Preface

This historical review on *River Blindness*, onchocerciasis, is written in honour of (i) the 120-year anniversary of the *Bernhard Nocht Institute for Tropical Medicine* (BNITM), founded in 1900 in Hamburg in the sequel of a tremendous cholera outbreak that hit Hamburg in 1892, (ii) the 75-year anniversaries of *Acta Tropica* and (iii) the *Swiss Tropical and Public Health Institute* (Swiss TPH), both founded in 1944 in Basel by the renowned scientist of tropical medicine *Rudolf Geigy* (1902-1995). Geigy was the first director of the former *Swiss Tropical Institute* (STI) and simultaneously the first editor of *Acta Tropica.*

River Blindness caused by the tissue filaria *Onchocerca volvulus* was one focus of research in the BNITM over almost 60 years documented in about 300 publications. Consequently, in this historical review article we have cited major articles based on research conducted at the BNITM.

In addition to this historical review article on onchocerciasis two historical articles on 75 year of both, *Acta Tropica* and Swiss TPH, are jointly published in in one issue of *Acta Tropica*.

Review

Onchocerciasis (River Blindness) – more than a Century of Research and Control

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Abstract

This review summarises more than a century of research on onchocerciasis, also known as river blindness, and its control. River blindness is an infection caused by the tissue filaria *Onchocerca volvulus* affecting the skin, subcutaneous tissue and eyes and leading to blindness in a minority of infected persons. The parasite is transmitted by its intermediate hosts *Simulium* spp. which breed in rivers. Featured are history and milestones in onchocerciasis research and control, state-of-the-art data on the parasite, its endobacteria *Wolbachia*, on the vectors, previous and current prevalence of the infection, its diagnostics, the interaction between the parasite and its host, immune responses and the pathology of onchocerciasis. Detailed information is documented on the time course of control programmes in the afflicted countries in Africa and the Americas, a long road from previous programmes to current successes in control of the transmission of this infectious disease. By development, adjustment and optimization of the control measures, transmission by the vector has been interrupted in foci of countries in the Americas, in Uganda, in Sudan and elsewhere, followed by onchocerciasis eliminations. The current state and future perspectives for control, elimination and eradication within the next 20-30 years are described and discussed. This review contributes to a deeper comprehension of this disease by a tissue-dwelling filaria and it will be helpful in efforts to control and eliminate other filarial infections.

1. Introduction and history

Onchocerciasis – commonly known as river blindness – is an infectious disease caused by the parasitic filaria *Onchocerca volvulus* Leuckart 1893 (Parsons, 1908) belonging to the tissue-residing nematodes (class Chromadorea). The name *Onchocerca* derived from a combination of the Greek words 'onchos' meaning 'hook' and 'kerkos' meaning 'tail'. The infection occurs primarily in sub-Saharan Africa, but it is also found in Yemen and until recently in foci of six countries within Central America (WHO, 1995; WHO 2020 fact sheets, 2019; WHO, 2020). The Global Burden of Disease Study 2010 (Hotez et al., 2014) quantified the burden of almost 300 diseases, including onchocerciasis, in terms of their relative impacts as disability-adjusted life years (DALYs) which was noted as 490,000 for onchocerciasis with 30 million infected people.

Primarily, the infection affects the skin and eyes and the pathology is caused by subcutaneous larvae (microfilariae). Microfilariae were first discovered in 1874 – almost 150 years ago - by John O'Neill, a British naval surgeon in the Gold Coast (Ghana), while examining skin-snips from so-called *craw-craw* patients suffering from intense acute dermatitis (O'Neill, 1875). Patrick Manson in 1890 first identified the adult microfilariae-releasing worms and in 1893 Rudolf Leuckart described their morphology from subcutaneous infestations as "*Filaria volvuloxus",* now known as *Onchocerca volvulus* (Leuckart 1893; Fülleborn, 1908). The genus name *Onchocerca* had been given to filarial worms infecting cattle by Diesing in 1841. In 1917 Rodolfo Robles (Robles, 1917) published details of the association of dermatitis with subcutaneous nodules, microfilariae and anterior ocular lesions based on research in Guatemala and named the causative worms *O. caecutiens* ("blinding") (Brumpt, 1919; Fülleborn, 1924). In 1927, while working in Sierra Leone, Blacklock discovered that blackflies, *Simulium* (*Edwardsellum*) *damnosum* Theobald transmitted *O. volvulus* causing onchocerciasis (Blacklock, 1927).

Chromosomes of *Simulium* were first described in 1937 (Painter et al., 1937) and those of the vectors in 1975 (Vajime and Dunbar, 1975), whereas for *Onchocerca* they were described later (Hirai et al., 1987; Post et al., 1989). The complete genome of *O. volvulus* was first published in 2016 by Choi et al. (2016) and Cotton et al. (2016). *Rickettsia*-like endobacteria, *Wolbachia*, were first reported in *Onchocerca* in 1977 by Kozek and Figueroa-Marroquin (1977) and the genome of *Wolbachia* was described in 1999 by Bandi et al. (1999) and Slatko et al. (1999).

A control programme in 11 West African countries applying vector control began with the Onchocerciasis Control Programme (OCP) in 1974 and ended in 2002 (see section 4.2.2.). The OCP started with vector control by insecticide and was expanded to include treatment of *Onchocerca*-infected people with the microfilaricide ivermectin in 1987. Treatment studies with doxycycline killing the *Wolbachia* endobacteria (Fig. 10) started in 2003 after initial *in vitro* experiments in 2000 (Hoerauf et al., 2000, 2001; Abegunde et al., 2016). Crump et al. (2012) described the onchocerciasis chronicle in detail and Table 1 summarises major milestones in the history of onchocerciasis research and control.

75 Table 1. Milestones in onchocerciasis research

76

Discovery	Characteristic	Discoverer /Originator	Year
Skin disease	"Craw-craw"	O'Neill	1875
Parasite	*Filaria volvulus*	Manson	1890
	Filaria volvuloxus	Leuckart, Fülleborn	1893, 1908
	Onchocerca volvulus	Railliet and Henry	1910
Pathology	Skin: dermatitis	O'Neill, Robles	1874, 1917
		Gasparini	1962
	Nodule, onchocercoma	Leuckart, Robles,	1893, 1917
		Büttner	1983
	Eye pathology, blindness	Brumpt, Robles	1919, 1917
		Fülleborn	1924
	Sowda(h)	Omar, Büttner	1979, 1982, 1983
	Neurologic disease: epilepsy, nodding disease, dwarfism	Druet-Cabanac Duke	1999 1998
Vector	*Simulium*	Blacklock	1927
	S. damnosum species complex: chromosomes	Vajime and Dunbar Painter	1975 1937
Phoretic host	Freshwater crab: *Potamonautes*	van Someren	1950
Onchocerca strains	Savannah - Forest	Duke	1967a
		Garms and Cheke	1985
		Cheke and Garms	2013
Endobacteria *Wolbachia*	*Simulium*	Hertig and Wolbach	1924
	Onchocerca	Kozek and Figueroa-Marroquin	1977
Onchocerca chromosomes, genome	Chromosomes	Hirai, Post	1987, 1989
	Gene codes	Unnasch and Williams	2000 2016
	Genome	Choi, Cotton	
Wolbachia genome	Gene codes	Bandi	1999
		Slatko	1999
		Unnasch	2000
Diagnostics	Dermatitis	O'Neill	1875
	Onchocercoma	Leuckart	1893
	Skin microfilariae	Picq	1971
	Mazzotti test	Mazzotti	1951
	ELISA, Antigen	Bartlett	1975
	DNA, PCR	Bradley	1991
	Biomarkers	Denery	2010

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2. Parasite *Onchocerca*

2.1. *O. volvulus* life cycle

2.1.1 Development of the filaria in the human host

The infective third stage larvae (L3) of the parasite with a length of 600-700 µm invade the skin when an *O. volvulus*-infected blackfly bites the human host for blood (Fig. 1; Fig. 2). The L3 larvae moult in the skin of the human host to fourth stage larvae which migrate in subcutaneous tissue and grow to the adult female and male stages in 6-12 months. The adult females measure 30-60 cm, while the males are only 1.5-4.5 cm long (Fig. 2). The host reaction against the parasites leads to the formation of nodules known as onchocercomata. Interestingly, the males of the cattle parasite *O. ochengi*, and probably those of *O. volvulus* too, migrate between the nodules, thus from female to female.

In a single day an inseminated adult female can release 1000-3000 microfilariae responsible for the symptoms of the disease. The parasite has an enormous reproductive capacity resulting in millions of microfilariae released from fertilized females during their lives. Schulz-Key and Karam (1986) calculated that the number of microfilariae released from one female during its life of 10-15 years was >10 million. The severity of the disease increases with the parasitic load and there is a direct relation between *O. volvulus* microfilarial load and host ocular morbidity (Little et al., 2004). The microfilariae leave the onchocercomata and move through the subcutaneous tissue to reach the cutis where they leave the host if taken up by a vector (Fig. 1).

2.1.2. Transmission by the vector *Simulium*

2.1.2.1. The genus *Simulium*

There are 2310 living species of blackflies in the family Simuliidae (order Diptera) and 18 known fossil taxa (Adler, 2019). Most species are of no economic importance but 1.5% of them are vectors of human pathogens causing onchocerciasis and mansonellosis (caused by *Mansonella ozzardi* in Brazil). Blackflies also transmit *Onchocerca* spp. to other vertebrates including cattle and, through their biting, they may also cause serious allergic reactions in cattle which can be fatal. In addition, they transmit protozoa to birds including *Leucocytozoon* spp. causing infections that are sometimes of economic importance for poultry. The major vectors of human onchocerciasis in Africa are members of the *S. damnosum* species complex of which at least 65 different forms have been described, with at least 15 of them acting as vectors (Adler et al., 2010).

In addition to their importance as vectors, blackflies can be serious biting pests of man and animals in both tropical and temperate climates, with examples including *S. erythrocephalum* in central Europe and *S. posticatum* in England. Particularly infamous was the Golubac fly *S. colombaschense* which in 1923 killed 22000 animals (sheep, goats, cattle) in the Danube valley in Yugoslavia, Hungary and Romania (Crosskey, 1990).

