,520 mf/mL, 109,000 mf/mL, 120,000 mf/mL 139,000 mf/mL, 152,940 mf/mL, 162,920 mf/mL, 199,000 mf/mL; and 217,000 mf/mL [6,7,13,20]. Nzolo *et al* analyzed 23 cases of possible Loa-related encephalopathy reported in 2011 within the passive surveillance system of SAEs following ivermectin MDA in Democratic Republic of Congo [34]. They concluded that encephalopathy could happen at low MFD, given that 61% of patients had MFD<1000 mf/mL after treatment which is unusual since the NPV at this cutoff is 93% for the predicting pre-treatment MFD<20,000 mf/mL. Nevertheless, there were no information available on when the TBS were drawn, and unaggregated data particularly on the MFD of patients with unfavorable outcomes should be reanalyzed carefully. Particularly, the finding of mf in the CSF without evidence of mf in peripheral blood in highly unusual and would require further investigation.

Our article therefore provides a set of abacuses and charts allowing to estimate, for a given MFD measured after treatment, the probability that the pre-treatment MFD was higher than thresholds commonly used in the literature on *Loa*-related adverse events, such as those exposing to a risk of marked adverse event (8,000 mf/mL) or to a risk of SAE (using the thresholds of 10,000 mf/mL as mentioned above, 20,000 mf/mL, 30,000 mf/mL, and 50,000 mf/mL). One of the limitations of the study is that the classification performances were lesser for the two higher thresholds ($T_{30,000}$ and $T_{50,000}$), in terms of PPV and sensitivity, contrasting with good performance outcomes. This is due to the fact that accuracy captured in a great extent the correct classification of MFD below the threshold, which represent the majority of observations, and left errors concentrated in the

classification of MFD above the threshold. For this reason, we focus our conclusions on thresholds up to $T_{20,000}$.

Inferring pre-treatment MFD from post-treatment measurements can be helpful both at the programmatic or individual levels and may rely on different cutoffs depending on whether NPV (and therefore sensitivity) is favored over PPV (and therefore specificity).
In clinical practice, an encephalopathy occurring shortly after ivermectin treatment can be considered as *L. loa*-related in case the post treatment MFD is above a threshold of 3000 mf/mL (this threshold favors specificity). A subject with a post-treatment MFD of >3500 mf/mL has a 69% risk of having had >20,000 mf/mL before treatment. At the exclusion of a grey zone, conversely, the post-treatment MFD can also help rule out the diagnosis. For instance, at D3-4, a subject with *L. loa* MFD <2500 mf/mL has a 92% chance of having a pre-treatment MFD <20,000 mf/mL; a subject with MFD <1500 mf/mL has a 78% probability of having an initial MFD <8,000 mf/mL; and a subject with MFD <2000 mf/mL from D5 onwards has an 85% chance of having an initial MFD <8,000 mf/mL. These NPV data are also important in that it is then incumbent on the clinician to carefully search for a differential diagnosis, especially when managing a coma which is the most feared clinical event. For individual purposes, MFD measured at D3-4 tended to perform slightly better than that measured later, which is explained by overdispersion of initial loads with high skewness and by post-treatment clustering with slightly faster reduction rates achieved in the patients with highest initial MFD. One should therefore keep in mind that in areas where loiasis is endemic, or for subjects returning from these areas, thick blood smears should be prepared if possible as soon as signs of concern appear after treatment.

For programmatic purposes, the thresholds with the best accuracy can be used to obtain reliable estimates of the number of attributable cases overall and to monitor the incidence of these effects. The semi-external validation sample we used confirms the general good prediction accuracy of pre-treatment MFD using post-treatment MFD, and adds that the threshold can likely be used with data obtained much later in a programmatic intent. The original definition included in the Twum-Danso classification when MFD were obtained 1-6 month after treatment was based on the estimation of a 73% relative reduction in the initial MFD (2700 mf/mL= (1-0.73) x 10,000 mf/mL). The threshold of 2700 mf/mL was then closer to the cutoffs we find can be used for predicting MFD exceeding 20,000 mf/mL with good accuracy and sensitivity. However, one should keep in mind that in considering that some SAEs are life-threatening events, medical care

for cases including *L. loa* MFD measurement should be prompted urgently, and that in case of an unfavorable outcome long-term follow-up would be missing, biasing estimates.

The predictive performance of post-treatment MFD for predicting pre-treatment MFD was not improved by taking into account age and sex of the subjects (data not shown). Nevertheless, we cannot exclude that other covariates which were not measured in the studies could help improve the classification performance. In addition, individual clinical and biological data gathered during the investigation of SAE cases reported to the MDP is of critical importance for understanding the underlying pathophysiology and might help develop prevention and management strategies.