115 Members of the genus *Simulium* (Diptera: Simuliidae) have aquatic immature stages. The adults lay
116 their eggs on trailing vegetation or rocks in streams or fast-flowing sections of rivers. Larvae hatch from
117 the eggs and pass through 6 to 11 instars before becoming pupae from which the adults later emerge (Fig.
118 3). The males do not blood-feed but may obtain sugar-feeds from plants. Most female *Simulium* are
119 haematophagous and it is this habit which links them to vectorial importance.
120 In Africa, the most important vectors are members of the *S. damnosum* species complex, but the
121 disease is also transmitted in East Africa by members of the *S. neavei* complex (subgenus *Lewisellum*, 9
122 species) which has its immature stages phoretic on freshwater crabs. The most important vectors within
123 the *S. neavei* complex are *S. neavei* in Uganda and *S. woodi* in Tanzania. In the Congo *S. albivirgulatum* is a
124 vector in the central basin region (Fain et al., 1981). Recently *S. dentulosum* and *S. vorax* have been found
125 biting man in the absence of *S. damnosum* s.l., *S. neavei* s.l. and *S. albivirgulatum* in the Ituri-Albert focus of
126 the Democratic Republic of Congo. Furthermore, DNA tests confirmed the presence of *O. volvulus* in both *S.*
127 *dentulosum* and S. *vorax* but few samples of the latter were available and none were infective. In contrast,
128 30% of 155 *S. dentulosum* were infected and 11% were infective, so a new vector species has been
129 confirmed (R.J. Post et al. unpubl. and pers. comm.).
130 A variety of vectors is or was responsible for transmission in central and southern America. Members
131 of the *S. ochraceum* and *S. metallicum* complexes were involved in Mexico, with the former most active in
132 transmission in Guatemala (Garms and Ochoa, 1979a) before elimination of the disease in that country
133 (Rodríguez-Pérez et al., 2015). In the remaining Amazonas focus that straddles the Venezuela-Brazil
134 border the main vectors are members of the *S. oyapockense* and *S. guianense* species complexes and *S.*
135 *incrustatum* (Shelley et al., 2010).
136
137 2.1.2.2. Development of the filaria in *Simulium*
138 The mouthparts of the female vectors of onchocerciasis do not penetrate the skin and absorb blood in
139 the manner of mosquitoes but rather they use their mandibles to rasp at the skin until bleeding occurs and
140 then the blood is lapped up from the resultant pool, hence they are known as pool-feeders (Fig. 3). Any *O.*
141 *volvulus* microfilariae (Fig. 2.1) that are within the pool may be ingested by the blackflies. In vectors with
142 pronounced buccopharangeal armatures such as members of the *S. ochraceum* complex, many
143 microfilariae may be killed at this stage (Omar and Garms, 1975). In contrast, *S. metallicum* complex
144 members lack such structures and if they ingest many microfilariae the flies may soon die shortly after
145 their blood-meals (Omar and Garms, 1977), although this does not appear to happen with the *S.*
146 *damnosum* complex which also lacks marked buccopharangeal armatures.
147 Once within the stomach with the blood meal the microfilariae must try to escape through the
148 stomach wall into the haemocoel (Fig. 1) before being trapped within the peritrophic matrix that can form
149 within 30 minutes. Bain et al. (1976) suggested that the reason that forest *S. damnosum* harbour higher
150 numbers of developing *O. volvulus* larvae than do savannah forms was because of differences between the

two vector groups in the structure and speed of development of the peritrophic matrix, with forest flies' membranes being less well sealed and slower to form.

Those microfilariae that reach the haemocoel move into the thoracic muscles, changing their shape to become "sausage stage" forms. These moult to the second stage (L2) and then moult again within the thoraces to become third stage larvae (L3) (Fig. 2.3) before emerging into the female's body cavity to become elongated infective L3 stage larvae that will be capable of infecting a new host (Fig. 1, Fig. 2.3). L3s penetrate several fly organs, the ovaries, the brain, antennae, and the palps, thereby debilitating the fly resulting sometimes in only about 1% of the flies carrying L3s surviving, according to results of a laboratory study involving *S. yahense* (Trpis et al., 2006). Because the development process of the *Simulium* stages takes 6-9 days and the gonotrophic cycle of the females is 2-4 days, it is usually only at their third bite that the flies can transmit infections.

Much of what is known about the transmission of onchocerciasis by different *S. damnosum* complex members was derived from research conducted during the WHO Onchocerciasis Control Programme in West Africa (OCP). As mentioned in a later section (see section 4.2.2.), the OCP was affected by reinvasions of controlled zones by immigrant flies bred outside the treated areas. Thus, it became important to identify which members of the *S. damnosum* complex were responsible in order to be able to locate and treat the sources. Garms (1978) showed that savannah species could be separated from forest species by a combination of the colour of the basal wing tufts and the ratio between the lengths of the thoraces and antennae, with the latter being longer and less compressed in forest forms for a given fly size. Later morphological studies (Garms et al., 1982; Garms and Zillmann, 1984; Garms and Cheke, 1985; Meredith et al., 1983)-allowed more of the species, or at least species groups, occurring in the OCP to be identified such that it was possible to compare their transmission abilities (Cheke and Garms, 2013). In general, forest forms carry more *O. volvulus* larvae per infected fly than the savannah forms.

2.2. Endobacterium *Wolbachia*

2.2.1. *Wolbachia* in the parasite *Onchocerca*

In 1977 Kozek and Figueroa-Marroquin (1977) found intracytoplasmic *Rickettsia*-like bacteria in *O. volvulus* and Sironi et al. (1995) provided molecular evidence for a close relative of the arthropod endosymbiont *Wolbachia* in a filarial worm. *Rickettsia*-like gram-negative endobacteria, alpha 2 proteobacteria, were originally detected in arthropods in 1924 by Hertig and Wolbach (1924), representing the eponym *Wolbachia* designated in 1936.

Wolbachia are found in the hypodermal cells of the lateral cords of adult filariae and in embryonic stages (Taylor and Hoerauf, 1999, Hoerauf et al., 2000) (Fig. 2.6). The absence of *Wolbachia* appears to be an ancestral condition (Bandi et al., 2001). The *Wolbachia* were shown to be mutualistic in *Onchocerca* (Comandatore et al., 2015), with the endobacteriae appearing to provide essential metabolites to the

187 filaria, which contribute to its reproduction and larval development, promoting fertility, embryogenesis
188 and viability of the filaria (Comandatore et al., 2015).
189 Products of the endosymbionts have been implicated in the pathogenesis of ocular onchocerciasis
190 (Saint André et al., 2002). Recent data support the hypothesis that suspected differences between severe
191 and mild strains of *O. volvulus* (see section 2.3.) may be a function of their relative *Wolbachia* burden
192 indicating that *Wolbachia* products may play a central role in the pathogenesis of ocular onchocerciasis
193 (Pearlman, 2003).
194 The genome of onchocercal *Wolbachia* (*wOv*) has been analysed (Unnasch and Williams, 2000; Choi et
195 al., 2016). The 956 kb genome contains 785 predicted protein-coding genes
196 (*http://exon.niaid.nih.gov/transcriptome/O_volvulus/v245/wOv_web/wOv_Web.xlsx*) including the most
197 abundant proteins: *Wolbachia* surface protein (WSP, wOv00566) and the chaperone DnaK (wOv00687)
198 (Choi et al., 2016). The proteins were mapped to functional categories, with the top five functions being (i)
199 translation, ribosomal structure, and biogenesis; (ii) post-translational modification, protein turnover,
200 and chaperone; (iii) energy production and conversion; (iv) coenzyme metabolism and cell envelope
201 biogenesis, and (v) outer membrane proteins (Bennuru et al., 2016).
202 The bacteria in the filariae represent a target for antibiotic therapy (D.W. Büttner, 1997, pers. comm.;
203 Hoerauf et al., 2000, 2002; Taylor et al., 2001). Immunological studies revealed that the hosting
204 endobacteria contribute to inflammatory reactions of the human host of the filariae (Pearlman, 2003).
205
206 2.2.2. *Wolbachia* in the vector *Simulium*
207 Yen (1975) first reported on intracellular *Wolbachia* in insects, long before the *Wolbachia* were
208 identified as intracellular bacteria in filariae. *Wolbachia* are responsible for cytoplasmic incompatibility in
209 *Culex pipiens* and numerous subsequent studies revealed that these endobacteria manipulate the
210 reproduction of their arthropod hosts and can move horizontally across species' boundaries. Meanwhile
211 *Wolbachia* have been demonstrated in numerous mosquito vector species of medical and veterinary
212 importance and have been used to control transmission of dengue fever by releasing *Aedes aegypti* vectors
213 infected with the wMel strain of *Wolbachia* (Hoffmann et al., 2011).
214 The presence of *Wolbachia* in onchocerciasis vectors was first demonstrated by Crainey et al. (2010)
215 who found the endosymbiont in larval samples of *Simulium* from Ghana. It is unclear if all individuals are
216 infected, as the *Wolbachia* were found in less than a quarter of specimens, but they have also been
217 detected in *S. squamosum* and *S. yahense* adults and in *S. oyapockense* s.l., with those in the latter differing
218 markedly from the types found in the *S. damnosum* complex (J.L. Crainey, 2019, pers. comm). If there are
219 consistent interspecific differences in the frequencies of occurrence and/or the varieties present in
220 different vectors, it is possible, given *Wolbachia*'s known manipulation of reproductive capacities and
221 vector status in other arthropods, that they could be of epidemiological importance, e.g. by accounting for
222 differences in parasite burdens between forest and savannah vectors in West Africa. *Wolbachia* may also

be implicated in why *Simulium* are so difficult to colonise in the laboratory, e.g. by male-killing, and this hurdle will need to be overcome if the potential of using *Wolbachia* in *Simulium* control can be realised. Nevertheless, progress towards such a goal has been made with the discovery of a prophage element within *S. squamosum* E that includes a SpvB-like protein at the extreme terminal end of its sequence which is suspected of having insecticidal properties (Crainey et al., 2017).