As loiasis was long deemed to be a benign condition there is very little information available on clinical and biological changes during the natural course of the disease. Such information may help refine risk modelling for the deployment of the onchocerciasis elimination strategy to onchocerciasis hypoendemic areas where loiasis is co-endemic. They may also help understand the pathophysiology of the diseases that have proven recently to have a burden on mortality of affected populations [35]. Efforts should be made by the international community of clinicians receiving imported cases of loiasis to gather a systematized and comprehensive set of clinical and biological information on their patients during treatment follow-up.

Efforts are needed to acknowledge whether there could be other diagnosis tools supporting the imputability of clinical events to loiasis. In this view, Ducorps *et al* [6,18] reported the important finding of microfilaruria (live microfilaria in urine samples) peaking around 3 days after treatment (present in up to 79% of individuals with initial MFD>30,000 versus 4% before treatment). Nevertheless, to our knowledge no other study investigated this finding similarly to what is seen in onchocerciasis. They also described that microfilaria were absent from CSF before treatment but live microfilariae were seen in up to 77% of individuals with initial MFD>30,000 mf/mL at day 3. Downie *et al* had already reported the presence of live microfilariae, evaluated using semi-quantitative methods, following DEC administration, and in all the 6 patients involved the outcome was fatal [36]. Thereby quantitation of microfilariae in other body fluids could provide insight into how high was the initial peripheral MFD. If lumbar punction can be complex depending on the setting, a urine sample could be a non-invasive and informative solution and the correlation of the two should be evaluated.

6. Conclusions

As ivermectin treatment might expand in the near future to onchocerciasis hypoendemic areas where loiasis is coendemic, it is key to classify SAE cases as probable or possible using strong criteria. In this study, we propose abacuses that can be used to assess this imputability in mass or individual treatments.

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5 Conclusion

Conclusion

Les résultats des deux études qui composent cette thèse sont discutés en détail dans les sections correspondantes. Nous en présentons ici une brève mise en perspective.

Dans la première partie de cette thèse nous avons mis en évidence que la prise en compte de certaines caractéristiques individuelles, comme l'âge et le sexe, peut influencer le niveau de risque de survenue d'évènements indésirables graves (EIG) lors d'un traitement par ivermectine. Ces résultats sont donc importants notamment afin de mieux définir la prise en charge thérapeutique de la loase au niveau individuel, par exemple dans les services de médecine du voyage amenés à recevoir des voyageurs ou expatriés revenant de zones d'endémie, ou encore des migrants originaires d'Afrique centrale.

La loase n'a jusque-là été prise en compte par la communauté internationale quasiment que pour les difficultés qu'elle posait pour l'extension des programmes de lutte contre les deux autres filarioses, occultant ainsi sa prise en charge individuelle. Cela s'explique en grande partie par l'habituelle bénignité qui lui était attribuée. Pourtant, la nuisance de la loase pour les populations locales est majeure puisqu'il s'agit d'une des causes de consultation les plus fréquentes en zone d'endémie, et la méta-analyse de Buell *et al*, suggère de considérer d'autres manifestations que les classiques signes cutanés, pour prendre en compte l'ensemble du fardeau de la maladie. Enfin des travaux récents ont démontré une nette surmortalité dans les populations fortement touchées. Ces résultats sont à même d'encourager dans les prochaines années à reconsidérer le statut de cette filariose négligée. Un projet de recherche en Afrique centrale visant à déterminer les conséquences cliniques de la loase est d'ailleurs en cours dans l'équipe d'accueil et a reçu un financement européen dans ce but. Les résultats sont largement attendus, car l'évaluation spécifique de la morbidité sous ses nombreuses pourra amener à reconsidérer son statut, et en particulier sa prise en compte dans d'éventuels programmes de lutte à grande échelle. Ainsi, les années à venir pourront amener une nécessité de traitement de la loase, étendue au-delà des seuls cas importés.

La stratégie thérapeutique optimale nécessite donc une attention importante, et il semble judicieux de mettre en place un Centre National de Référence (CNR) des Filarioses afin de faciliter leur diagnostic et traitement sur le territoire Français. En effet, le diagnostic en France métropolitaine est en général limité à celui qui peut être effectué par goutte épaisse calibrée et sérologie pan-

filarienne, alors qu'il existe un nombre important de tests diagnostiques déjà déployés dans les programmes ou utilisés par des équipes de recherche. Néanmoins, ces tests alternatifs nécessitent une expertise pointue quant à leur interprétation, eu égard aux fréquentes réactions croisées entre les espèces de filaires, brièvement abordées dans l'introduction de ce document. En outre, l'existence d'un tel CNR permettrait de mettre en place des cohortes prospectives de patients afin de mieux définir les stratégies thérapeutiques, et de recueillir des éléments biologiques permettant peut-être d'éclairer la physiopathologie des évènements indésirables survenant dans les suites du traitement. Par ailleurs, la prévalence majeure en zone forestière d'Afrique centrale, devrait conduire à discuter l'intérêt d'un dépistage systématique des migrants, à l'instar de ce qui est fait pour la bilharziose, dont la conduite nécessitera une structure adaptée à effectuer un diagnostic d'espèce.

Un autre aspect de ces résultats est qu'ils doivent être également resitués dans le contexte d'incertitude quant aux mécanismes physiopathologiques sous-tendant les effets indésirables liés à l'administration d'ivermectine chez les patients présentant de fortes densités microfilariennes. La compréhension de ces mécanismes pourrait aider à améliorer la prise en charge notamment des encéphalopathies, qui exposent actuellement ces patients à un risque de décès ou de séquelles permanentes, et dont la seule prise en charge actuelle est purement symptomatique. Si l'hypothèse la plus courue est l'existence de mécanismes inflammatoires initiés par une décharge majeure d'antigènes étrangers occasionnée par la lyse microfilarienne, ils ne sont pas totalement élucidés. L'administration de corticostéroïdes, actuellement non recommandée, devra alors être évaluée en fonction du risque lié aux capacités locales de prévention et gestion des complications de décubitus. D'autres thérapeutiques spécifiques pourront également être envisagées, comme la récente tentative avec un inhibiteur de l'activation des éosinophiles sans que les résultats n'aient été concluants. En ce sens, l'un des éléments qui mérite notre attention, est le sur-risque à âge égal des hommes par rapport aux femmes dans l'occurrence d'un tel événement indésirable grave. S'il peut certes être expliqué par des facteurs confondants qui n'ont pas pu être mesurés dans ces études, et qui en constituent d'ailleurs une des principales limites, il est également possible que les processus physiopathologiques soit dépendants du sexe et nous apportent ainsi un indice sur certains des mécanismes mis en œuvre.

Les deux cas récents d'encéphalopathie à la suite de la prise d'albendazole chez des patients avec >30.000 mf/mL sont troublants, car les mécanismes d'action des deux antiparasitaires sont

dissemblables. Néanmoins, ils rendent encore plus prégnante la nécessité de comprendre et développer des alternatives lorsque les densités microfilariennes sont très élevées, car même si ces cas sont rares chez le voyageur et l'expatrié, ils peuvent éventuellement survenir chez le migrant originaire de zone d'endémie. Dans ce cas de figure, les auteurs américains et français recommandent que le traitement soit conduit au sein de centres spécialisés. Si l'aphérèse reste peu utilisée il est néanmoins important de réfléchir au niveau local à des protocoles en prévision, afin d'évaluer sa faisabilité. La question de l'indication thérapeutique est rarement discutable, dans le cadre des services de médecine du voyage, puisque la consultation est généralement motivée par des symptômes (œdèmes de Calabar le plus souvent pour les voyageurs) ou la découverte fortuite d'une hyperéosinophilie sur un bilan sanguin, en l'absence d'un dépistage systématique. Aussi, il incombe d'évaluer des alternatives, dont certaines sont actuellement testées par l'équipe d'accueil, comme par exemple le lévamisole, d'efficacité moindre, et entraînant de fait une lyse microfilarienne moins marquée, puisqu'il est assez communément admis que cette lyse constitue le *primum movens* de la cascade conduisant à l'effet indésirable grave.

Ensuite, la deuxième étude se place au temps post-thérapeutique. En effet, il arrive que la densité microfilarienne avant traitement ne soit pas connue au moment de la survenue d'une encéphalite ou d'un autre EIG. C'est par nature le cas dans le cadre des programmes de traitement de masse, où la goutte épaisse calibrée n'est réalisée au mieux que 3 à 7 jours après le traitement compte tenu du délai d'apparition des symptômes. On peut également imaginer que cette situation puisse survenir en médecine individuelle, par exemple au décours du traitement d'une gale chez un migrant, sans s'être assuré de son statut vis-à-vis de la loase.