2.3. Phylogeny and biology of *Onchocerca*

The phylogenetic tree of the genus *Onchocerca* Leuckart comprises 14 species divided into three clades (Lefoulon et al., 2017). The third clade is composed of *O. volvulus* and the related species *O. ochengi*, *O. gibsoni* and *O. gutturosa* which parasitize domesticated bovids. *O. volvulus* is genetically most closely related to *O. ochengi* (https://parasite.wormbase.org/Onchocerca_ochengi_prjeb1465/Info/Index). The *O. volvulus / O. ochengi* sister relationship supports the scenario that the human parasite resulted from a host transfer by the bovine *O. ochengi*, or its ancestor (Bain, 2002; Morales-Hojas et al., 2006), possibly during the course of cattle domestication and hence within the last 10,000 years, with *O. ochengi* switching into humans to become *O. volvulus* (Lefoulon et al., 2017).

On the basis of the genetic similarity of *O. volvulus* and *O. ochengi*, the bovine infection by *O. ochengi* has become famous as a natural model or 'analogue' of human onchocerciasis (Trees et al., 2000; Makepeace and Tanya, 2016). A multitude of experimental joint studies by the University of Ngaoundéré and the University of Tübingen, Germany, demonstrated similarities in the stage-specific proteome (Armstrong et al., 2016), in excretory-secretory (E/S) peptides (Eberle et al., 2015), in immune recognition of ES proteins (Manchang et al., 2015), in cross-protection (Wahl et al., 1998), in cross-vaccination (Achukqui et al., 2007), and in the conserved nature of circulating miRNA (Quintana et al., 2015). Further, similarities in the immune antigen recognition pattern was reported in *O. ochengi*-infected cattle and in an *O. volvulus*-infected chimpanzee (Graham et al., 2000) confirming the use of the primate as a surrogate host for *Onchocerca* infection . The comparability of both infections, nevertheless, appears to be limited since in the evolutionarily primordial *O. ochengi* infections the parasite is highly adapted to its bovine host eliciting minimal pathology, whereas in the evolutionarily younger parasitism by *O. volvulus* severe damage often results (see section 3.3.).
(https://pubmed.ncbi.nlm.nih.gov/27869790/?from_sort=pubdate&from_term=Cotton+JA&from_cauthor_id=27881553&from_pos=4).

Differences between the manifestation of onchocerciasis in forest and savannah regions, in particular between blinding rates, gave rise to a two-strain hypothesis (Duke et al. 1966). Analyses of entomological data (Cheke and Garms, 2013) and a reanalysis of pre-control blindness data (Cheke et al., 2020) have led to this hypothesis being questioned. Although some molecular studies of different *O. volvulus* populations revealed differences between savannah and forest strains, for instance by being distinguishable using the O-150 repeat region sequence (Erttmann et al., 1987; Zimmermann et al., 1992), other studies did not

(Morales-Hojas et al., 2007). Recent studies involving nuclear DNA have not confirmed clear cut distinctions but did show that parasites from the two zones can and do interbreed (Choi et al., 2016).

The complete genome of the mitochondria of *O. volvulus* (https://parasite.wormbase.org/Onchocerca_volvulus_prjeb513/Info/Index) was published by Crainey et al. (2016) while the total genome of *O. volvulus* comprises a 97 Mb nuclear genome coding 12,143 protein-coding genes, and the onchocercal *Wolbachia* have a 956 kb genome containing 785 predicted protein-coding genes (Cotton et al., 2016; http://parasite.wormbase.org/Onchocerca_volvulus_prjeb513/Info/Index; *http://exon.niaid.nih.gov/transcriptome/O_volvulus/v245/wOv_web/wOv_Web.xlsx*). Nine percent of the genes are *O. volvulus*-specific (Unnasch et al., 2000; Cotton et al., 2016; Choi et al., 2016). Recent reports on the transcriptome and proteome of *O. volvulus* and its *Wolbachia* endosymbiont (Bennuru et al., 2016) open up candidate molecules for diagnosis, new biomarkers, vaccine and drug targets. Further, the proteome of *O. volvulus* identified various mimics and antagonists of human cytokines and chemokines. Furthermore, the genome encodes numerous serine protease inhibitors such as serpins, as well as cysteine protease inhibitors like cystatin (Cotton et al., 2016). These proteins can interfere with antigen processing and presentation indicating parasite interference with host immune responses, thereby facilitating and promoting their survival in immunocompetent hosts. Interestingly, distinct encoded proteins are similar to human autoantigens, which may be implicated in the pathogenesis of eye diseases and nodding syndrome.

Onchocerciasis is very probably an anthroponosis. Humans are almost certainly the unique host of *O. volvulus* – although there are two reports indicating that primates can also host *O. volvulus*. Caballero and Barrera (1958) reported recovery of a nodule containing fertile *O. volvulus* adults from a golden spider monkey (*Ateles geoffroyi*) captured in Chiapas (Mexico), and a natural infection with *O. volvulus* has been found in a gorilla (*Gorilla gorilla*) by van den Berghe et al. (1964) in the Congo. Neumann et al. (1964) reported experimental onchocercal ocular lesions in chimpanzees (*Pan troglodytes*) and these primates were used as surrogate hosts in experimental infections for a long period to investigate humoral and cell-mediated immune responses, vaccination and drug effects (Greene, 1987; Taylor et al., 1988; Soboslay et al., 1991; Prince et al., 1992) until 2013 when the USA's National Institutes of Health (NIH) banned invasive research on chimpanzees (Knight, 2008).

3. Disease

3.1. Prevalence

Estimates of prevalence vary substantially. Thus, the WHO stated for 1983 that globally 85.5 million people were at risk and about 37 million people were infected with *O. volvulus* (Amazigo et al., 2008), with 0.34 million of the infected blinded by onchocerciasis (WHO, 1987). For 1995, the WHO noted 123 million at risk, 17.7 million infected people and 0.27 million blinded people (WHO fact sheets, 2019, 2020; Fig. 4).

Onchocerciasis is almost exclusively (>99%) prevalent in 31 countries of sub-Saharan Africa, but about 20,000 infected persons live in Yemen (Büttner et al., 1982; Connor et al., 1983; WHO 2019). In terms of populations living in areas where more than 50% live in areas where the predicted nodule prevalence is greater than 20%, the main countries are the Democratic Republic of Congo with 23.3 million people, Nigeria (14.3 million), Ethiopia (5.9 million) and Cameroon (5.2 million)(Zouré et al., 2014). In central Africa – the Central African Republic, Gabon, Democratic Republic of Congo, Angola, Sudan, Ethiopia, Uganda, Nigeria, Cameroon – onchocerciasis is co-endemic with loiasis. Loiasis, caused by the filaria *Loa loa* and transmitted by horseflies (*Chrysops dimidiatus* and *C. silaceus*) affect the eyes (African eye worm) (Vinkeles Melchers et al., 2020). Loiasis coinfection is a major concern for onchocerciasis elimination in Africa (see 4.1.).

Onchocerciasis also occurred in 13 isolated foci in six countries of Latin America, infecting 97 200 people with 500,000 people at risk (Sauerbrey, 2018; CDC 2013). Active transmission currently is limited to two foci among Yanomami indigenes in adjacent border areas of Venezuela and Brazil (CDC, 2013) (see section 4.3.3.). The fact that *O. volvulus* populations of African savannah and Central America are genetically indistinguishable, indicates that onchocerciasis was introduced into America by the entry of infected Africans from the savannah (Crump et al., 2012).

3.2. Diagnostics

Tests for diagnosing onchocerciasis are summarised in Table 2. Onchocerciasis is primarily diagnosed clinically by detecting onchodermatitis, by subcutaneous nodules (onchocercomata), often located at the hips, and by detection of microfilariae in skin snips (microfilaridermia) requiring a microscopic examination (Picq et al., 1971; Albiez et al., 1988a; Alhassan et al., 2016). Skin patch testing (Mazzotti reaction) with diethylcarbamazine (DEC) can indicate microfilaridermia (Mazzotti, 1951). Awadzi et al. (2015) reported a clinical evaluation of a transdermal delivery technology-based patch for the diagnosis of *O. volvulus* infection via skin exposure to diethylcarbamazine. Ocular status can also help diagnosis, if pathological findings such as punctate keratitis or even microfilariae in the anterior chamber are noted (O'Day and Mackenzie, 1985).

Laboratory analyses have been used since 1975 (Bartlett et al., 1975) to detect serum antibodies against *Onchocerca* surface proteins, preferentially IgG4, in infected persons by applying enzyme-linked immunosorbent assays (ELISA), by a fluorescent antibody staining technique or more recently by rapid-format antibody card test (Bartlett et al., 1975; Weil et al., 2000). As target antigens numerous *O. volvulus*-specific proteins have been investigated, in particular low molecular weight antigens such as Ov16 in addition to numerous additional proteins or hybrid proteins (Ov33, Ov10, Ov20 (Ov-FAR-1), Ov-RAL-2, Ov7, OvSOD1, Ov-ENO, Ov103, Ov9.3, OvMSA-1) (Lucius et al., 1988; Lobos et al., 1991; Mpagi et al., 2000; Andrews et al., 2008; McNulty et al., 2015; Unnasch et al., 2018). However, the sensitivity and species

specificity of antigen recognition assays are mostly of limited value because of cross-reactions with proteins from other filariae.

Ov16 was identified as highly diagnostic, mostly applied antigen (Lobos et al., 1991; Denery 2010; Lont et al., 2017; Bennuru et al., 2020). Subsequently, peptide epitopes (OvMP-23, OvNMP-48; OvOC9384, OvOC198, and OvOC5528; rOVOC10469 and rOVOC3261) (Gonzalez-Moa, 2018; Lagatie et al., 2019; Bennuru et al., 2018) were applied in ELISA analysis verifying the sensitivity and specificity by receiver operating characteristic (ROC) analysis. The lateral flow rapid assay with Ov16 and rOVOC3261 was developed as the best antigen-antibody test with 94% sensitivity and applied as the current diagnostic tool to verify interruption of transmission of *O. volvulus* (Vlaminck et al., 2015; Unnasch et al., 2018).

Some molecular biological analyses with high specificity have been developed such as real time polymerase chain reaction RT-PCR and colorimetric loop-mediated isothermal amplification (LAMP, Alhassan, 2016). The amplification assay targets a repeated *O. volvulus* sequence O-150, present in the *O. volvulus* genome with a unit length of roughly 150 bp.