Lors de l'occurrence d'une encéphalopathie suite à la prise d'ivermectine, plusieurs mécanismes peuvent être incriminés, comme le soulèvent des études de pharmacovigilance. Un déficit en P-gp (P-glycoprotéine) peut en effet entraîner une accumulation d'ivermectine au sein du parenchyme cérébral conduisant à une encéphalopathie toxique. Néanmoins, chez un patient découvert porteur de microfilaires de *L. loa* après un tel événement il convient d'étudier l'imputabilité de *L. loa* et de l'ivermectine dans sa survenue. Cela sera d'une importance encore plus capitale si un traitement spécifique prouve son efficacité. Néanmoins dans l'intervalle, l'exclusion ou la présomption d'exclusion de ce diagnostic (en utilisant des seuils à valeur prédictive négative élevée) sont importantes dans l'enquête médicale car elles imposent la recherche de diagnostics différentiels. La surveillance des programmes nécessite également l'établissement de l'imputabilité entre le traitement et l'effet indésirable grave, et à des fins statistiques peut utiliser les seuils donnant la

meilleure précision de classification. Dans ce travail nous proposons donc des abaques pour établir la plausibilité de différents seuils de microfilarémie avant traitement à partir des densités microfilariennes mesurées *a posteriori*, qui pourraient permettre d'actualiser la définition d'encéphalopathie liée à la loase proposée lors de la réunion d'un comité expert du Mectizan® Donation Program à Paris en 1995. Une définition précise est en effet, en médecine, un préalable nécessaire à l'interopérabilité des données et à la mise en œuvre de programmes de recherche.

Par les modestes éléments issus de ce travail, nous espérons donc pouvoir contribuer à progresser sur la caractérisation du risque d'effets indésirables graves lors du traitement de la loase par ivermectine, et ce dans une perspective de prise en charge individuelle comme collective.

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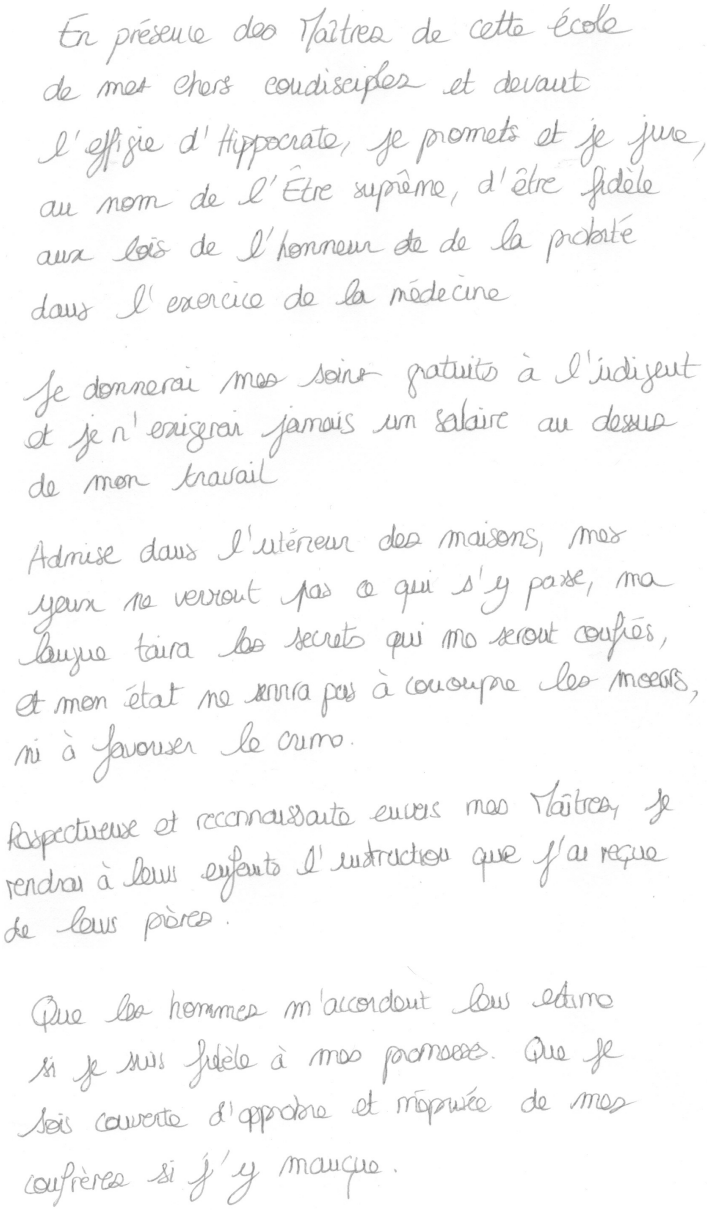
Serment d'Hippocrate



En présence des Maîtres de cette école
de mes chers condisciples et devant
l'effigie d'Hippocrate, je promets et je jure,
au nom de l'Être suprême, d'être fidèle
aux lois de l'honneur et de la probité
dans l'exercice de la médecine

Je donnerai mes soins gratuits à l'indigent
et je n'exigerai jamais un salaire au dessus
de mon travail

Admise dans l'intérieur des maisons, mes
yeux ne verront pas ce qui s'y passe, ma
langue taira les secrets qui me seront confiés,
et mon état ne servira pas à corrompre les mœurs,
ni à favoriser le crime.

Respectueuse et reconnaissante envers mes Maîtres, je
rendrai à leurs enfants l'instruction que j'ai reçue
de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses. Que je
sois couverte d'opprobre et méprisée de mes
confrères si j'y manque.

Résumé

Introduction : La loase (filariose à *Loa loa*) est souvent considérée comme une maladie bénigne mais les individus présentant une forte densité microfilarienne (DMF) dans le sang risquent de développer une encéphalopathie après la prise d'ivermectine (IVM). Les programmes de lutte contre l'onchocercose étant basés sur le traitement de masse des populations par l'IVM, ces événements indésirables graves (EIG) entravent leur déploiement en Afrique centrale. Ce travail vise à mieux caractériser ce risque (i) avant traitement, en étudiant l'influence de facteurs individuels sur le niveau de risque, et (ii) après traitement, en évaluant dans quelle mesure les DMF pré-traitement peuvent être évaluées à partir des DMF mesurées après traitement.
Méthodes : (i) Les données de deux essais cliniques menés en 1995 et 2005 au Cameroun ont été combinées pour modéliser, par une régression logistique incluant l'âge, le sexe et la DMF (transformée par un polynôme fractionnaire), le risque d'EIG. (ii) Les données de six essais cliniques avec mesure des DMF avant et après traitement par IVM ont été utilisées pour calculer la sensibilité, la spécificité et les valeurs prédictives positive et négative de différents seuils de DMF post-traitement pour classer les individus dans les catégories de risque habituellement retenues avant traitement.
Résultats : Nous avons précisé comment certains facteurs individuels (âge et sexe) peuvent influencer le niveau de risque d'EIG post-IVM et montré que le seuil au-delà duquel l'IVM devrait être contre-indiquée pourrait être adapté en fonction de ces facteurs. Nous montrons également que le seuil de DMF post-traitement (1.000 mf/mL) utilisé pour imputer à l'IVM et *L. loa* la survenue d'un EIG est probablement trop bas, et proposons des abaques qui peuvent être utilisées pour évaluer cette imputabilité lors de traitements de masse ou de traitements individuels.
Conclusions : La prise en charge thérapeutique de la loase est encore mal définie. La démonstration récente de son impact sur l'espérance de vie devrait conduire à définir des stratégies de prise en charge adéquates de la loase et de ses complications après traitement, y compris dans les pays du Nord.

Mots-clés : Loase ; Afrique centrale ; ivermectine ; densité microfilarienne ; événements indésirables graves ; encéphalopathie ; santé publique ; stratégie thérapeutique.

Abstract

Introduction: Loiasis (*Loa loa* filariasis) is often deemed to be a benign condition but individuals with high microfilarial densities (MFD) are at risk of encephalopathy following ivermectin administration (IVM). As onchocerciasis control programs are based on mass drug administration of ivermectin, these serious adverse events (SAE) hamper their deployment in Central Africa. This thesis aims to better characterize the risk (i) before treatment, by investigating the influence of individual factors on the level of risk, and (ii) after treatment to determine to which extent the pre-treatment MFD can be inferred from the MFD obtained after treatment.
Methods: (i) Data from two clinical trials conducted in 1995-1996 and 2005 in Cameroon were pooled to model the risk of SAE as a logistic function of age, sex, and MFD (as a fractional polynomial). (ii) Data from six clinical trials with pre- and post-IVM MFD measurements were used to calculate the sensitivity, specificity, and positive and negative predictive values of different post-IVM MFD cutoffs for classifying individuals according to the commonly used pre-treatment thresholds.
Results: We outlined how individual factors (age and sex) can influence the level of risk of post-IVM SAE and showed that the threshold above which IVM should be contraindicated could be adapted according to these factors. We also show that the post-treatment threshold of 1,000 mf/mL used to impute the occurrence of a SAE to IVM and *L. loa* is probably too low, and propose abacuses that can be used to assess this imputability in mass or individual treatments.
Conclusions: The therapeutic management of loiasis is still poorly defined. The recent demonstration of its impact on life expectancy should lead to the definition of adequate management strategies for loiasis and its complications after treatment, including in Northern settings.

Keywords: Loiasis; Central Africa; ivermectin; microfilarial density; serious adverse events; encephalopathy; Public Health; therapeutic strategy.