Recently circulating biomarkers, e.g. peptides (OvOC3261, N-acetyl-tyramine- O-glucuronide, NATOG) (Globisch et al., 2013) or lipids (phospholipid, glycerophosphorlipid) as well as micro RNA have been developed as promising proof-of-contact diagnostic tests (Quintana et al., 2015; Lagatie et al., 2016; Gonzalez-Moa et al., 2018; Bennuru et al., 2020; Macfarlane et al., 2020).

Table 2. Diagnostic tests for detection of *O. volvulus* infection

Test	Target	Principle	Reference
Biopsy	Microfilaria	Microscopic detection of microfilariae in a skin snip biopsy	Picq 1971 Alhassan 2016
Mazzotti patch test	Microfilaria	Microfilaria-induced inflammatory reaction by provocation with DEC	Mazzotti 1958 Awadzi 2015
Antibody detection (ELISA)	*Onchocerca* antigens, hybrid: Ov16, Ov20 (Ov-FAR-1), Ov33, Ov10, Ov7, Ov103, OvSOD1, Oc9.3, Ov-MSA-1	Recognition of surface or secreted antigens of *Onchocerca* by serum IgG (IgG1, IgG4), IgM in infected humans	Lucius 1988 Lobos 1990 Andrews 2008 Burbela 2010 McNulty 2015 Lagatie 2018 Unnasch 2018
	Peptide epitope OvMP-23, OvNMP-48 OvOC9384, OvOC198, OvOC5528	Recognition by IgG	Lagatie 2019 Gonzalez-Moa 2018
	Ov16 and rOVOC3261	Antigen recognition by a Point-of-Care lateral flow rapid assay	Steel 2015 Bennuru 2020
qPCR[1] LAMP[2]	Genes: O-150 Cox1 miRNA[3]	DNA amplification qPCR, LAMP	Zimmermann 1994 Alhassan 2016 Macfarlane 2020
Biomarker Lateral flow immunoassay, Mass spectrometry	NATOG[4] Phospholipids OvOC3261 OvOC9384, OVOC9087, OVOC835, OVOC224	Lateral flow immunoassay, Liquid chromatography tandem mass spectrometry method (LC-MS/MS)	Denery 2010 Globisch 2013 Bennuru 2018 Bennuru 2020

[1] quantitative polymerase chain reaction, [2]Loop-mediated isothermal amplification, [3]microRNA, [4]NATOG, N-acetyltyramine-O-glucuronide

3.3. Pathology

The primary manifestation of an *O. volvulus* infection is itching of the skin. The skin affliction results from the migration of a myriad of microfilariae from the subcutaneous nodules (onchocercomata), harbouring fertilised adult female and male filariae, into the adjacent skin. In the course of the infection an acute papular rash develops into a chronic papular dermatitis which may be associated with lichenification, development of papules, atrophy, and depigmentation. The skin manifestation may

363 comprise so-called “leopard, elephant or lizard skin”. In addition, oedema and lymphadenopathy can occur
364 and so-called “hanging groins” (Puente et al., 2018).
365 A distinct variation of skin pathology (Fig. 5) expressing severe chronic onchodermatitis with dark
366 black hyperpigmentation and plaques, designated as sowda(h) (arabic word “aswad” for black) (Fig. 5.3),
367 was originally observed in the Yemen by Gasparini (1962) and subsequently investigated by numerous
368 scientists (Büttner et al., 1982; Connor et al., 1983; Ottesen, 1995; Richard-Lenoble et al., 2001, Al-Kubati
369 et al., 2018). Sowda patients were also found in other endemic countries including Nigeria, Sudan,
370 Ethiopia, Liberia, Guatemala and Ecuador (see section 4.3.1.). Patients with sowda manifestations
371 exhibited generally low densities of microfilariae (Büttner and Racz, 1983; Büttner, 1984; Connor et al,
372 1983; Richard-Lenoble et al., 2001).
373 Adult female worms induce an inflammatory response in the infected host and infiltration of immune
374 cells leads to the formation of a granuloma and then a subcutaneous nodule, an onchocercoma (Burchard
375 et al., 1979) (Fig. 5.6). Also, excreted filarial proteolytic, angiogenic and collagen-inducing proteins
376 promote the formation of the nodule or connective tissue-degrading activity (Haffner et al., 1998). The
377 onchocercomata harbour 2-20 fixed and clustering females and 1-10 males migrating from nodule to
378 nodule.
379 The most aggravating pathology in onchocerciasis is represented by severe visual impairment afflicting
380 500,000 people and blindness occurring in approximately 270,000 persons rendering river blindness the
381 second most frequent cause of infectious blindness (Albiez et al., 1981; Hall and Pearlman, 1999). Most
382 affected are patients with onchocercomata in the upper part of the body, including the head when
383 microfilariae invade the eyes. The host’s reaction to the infiltrated microfilariae initiate corneal opacities
384 or punctate keratitis that can develop into corneal scarring and a sclerosing keratitis.
385 Rarely, a disfiguring manifestation involving retarded growth (dwarfism, Nakalanga syndrome)
386 occurs in onchocerciasis patients (Duke, 1998). Further pathogenic features are varying neurological
387 diseases, nodding syndrome and epilepsy associated with autoimmunity (Colebunders et al., 2017;
388 Johnson et al., 2017).
389
390 3.4. Parasite– Host interaction
391
392 The parasite *Onchocerca*, residing and developing in a human host, can survive because its resilient
393 cuticle surface resists the host’s efforts to cope with the invading parasite. In addition, the parasite
394 synthesizes and releases a myriad of intercepting excretory/secretory (E/S) molecules, via extracellular
395 vesicles or directly. These molecules include antioxidants, protease-inhibitors, carbohydrate- and lipid-
396 binding molecules and cytokine regulators, which mitigate and detoxify the offending host’s components
397 (Hewitson et al., 2009; Njume et al., 2019). *O. volvulus* microfilariae also release matrix-degrading serine
398 and metalloproteases which can degrade components of the dermal extracellular matrix and elastic fibres

of host tissue, as observed in chronic onchocerciasis (Haffner et al., 1998). Vital secreted defence compounds of the filaria represent antioxidants like superoxide dismutase, peroxidoxin and thioredoxin peroxidase. Also, proteinase inhibitors, onchocystatin and serpin, are released as protection against host immune attack (Henkle-Dührsen and Kampkötter, 2001; Schönemeyer et al., 2001; Hewitson et al., 2009).

In the course of the infection the host elicits a sequence of defence mechanisms reviewed by Ottesen (1995), Brattig (2004a) and Maizels et al. (2018). In response to the filarial antigens the B-lymphocytes of the host produce antibodies, predominantly immunoglobulin G4 (IgG4) and IgE antibody isotypes (Brattig et al., 1994; Garraud et al, 1996; Adjobimey and Hoerauf, 2010). The blocking IgG4 type antibodies enhance the parasite's potential for host response evasion by inhibiting detrimental reactions since (i) IgG4 represent non-complement-fixing immunoglobulins and (ii) IgG4 cannot induce antibody-dependent cell-mediated cytotoxicity (ADCC) (Adjobimey and Hoerauf, 2010). Hence, high IgG4 concentrations are found in immunosuppressed patients with high microfilarial loads (Adjobemey and Hoerauf, 2010; Ottesen, 1995).

The defence mechanisms also include cellular responses of the adaptive and innate immune system: lymphocyte and granulocyte populations are activated to secrete cytokines and toxic compounds which affect the parasite (Ottesen 1995; Maizels et al. 2018). In *Onchocerca*-infected individuals the T helper lymphocyte populations Th1, Th2, Th17 and regulatory T cells (Treg) are stimulated - predominantly occurring as a Th2-response (Brattig et al., 1987; Plier et al., 1995; Timmann et al., 2003; Allen and Sutherland, 2014). The helminth initiated lymphocyte subsets produce the cytokines IL-4, IL-13, IL-5, IL-10, and TGF-beta which subsequently initiate multiple reactions from the innate immune system (Turaga et al., 2000; Brattig et al., 1997; 2002; Soboslay et al., 1999; Dötze et al., 2000; Hoerauf and Brattig, 2002).

Characteristic of the innate immune response are eosinophilic and neutrophilic granulocytes, mast cells and alternatively activated macrophages (Brattig, 2004a; Maizels et al., 2018). Predominant eosinophilic granulocytes are activated by IL-5, released from Th2 cells, and their infiltration in the tissue is regulated by IL-4 and IL-13. Such activated eosinophils adhere and degranulate at the surface of microfilariae (Fig. 7.1-2) and infective larvae (Fig. 7.3-4) (Medina-De la Garza et al., 1990; Strote et al., 1990; Brattig et al., 1991; Abraham et al., 2004). Eosinophilic effector cells produce reactive oxygen species and secrete, via extracellular granules, multiple toxic molecules including oxygen radicals, eosinophil peroxidase, major basic proteins, eosinophil cationic proteins , eosinophil-derived neurotoxin and cytokines such as IL-10 and even IL-13 (Tischendorf et al., 1992; Pearlman 1997; Weller and Spencer, 2017). In addition to the eosinophils, mast cells are also operative in the host responses against helminths (Ottesen, 1995; Korten et al. 1998). The Th1-associated response of neutrophilic granulocytes reflect the presence of the endobacteria (see section 3.5.) (Brattig et al., 2001; Tamarozzi et al., 2016). In addition to anti-parasitic reactions, the innate immune system is involved in wound repair mechanisms (Weller and Spencer, 2017).

These multifarious reactions result in an inflammatory or immunosuppressed status which affect both competitors (Mackenzie et al., 1985; Ottesen, 1995; Brattig, 2004a). Hence, the pathogenesis of onchocerciasis is considered to be a consequence of long-standing reciprocal reactions of both parasite and host. The genetic constitution of the host represents one basic factor determining the variability of the host reactivities (Meyer et al., 1994; Timmann et al., 2008), and the presentation of a spectrum of disease manifestations (Ottesen, 1995, Büttner, 1984; Lucius et al., 1986; Hoerauf et al., 2003a; Brattig, 2004a).

Patients with a hyperreactive form of onchocerciasis, Sowda(h) (see section 3.3.) exhibit a particular host-parasite interaction (Bartlett et al., 1978; Connor et al., 1983; Ottesen, 1995; Brattig, 2004a). The high inflammatory potential visibly manifests in the skin showing hyper-pigmentation, lesions, pruritus and lichenification (Fig. 5). This activated state corresponds with strong cellular immune responses. Characteristic are Th2 and Th17-Th2 lymphocytes and their secreted products such as IL-13, IL-4 and IL-17; they are associated with low Treg cells ($CD4^{+}CD25^{hi}Foxp3^{+}$) reactivity (Brattig et al., 1987; Hoerauf et al., 2002; Katawa et al., 2015). Furthermore, high numbers of eosinophlic granulocytes,together with their released toxic cell products, and mast cells occur in hyperreactive onchocerciasis (Medina-De la Garza et al., 1990; Rubio-de Krömer et al., 1995; Tischendorf et al., 1992; Hoerauf et al., 2002). Although only a small number of microfilariae occur in the skin, the lack of Treg cells results in uncontrolled inflammatory responses (Brattig 2004a; Hoerauf and Brattig, 2002; Katawa et al., 2015). Serologically, strongly increased antibody including autoantibody responses are characteristic of sowda patients (Brattig et al., 1994; Gallin et al., 1995) (see section 3.3.). In consequence, these strong immune responses are associated with the reported low level of microfilarial density (Omar et al., 1979; Büttner and Racz., 1982, 1983; Siddiqui and Khawajah, 1991).

One major option for an effective host immune response is a prophylactic vaccine against the parasite, notably that spurred on and advanced by Sarah Lustigman (Lustigman et al., 2002, 2018; Hotez et al., 2015; George et al., 2019). Vaccines are aimed at preventing infection by infective larvae (anti-L3), and/or reducing microfilariae thereby complementing the control or elimination of onchocerciasis. Numerous proteins released by the filariae have been investigated for their vaccine potential; these comprise Ov-103, Ov-RAL-2, Ov-CHI-1, Ov_ALT-1, Ov-B20, Ov28CRP, Ov-GAPDH (Steisslinger et al., 2015; Lagatie et al., 2018; Lustigman et al., 2018). The alum-adjuvanted vaccine consisting of Ov-103, expressed at the surface of microfilariae, and Ov-RAL-2, found in the hypodermis of infective larvae, have the potential of reducing the infection by inhibition of moulting and survival of larvae. The development of cytophilic antibodies against the antigens and of interleukins effect antibody-dependent cellular cytotoxicity (George et al., 2019). Further, an immunomics approach with serum samples from putatively immune individuals has been applied (Bennuru et al., 2016). Recently a multi-epitope subunit vaccine coding for selected B-cell and T-cell epitopes, was constructed representing a novel approach for generating a specific immune response thereby avoiding responses against other unfavourable epitopes in the complete antigen (Shey et al., 2019). Another optional vaccine consists of nanoparticles or the use of non-protein molecules such

as carbohydrates, like the specific glycoform of glycosyl-phosphatidylinositol, that can act as vaccine candidates, as indicated for microbes (Jaurique and Seeberger, 2017).

3.5. Role of *Wolbachia* in onchocerciasis

The *Wolbachia* endobacteria are obligatory symbionts contributing to the viability of the parasite, its growth and development. The endobacteria are transovarially transmitted like mitochondria to the next filarial generation. Thus, antibiotics deployed to antagonize the endobacterial symbiotic role result in disruption of embryogenesis in female filariae.

Immunologically, the *Wolbachia* stimulate innate and adaptive immune responses. The bacteria-derived surface-associated and released molecules play immunological and pathological roles in onchocerciasis. In particular, endotoxin-like molecules induce Th1-type inflammatory reactions as known in all gram-negative lipopolysaccharide-exposing bacteria (Brattig et al., 2000; 2004b). In contrast to the helminth-characteristic type 2 (Th2) and Th3 immune responses, the *Wolbachia* provoke bacteria-typical predominant type 1 (Th1) reactions. Neutrophils - characteristically activated against bacteria - accumulate within an onchocercoma at the surface of a female comprising a multitude of *Wolbachia* in the lateral cord (see section 3.3., Fig. 7.5) (Brattig et al., 2001; Tamarozzi et al., 2016) - but neutrophils are absent in the onchocercoma on the surface of a female when the onchocerciasis patient has been treated with antibacterial doxycycline eliminating the *Wolbachia* (Fig. 9) (Brattig et al., 2001; 2004; Pearlman, 2003; Saint André et al., 2002). Subsequently, high peripheral levels of TNF-alpha, IL-1 beta, IL-6, IL-8 and antibacterial acute phase reactants arise on site and in the circulation. The *Wolbachia* surface protein (WSP) and heat-shock protein induce Th1-associated cytokines, TLR2/4 and IgG1 antibody responses (Pearlman, 2003; Brattig, 2004b; Kamalakannan et al., 2012; Tamarozzi et al., 2016).

The endotoxin-like and other products of the *Wolbachia* initiate a major proinflammatory stimulus in the eye disease leading to keratitis. *Wolbachia*, in addition, are associated with the severity of adverse reactions after chemotherapy of onchocerciasis with anti-filarial drugs. *Wolbachia* thus represent a target for therapy (Saint Andre et al., 2002; Pearlman, 2003).

4. Onchocerciasis control and elimination programmes

4.1. Elimination of onchocerciasis by chemotherapy of infected patients

Table 3 summarises past, present and potential future therapeutic agents for treatment of onchocerciasis. The first therapeutic agent against parasitic infections was suramin (Germanin; Bayer AG), a complex compound with four aromatic benzene rings and a functional urea group, which was introduced in 1949 (Wilson and Wormall, 1949). Suramin is a micro- and macrofilaricide, i.e. it not only kills microfilariae but also adult filariae. Suramin damages the intestinal epithelium of the filaria. Suramin, however, is inherently dangerous because of its high protein-binding affinity and alteration of enzyme

function; thus, it carries the risk of dermatitis, diarrhoea, optic neuropathy, nephrotoxicity, and even the occasional death. A three-year study in the Onchocerciasis Control Programme advised against suramin treatment (Rolland et al., 1980) and it is contraindicated in pregnancy.

Diethylcarbamazine (DEC, Hetrazan. PharmaCompass) a piperazine derivative, has been used as therapy against onchocerciasis since 1950 (Ruiz Reyes, 1951). It is also a micro- and macrofilaricide affecting the neuromuscular system of the parasites and promotes cellular cytotoxicity mediated by immune factors. In addition, DEC provokes various side effects such as itching and urticaria (reactions to disintegrating microfilariae) facial swelling, headache, nausea, vomiting, fever, joint pain and anorexia. DEC is used in a patch test (Mazzotti) for detection of skin microfilariae (see section 3.2.).

Kuesel (2016) reviewed the path from discovery of new compounds (see below) to their qualification for large scale use and the support of regulatory authorities provides for development of drugs for neglected tropical diseases.

Ivermectin (Mectizan^{R}, Merck) a macrocyclic lactone, derived from *Streptomyces*, is an endectocide. In 2015, the Nobel Prize in physiology or medicine was jointly awarded to W. Campbell (University of Wisconsin) and S. Omura (Kitasato University) at the Karolinska Institute (Sweden) for their discovery and exploration of ivermectin and its mode of action, resulting in a novel therapy against onchocerciasis and other nematode infections (Aziz et al., 1982; Campbell et al., 1983, 2016; Ömura, 2016; van Voorhis et al., 2015) (Fig. 8). This molecule binds to the inhibitory neurotransmitter GABA on neurons and muscles resulting in an irreversible activation of a chloride influx, in a hyperpolarization of the membrane, and in paralysis and death of microfilariae. Ivermectin expresses micro- but not macrofilaricidal activity, although it causes long-term sterility of the adult female worms. Ivermectin was introduced for anti-filarial treatment in 1981. Albiez et al. (1988b) showed that ivermectin was a more effective microfilaricidal agent than DEC that caused more frequent and severe side effects. Initially, ivermectin was administered once a year (150 µg/kg) , but lately it is increasingly administered bi-annually (Frempong et al., 2016). A 3-monthly treatment with ivermectin even may be most effective to prevent the appearance of onchocercomata (Campillo et al., 2020). The 3-monthly treatments not only target microfilariae, but probably in addition the moulting of third to fourth stage larvae and possibly can affect immature adults suggesting a prophylactic effect. Further, Navarro et al. (2020) reviewed data on the safety of high doses of ivermectin (>400 up to 800 µg/kg) but did not exclude ocular adverse events.

Ivermectin is donated free of charge by the Mectizan Donation Program and was distributed amongst communities by the African Programme for Onchocerciasis Control (APOC) and by various Non-Governmental Organisations (NGOs) such as Sight Savers, Lions International Sight First Programme, The Carter Foundation and the Helen Keller Foundation. Latterly, the Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN) has responsibility for oversight of ivermectin distribution in Africa. The programme reaches more than 300 million people in the affected areas of 35 countries annually, with more than 3.4 billion treatments donated since 1987. (The Mectizan^{R} Donotion

544 Program (MDP) https://www.merck.com/about/featured-stories/mectizan.html,
545 https://www.cartercenter.org/health/river_blindness/index.html).
546 The drug has rare adverse effects such as red eyes and dry and burning skin. However, ivermectin is
547 contraindicated in persons with loiasis due to the risk of ivermectin-associated severe inflammation since
548 treatment with ivermectin may result in adverse reactions in patients with both onchocerciasis and loiasis
549 (Gardon et al., 1997) (see section 3.1.). In a 'test-and-treat' (TNT) strategy a rapid test (*Loa*Scope) has
550 been introduced for loiasis-endemic areas identifying individuals with levels of *Loa loa* microfilaremia
551 associated with a risk of post-ivermectin severe adverse events. *Loa*Scope-positive individuals were
552 excluded from ivermectin treatment (Boussinesq et al., 2018). Adverse effects after ivermectin treatment
553 have been observed at a rate of about 9% with cases showing hypotension or dyspnoea (De Sole et al.,
554 1989). Bockarie et al. (2013) discussed the option of preventive chemotherapy as a strategy for
555 elimination of onchocerciasis by treating populations at risk, to prevent transmission or morbidity.
556 Moxidectin, a milbemycin macrocyclic lactone, related to ivermectin, has been used since 1995 as an
557 anthelminthic in veterinary medicine against various *Onchocerca* species (Monahan et al., 1995). Opoku et
558 al. (2018) conducted a randomised, controlled, double-blind phase 3 trial in the Democratic Republic of
559 Congo, Ghana and Liberia and stated that skin microfilarial loads were lower after moxidectin treatment
560 than after ivermectin treatment. Moxidectin would therefore be expected to reduce parasite transmission
561 between treatment rounds more than ivermectin could, thus accelerating progress towards elimination.
562 Moxidectin has microfilaricidal and embryostatic effects after a single dose and expresses a
563 macrofilaricidal effect upon repeated doses. Several studies indicate that moxidectin has a higher efficacy
564 than ivermectin (Awadzi et al., 2014). Besides moxidectin, also flubendazole and emodepside had been
565 investigated as candidate drugs (Kuesel, 2016).
566 Recently, metabolic chokepoint compounds have been identified which were either produced or
567 consumed by a single enzyme reaction. The respective checkpoint enzymes that govern these reactions
568 have been investigated (Taylor et al., 2013). Inhibition of such enzymes either leads to a toxic
569 accumulation or lack of a compound necessary for subsequent reaction. Taylor reported anti-filarial
570 effects on *Onchocerca* microfilariae by perhexiline, a piperidine derivative affecting carnitine o-
571 palmitoyltransferase and the fatty acid oxidation pathway. Most recently, benzimidazole-benzoxborole
572 hybrids, amide- or ketone-linked, termed 8a (AN8799) or 21 (AN15470), have been reported as promising
573 macrofilaricidal agents tested to date in animal models (Akama et al., 2020).
574 Since 1998 antibiotic therapy has demonstrated depletion of *Wolbachia* endobacteria in *O. volvulus*
575 and other filariae (Hoerauf et al., 2000, 2001). Doxycycline was proposed for treatment of onchocerciasis
576 in addition to ivermectin since adult females were sterilized when the antibiotic killed the *Wolbachia* (Fig.
577 9). However, a general implementation of doxycycline for filariasis therapy was hardly feasible because of
578 the frequency and duration of the required treatment of 100 or 200 mg daily for 4-6 weeks. Also, adverse
579 reactions have been reported and no pregnant women and children can take doxycycline (Hoerauf et al.,

2003b, 2008; Abegunde et al., 2016).

Since 2014 an Anti-*Wolbachia* Consortium (A-WOL) at the Liverpool School of Tropical Medicine, has been active among others in the field of antiwolbachial drug discovery to treat filarial infections. There are numerous ongoing studies on novel alternate drugs against *Wolbachia* with excellent potential. The tylosin analog ABBV-4083 (TylAMac), a macrolide antibiotic, is an inhibitor of bacterial protein synthesis. ABBV-4083 resulted in a >99% elimination of *Wolbachia* as measured 16 weeks after treatment initiation, blocking the embryogenesis and leading to a complete clearance of circulating microfilariae. ABBV-4083 expressed relatively low activity against microfilariae of *L. loa*. A successfully completed phase I clinical trial assessing the safety and tolerability of ABBV-4083 has provided encouraging findings to support advancement of ABBV-4083 to phase II clinical trials (von Geldern et al., 2019; https://www.dndi.org/diseases-projects/portfolio/abbv-4083/).

There are other attractive non-macrolid antibiotic anti-Wolbachial compounds (AWZ=anti-*Wolbachia*) such as the heterocyclic thienopyrimidine/quinazoline scaffold AWZ1066 and its enantiomers AWZ1066-S and –R expressing drug metabolism/pharmacokinetic features (Hong et al., 2019). AWZ1066S is a highly specific anti-*Wolbachia* candidate selected through a lead optimization programme focused on balancing efficacy, safety and drug metabolism/ pharmacokinetic (DMPK) features of a thienopyrimidine /quinazoline scaffold derived from phenotypic screening. AWZ1066S shows superior efficacy to existing anti-*Wolbachia* therapies in validated pre-clinical models of infection and has DMPK characteristics that are compatible with a short therapeutic regimen of 7 days or less. This candidate molecule is well-positioned for onward development and has the potential to make a significant impact on communities affected by filariasis. Furthermore, some intriguing future anti-Wolbachial candidate molecules include the heterocyclic quinazolines CRB417 and CRB490 with excellent efficacy and properties (Bakowski and McNamara, 2019). Very recently, *in vivo* efficacy of boron-pleuromutilin AN11251 against *Wolbachia* in the rodent filarial nematode *Litomosoides sigmodontis* model has been demonstrated to be superior to doxycycline (Ehrens et al., 2020). Thus, AN11251 treatment resulted in a *Wolbachia* FtsZ/actin reduction of 94% compared to <40% with doxycycline.

608 Table 3. Therapeutic agents for treatment of onchocerciasis

609

Target	Therapeutic agents	Originator / Operator	Start of treatment
Onchocerca	Suramin	Wilson and Wormall	1949
	Diethylcarbamazine, DEC (Hetrazan)	Ruiz Reyes	1951
	Ivermectin	Aziz	1982
		Campbell	1983, 2016
		Ömura	2016
		Nobel prize, Karolinska Institute, Sweden	2015
		van Voorhis	2015
	Moxidectin, Milbemycin	Monahan	1995
		Opoku	2018
Wolbachia	Doxycycline	Hoerauf	2002
	Doxycycline versus Ivermectin	Abegunde	2016
	Tolosin A analog: ABBV-4083, TylAMac	von Geldern	2019
		Taylor	2019
	AWZ1066S, CRB490/417	Hong	2019

610

611

612 4.2. *Vector control*

613

614 4.2.1. Vector control 1932-1974

615 The first known attempt to control onchocerciasis by vector control was in Mexico in 1932. This and
616 many other vector control efforts by both vegetation removal and chemical applications were reviewed by
617 Davies (1994). There were aerial treatments with the organochlorine *Dichloro-diphenyl-trichloro-ethane*
618 (DDT) of the River Congo at Kinshasa, now in the Democratic Republic of Congo, from 1948 to 1952 which
619 led to the temporary disappearance of *S. damnosum* s.l., after which the vector populations have never
620 recovered to their pre-control levels. DDT was in addition successfully used in Kenya and Uganda. In 1943,
621 bush-clearing led to the disappearance by 1947 of vectors from the small (42 km^2) Riana focus in Kenya
622 and, in 1946, the vector *S. neavei* was eliminated from a focus in the Kodera district of Kenya by dripping
623 DDT into rivers (McMahon et al., 1958), even though it was not known until 1950 that the species'
624 immature stages were phoretic on crabs. Also, in Kenya, DDT was successfully used to eradicate
625 onchocerciasis vectors from foci in Kissy/Kericho and North Nyaza. A similar success was achieved in
626 neighbouring Uganda, when DDT was used again to eliminate *S. damnosum* s.l. from the Victoria Falls by
627 1973.

628 Other control programmes were maintained in West Africa, for instance in Côte d'Ivoire from 1965 to
629 1971. DDT was phased out in favour of temephos, which was first used for *Simulium* control in the Sanaga
630 river, Cameroon, in 1972, and temephos was the insecticide of choice used by OCP from 1975 (see below).
631 This was after it was realised that localised control was only effective in isolated foci, when a plan for the
632 massive Onchocerciasis Control Programme in the Volta Basin of West Africa (OCP) was initiated
633 (https://www.who.int/blindness/partnerships/onchocerciasis_OCP/en/).
634
635 4.2.2. The World Health Organization Onchocerciasis Control Programme in the Volta Basin of West Africa
636 (OCP)
637 At a meeting in Tunis during 1-8 July 1968 on the feasibility of onchocerciasis control it was agreed to
638 plan a control campaign covering seven countries around the Volta Basin of West Africa
639 (WHO/ONCHO/69.75 Joint US-AID/OCCGE/WHO Technical Meeting on the Feasibility of onchocerciasis
640 control. Tunis, 1-8 July 1968, Report). This led to the production of a proposal to the Governments of
641 Dahomey (now the Republic of Benin), Ghana, Ivory Coast (= Côte d'Ivoire), Mali, Niger, Togo and Upper
642 Volta (now Burkina Faso) for the initiation of a control programme using aerial applications of insecticide
643 to the vector's breeding sites in rivers (WHO, 1973)
644 The OCP programme was established in 1974 and spraying started in 1975, with the aim of interrupting
645 transmission for twenty years to allow for all existing adult worms to die (WHO/OCP/1973). This would
646 intend to protect areas previously abandoned due to the severity of the disease and allow re-population
647 and increased agricultural production. It was thought at the time that 5.9 million people would have been
648 infected in the above seven countries in 1975. Later the programme was extended to include Guinea,
649 Guinea-Bissau, the western part of Mali, Senegal and Sierra Leone where a further 6.8 million people
650 would have been infected, but revised estimates suggest that these were underestimates and that 17.8
651 million were infected in the 11 countries of the extended OCP (O'Hanlon et al., 2016).
652 Detailed descriptions of the history and the structure of the OCP, the methods, and the results during
653 the first five years of the programme were provided by Walsh et al. (1978, 1979) and updated by
654 Philippon et al. (1990). To assess the results of the vector control measures from November 1974 to
655 October 1978 almost 1.2 million *S. damnosum* females were caught in over 52,000 man-days of catching
656 and 674,000 flies were dissected to determine Annual Biting Rates (ABRs) and Annual Transmission
657 Potentials (ATPs) (Walsh et al., 1978).
658 Up to 6000 km of rivers were sprayed weekly from the air in the original 7 countries in the dry
659 seasons and 18,000 km in the rainy seasons. Eventually, vector control was expanded into the southern
660 and western extension areas bringing the total OCP area to 1 235 000 km^2 with a population of 30 million
661 and increasing the lengths of rivers under control to 50 000 km (Samba, 1994).
662 The OCP did not succeed without overcoming a variety of operational problems. The first of these was
663 the continuing presence of adult flies from the starts of rainy seasons at treated sites lacking larvae or

pupae and it was deduced, and later shown by experimental treatments of potential sources, that there was a reinvasion of the treated zone by flies bred outside it (Garms et al., 1979b). It was later established that the flies involved in studies in Côte d'Ivoire, in the central OCP area, were mostly savannah members of the *S. damnosum* complex (*S. damnosum* s.str. and *S. sirbanum*) and that they could migrate enormous distances of up to 500 km (Baker et al., 1990). Furthermore, they were parous and many carried infective larvae so they were of epidemiological importance (Garms et al., 1979b). A similar phenomenon also occurred in the east of the OCP, where *S. squamosum* was additionally involved (Cheke and Garms, 1983), and in the west where savannah flies were found to migrate both northeastwards and southeastwards out of and into Guinea, respectively (Baker et al., 1990).

Despite supplementing insecticidal control with mass drug administration of the microfilaricidal compound ivermectin, onchocerciasis control was not complete in some areas. Some rivers continued to have *S. damnosum* s.l. larvae present after extensive treatment cycles and infective adult flies were still being caught. After the main OCP ceased operations in 2002 such areas, designated as special intervention zones, continued to be treated with insecticides until 2001).

The great success of the OCP by 2002 was to have freed for agriculture 250,000 km^2 of fertile land from the threat of onchocerciasis, 40 million people had been protected from the disease and 600,000 cases of blindness prevented in seven countries (WHO, 2002). After the cessation of OCP, responsibility for continuing onchocerciasis control was devolved to the eleven member countries' governments.

4.2.3. The African Programme for Onchocerciasis Control (APOC)

In 1995 WHO had instigated the African Programme for Onchocerciasis Control (APOC) aiming to promote control (and from 2009 elimination) by establishing self-sustaining community-directed treatment with ivermectin (CDTI), and, where appropriate, vector control with environmentally safe methods. The participating 19 countries were the remaining non-OCP endemic countries: Angola, Burundi, Cameroon, Central African Republic, Chad, Democratic Republic of Congo, Equatorial Guinea, Ethiopia, Gabon, Kenya, Liberia, Malawi, Mozambique, Nigeria, Rwanda, Sudan, Tanzania and Uganda. APOC's vector control activities were restricted to a few isolated foci, notably in Bioko (Equatorial Guinea) (Traoré et al., 2009), Tanzania and Uganda (Garms et al., 2009; https://www.who.int/apoc/vector/en/). APOC terminated in December 2015 and WHO's action on onchocerciasis control was subsumed in May 2016 within the Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN) that deals not only with onchocerciasis but also with lymphatic filariasis, loiasis, schistosomiasis, soil-transmitted helminthiasis and trachoma (http://espen.afro.who.int/; Hopkins, 2016).

4.3. Current status of onchocerciasis in selected countries

According to WHO (2017) onchocerciasis control with mass drug administration (MDA) was still continuing in 2017 in the African Region in Angola, Benin, Burkina Faso, Burundi, Cameroon, Central

African Republic, Chad, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Ghana, Guinea, Guinea Bissau, Liberia, Malawi, Mali, Mozambique, Nigeria, Senegal, Sierra Leone, South Sudan, Togo, Uganda and the United Republic of Tanzania. In the Eastern Mediterranean Region, MDA continued in Sudan and Yemen. The results of evaluations of CDTI were separated into those campaigns that were reported as being where criteria for stopping CDTI had been met or were close to elimination, on track to elimination or showing unsatisfactory progress.

4.3.1. Africa

4.3.1.1. Guinea

The first research on onchocerciasis was conducted by staff of the Bernhard Nocht Institute in the 1960s. Knüttgen (1964) and Knüttgen and Büttner (1968) examined 18,634 people in northeastern Guinea and reported that 45.8% carried microfilariae and 24% had nodules, with blindness rates varying from 1.07 to 4.56%. Subsequently, Knüttgen (1971) and De Sole et al. (1991) summarized the epidemiological situation. Garms and Post (1966) were the first to report the presence of *S. damnosum* s.l. and later Garms and Vajime (1975) found that, of the then known cytospecies, *S. yahense*, *S. sanctipauli*, *S. soubrense*, *S. damnosum* s.str. and *S. sirbanum* were present. This information was updated by Boakye et al. (1998). Guinea was part of the western extension of the OCP and was identified as a source of flies reinvading northern Cote d'Ivoire and Burkina Faso, involving distances of up to 500 km (Baker et al., 1990; see section 4.2.2.). According to WHO 2018a,b in 2017 almost 7 million people in 24 districts still required MDA with a reported coverage of 72.3%.

4.3.1.2. Liberia

Liberia was never a member of the OCP but onchocerciasis and its vectors were studied extensively by teams from the Bernhard Nocht Institute for Tropical Medicine, which established the Liberian Research Unit field station at Bong town, in 1968. The extent of onchocerciasis in the country was described by Frentzel-Beyme (1973, 1975a,b). Interestingly, the clinical state of onchocerciasis known as sowda is frequent in Liberia (Darge and Büttner, 1995) (see section 3.3.). Garms and Vajime (1975a) showed that *S. damnosum* s.str. and *S. sirbanum* occurred in the savannah areas, while in the forest *S. yahense* and a variety of members of the *S. sanctipauli* sub-complex are present, of which *S. yahense* is the most important vector (Garms, 1987; Trpis, 2006). The form of the *S. sanctipauli* complex occurring in the St. Paul river was originally described by Vajime and Dunbar (1975) as *S. sanctipauli* s.str. but after re-examinations of cytotaxonomic material Post (1986) pointed out that its chromosome patterns actually showed it to be a form of *S. soubrense*.

Furthermore, those populations are genetically distinct from the Farmington form present in the Farmington river (Kashan and Garms, 1987; Güzelhan and Garms, 1991). In addition *S. sanctipauli* s.str. does occur in Liberia too, but only in forest/savannah mosaic habitats in the Cestos, Mano and Makona

736 rivers. Also, *S. soubrense* B (= *S. leonense*) was recorded in the Farmington river (Güzelhan and Garms,
737 1991). Anthropogenic factors have influenced vector dissemination as extensive deforestation associated
738 with iron mining activities allowed savannah forms (*S. damnosum* s.str. and *S. sirbanum*) to invade
739 previously forested areas as far south as Bong (Garms 1987; Garms et al., 1991).
740 Treatments with ivermectin began in 1999 but Liberia has also been the site of successful trials of a new
741 macro- and microfilaricide, moxidectin (Opoku et al., 2018; see section 4.1).
742
743 4.3.1.3. Cameroon
744 At the beginning of the 1990s it was estimated that 1,300,000 people were infected in Cameroon, of
745 whom 26,000 were blind (WHO, 1995). Major advances in onchocerciasis research were made from a base
746 at Kumba in Cameroon by Duke and his colleagues who developed the concept of *Onchocerca–Simulium*
747 complexes involving forest and savannah strains of the parasite (Duke et al., 1966; Duke 1967a; Lewis and
748 Duke, 1966).
749 Non-*volvulus* species of *Onchocerca* are more commonly found in *S. damnosum s.l.* in Cameroon than is
750 usual in many other African countries (Duke 1967b). This necessitates care in the analysis of the results
751 of *Onchocerca* parasites counted in the vectors. The most important of these is *O. ochengi*, a cattle parasite,
752 the impact of which on the transmission of *O. volvulus* was discussed by Eisenbarth et al. (2016)
753 Detailed studies in Cameroon of the vectorial abilities of *S. damnosum* s.str. and *S. sirbanum* have been
754 conducted (Renz 1987, Renz and Wenk 1987) and on *S. squamosum* B in the Sanaga valley by Demanou et
755 al. (2003), who also discussed data from Kumba on *S. squamosum* A and C.
756 Studies in Cameroon have highlighted the slow progress towards elimination based on ivermectin.
757 Katabarwa et al. (2013) described how only 3 of 11 health districts were close to elimination after 15
758 years of treatment. Continuing transmission and prevalence of up to 52.7% were also reported for areas
759 in the southwest by Wanji et al. (2015a) after 10 years of ivermectin distribution by CDTI. In another
760 study it was reported that 15.5% of 2,364 people had never taken ivermectin (Wanji et al., 2015b). Similar
761 results with onchocerciasis remaining at mesoendemic levels in the Centre and Littoral Regions and in the
762 Vina du Nord River Valley after 15 and 25 years of CDTI, respectively, were documented by Kamga et al.
763 (2016) and Eisenbarth et al. (2016).
764 It is unlikely that a long-term solution to the control of biting fly numbers or of onchocerciasis will be
765 possible in the long-term without complementary vector control. Whilst, in theory, ivermectin
766 distribution will interrupt transmission if distribution is maintained at 100% coverage for more than 25
767 years, in practice this is unlikely to be achieved because of (a) insufficient coverage for logistic and
768 management reasons; (b) lack of acceptability of the drug in loiasis areas; and (c) the emergence of
769 resistance to ivermectin, as “non-responders” (defined as individuals with microfilaria (mf) counts in skin
770 >10 mf/snip after nine or more rounds of ivermectin treatment) have already been found in Ghana
771 (Dadzie *et al*. 2003, Awadzi *et al.* 2004), with further evidence for it in Cameroon (Bourginat et al 2007).

According to WHO (2018a,b), in 2017 more than 11 million people in 112 of 113 districts required MDA and 71% were treated.

4.3.1.4. Uganda

In Uganda, where approximately 1.4 million people had been infected with onchocerciasis (Ndyomugyenyi 1998) and the disease existed in 17 foci, about 2.8 million people required MDA in 2017 (WHO 2018a,b), but not in 8 formerly endemic districts after onchocerciasis had been eliminated by MDA and vector control. So far Uganda, together with Kenya, Equatorial Guinea, Sudan and Ethiopia are the only African countries where onchocerciasis foci have been eliminated. In Uganda onchocerciasis is transmitted by two vectors, both of which were described from there: *S. damnosum* Theobald 1903 and *S. neavei* Roubaud 1915 (Adler, 2019). The larvae of *S. neavei* develop in a phoretic association on freshwater crabs of the genus *Potamonautes* and *S. neavei* is or was the vector in most of the smaller isolated foci. Uganda was one of the first countries where large scale vector control projects were carried out. From 1951 to 1973 there were 11 vector control projects, all with DDT (Davies 1994). Particularly famous were the projects on the important Victoria Nile focus where *S. damnosum* was breeding in a series of 70 km of rapids below the Owen dam. The application of 1973 was completely successful (McCrae, 1978), no flies have been found up to the present day (Davies, 1994), but it had never been formally verified that the transmission had been stopped. However, a recent study showed a total of 2953 serum samples taken from children younger than ten years and tested using the Ov16 ELISA test (see section 3.2.) were all negative (Katabarwa et al., 2020). Fly catches were carried out at the historical catching sites for at least a year. No *S. damnosum* were collected, indicating that the former vector never came back. However, 854 *Simulium adersi* Pomeroy (Subgenus *Meilloniellum*) were caught, which all turned out to be negative when tested by PCR. *S. adersi* is not known to be a vector of onchocerciasis, but can be infected experimentally (Wegesa, 1970).

Of the original 17 onchocerciasis foci in Uganda (Fig. 10) in only one, the Lhubiriha focus in Kasese District bordering D.R. Congo (Fig. 10.2, focus 14; red) is transmission by *S. kilibanum* (*S. damnosum* complex) still continuing. Interruption of the transmission by *S. damnosum* has now probably been achieved in the Mid North Focus (Fig. 10.2, focus 14; light green), mainly by vector control using temephos, but also experimentally by clearing of vegetation, window traps and CDTI. Vector control was also primarily responsible for the elimination of the Kashoya-Kitomi *S. neavei* focus (Lakwo et al., 2017). In most Ugandan foci where onchocerciasis has been eliminated by CDTI and vector control, *Simulium neavei* was the vector. Many of such successes followed on from research and control work begun in 1991 in a cooperation between the German Technical Cooperation Agency (GTZ), the Bernhard Nocht Institute for Tropical Medicine, Basic Health Services Project, and the V,ector Control Unit of the Ministry of Health in Kabarole District (now Kabarole and Kyenjojo districts) in Western Uganda.

When annual distribution of ivermectin began in 1991 no vector control was planned, but treatments were accompanied by studies on the transmission by the vector *S. neavei*. After 4 years, there was no clear effect on the transmission and 1000 parous flies still had 151 infective larvae in their heads. In view of these results and at the request of the local government it was decided to enhance the effect by vector control. Before starting this, it had been confirmed that temephos, which had been used for 25 years in the OCP (see section 4.2.2.), could be used safely, in particular, without harming the phoretic host crabs *P. Aloysiisabaudiae* (Garms et al., 2017). After only a few monthly applications from mid-1995 to the end of 1996, *S. neavei* had disappeared from the main Itwara focus and never came back. Sub-foci on the Siisa and Aswa rivers took a bit longer, but no positive crabs or biting flies were seen any more throughout the focus after February 2003 (Garms et al., 2009; Michael et al., 2020).

Of especial interest was the Imaramagambo focus in south-western Uganda, where vector control had been planned, but when it turned out that there was no transmission anymore, it was noticed that the vector *S. neavei* and its phoretic host, the freshwater crab, had both disappeared, possibly because of runoff into rivers of agricultural chemicals used intensively on the nearby tea plantations (Katabarwa et al., 2016). The flies also disappeared from areas in the Ruwenzori valley to the northwest of the Itwara focus (Garms et al., 1994) and habitat changes have also contributed to reductions in transmission elsewhere in Uganda, as Fischer et al. (1997) reported a reduced prevalence of onchocerciasis following deforestation. In addition, by 2017 MDA was leading to interruptions or suspected interruptions of transmission in five other foci where *S. neavei* was the vector (Katabarwa et al., 2018). The Madi Mid North focus, where *S. damnosum* s.l. is the vector, is likely to be the most intractable area but details of the cytoform present in that region have not been published. In western Uganda the following *S. damnosum* cytoforms have been recorded: *S. kilibanum*, "Sebwe", "Nkusi" and *S. pandanophilum*, of which only *S. kilibanum* is anthropophilic and of vectorial importance (Krüger et al., 1999).

Control of *S. damnosum* s.l. by removing the trailing vegetation upon which immature stages develop was attempted in Mexico from 1932 to 1940 without success, in D.R. Congo in the early 1940s with only partial success, and in Malawi in the early 1990s by destruction of the aquatic plant *Hydrostachys* sp. (M. J. Roberts, unpubl., Burnham 1992, Davis, 1994). Also, Baker and Abdelnur (1986a,b) showed that in a rocky breeding site of the Bussere River in south-western Sudan a small team armed with axes, saws and sickles could do much to reduce larval and pupal supports in the breeding sites caused by vegetation trailing in fast water flow. A similar strategy has also recently been applied in Uganda (Jacob et al., 2018; Smith et al. 2019) but it is unlikely to provide a long-term solution as it requires regular "slash and clear" and, besides, the vectors will adapt and breed on other substrates such as rocks, which they often use when no trailing vegetation is present. In addition, large torrential rivers and rapids, particularly those in the middles of wide rivers cannot be completely cleared.

4.3.1.5. Ghana

As mentioned in the historical introduction, Ghana was the site where onchocerciasis was first recorded (O'Neill, 1875). Crisp (1956) described the geographical extent and severity of the disease in the north and provided plans for a vector control campaign, while Waddy (1969) elaborated these with proposals that culminated in the OCP. Ghana was one of the original seven OCP countries, with the west of the country targeted at the outset in 1975. Most of the rest of the country north of the Volta Lake was included in Phase II soon afterwards, with areas south of the lake included from 1988 onwards as part of the southeastern extension. Most of the southwestern forested areas were not included in the vector control campaign, but were subject to MDA with ivermectin, following the first successful trials that were conducted in 1987 at Asubende on the River Pru (Remme et al., 1989).

The initial euphoria about possible elimination of onchocerciasis from Africa using ivermectin distributions was dealt a blow when incipient resistance to the drug was detected in Ghanaian patients (Awadzi et al., 2004). Later, cohorts of patients were found in the Brong-Ahafo and Northern Regions to be being re-populated with microfilariae sooner than was to be expected and these "non-responders" (Osei-Atweneboana et al., 2007) were also possibly harbouring resistant worms (Osei-Atweneboana et al., 2011).

Despite the activities of the OCP and subsequent continuations of ivermectin distributions, some transmission continues (Kutin et al., 2004, Garms et al., 2015), including in areas where there had been vector control (Lamberton et al., 2015, F.B.D. Vereigh, pers.comm.to RAC July 2019).

The ivermectin distributions were originally annual but it is now the policy in Ghana to distribute bi-annually. This has succeeded in reducing transmission and infection rates in some areas but not everywhere that has been studied (Frempong et al., 2016, F.B.D. Vereigh, pers. comm.). Another consideration relevant to continuing transmission is the lack of complete compliance with the drug distribution programmes. Agyemang et al. (2018) investigated compliance in the Upper Denkyira East Municipal area and reported that it was lower than given in official reports, with results ranging from 7 to 51% with an overall compliance of only 21%, even less than the 24.4% reported earlier by Kutin et al. (2004).

Ghana has a high diversity of *S. damnosum* cytoforms, including some sites where up to five different varieties could be found breeding sympatrically. Details of the vectors present and how their geographical distributions have varied from the 1970s until 2011 were summarized by Post et al. (2013), with fluctuations attributable to deforestation (Wilson et al., 2002), extinction due to vector control (Cheke et al., 2008) and pollution resulting from illegal gold-mining activities in rivers such as the Pra and Offin (Garms et al., 2015), although the mining (locally known as "Galamsy") has now been curtailed by Government actions. According to WHO (2018a,b) in Ghana in 2017 of about 8 million infected people 4.4 million (54,6%) in 84 of 85 endemic districts received MDA.

4.3.1.6. Ethiopia

879 Onchocerciasis is highly endemic in Ethiopia, with more than 20 million people infected or at risk
880 (Anon, 2015). The disease is mostly found in southwestern, western and northwestern parts of the
881 country, being particularly associated with coffee growing areas in the southwest and with cotton and oil
882 seed farming areas in the northwest. The main vectors are members of the *S. damnosum* complex (Hadis et
883 al. 2005), but *S. ethiopiense*, a member of the *S. neavei* group phoretic on crabs (*Potamonautes antheus*), is
884 suspected of being a secondary vector in the southwestern midlands and the highlands where it is often
885 sympatric with *S. damnosum* s.l. (White 1977).
886 Onchocerciasis control with ivermectin began in 2001 and by 2015 there were 18 CDTI project zones in
887 the country (Anon 2015). At present the country has some areas in various stages of post treatment
888 surveillance (PTS), for instance in the Metema area (see below; 4.3.1.7.). Onchocerciasis has disappeared
889 from the Tigray region in the absence of any control measures, probably in the wake of human migrations
890 and the establishment of commercial farming (Katabarwa et al., 2014b). In 2017, 17.5 million people
891 required MDA, with 194 of 199 endemic districts receiving it (WHO 2018a,b).
892
893 4.3.1.7. Sudan and South Sudan
894 4.3.1.7.1. Sudan
895 There are three main areas in Sudan where onchocerciasis occurs or occurred. Principal amongst
896 these was the Abu Hamed focus in River Nile State where the first case of the elimination of an
897 onchocerciasis focus in Africa was achieved following ivermectin distribution (Zarroug et al., 2016),
898 although it was probably assisted by the flooding of all of the western breeding sites of the vector in the
899 River Nile by the construction of the Merowe dam (Zarroug et al., 2014). The vector there is a unique form,
900 the *hamedense* form of *S. damnosum* (Higazi et al., 2001), which had led to prevalence of 37% in
901 populations of up to 120,000 people, with high proportions of sowda (see section 3.3.)
902 A coordinated interruption of onchocerciasis transmission, which met the criteria set forth by WHO
903 guidelines for interruption of transmission of *O. volvulus,* has been achieved at the cross-border focus
904 where the Galabat focus adjoins the Ethiopian Metema focus. This success, the first such cross-border
905 initiative in Africa, was accomplished by a combination of annual and semi-annual ivermectin MDA
906 (Katabarwa et al. 2020b).
907
908 4.3.1.7.2. South Sudan
909 About half the population of South Sudan is affected by onchocerciasis with particularly high
910 endemicity in Western Equatoria, and the Northern and Western Bahr el Ghazal areas. CDTI was begun in
911 the mid-1990s and 5,605,726 people were being targeted in 2009 (Lugga and Chane 2011). Recent zones
912 for CDTI were mapped in the context of research on control of nodding syndrome in the country.
913 Pioneering investigations on the biology of the vectors was conducted in South Sudan by Lewis (1953)
914 and by Baker and Abdelnur (1986).

915

916 4.3.2. Yemen (Arabian Peninsula)

917 Yemen is the only country in the Eastern Mediterranean with onchocerciasis, where it is most
918 prevalent along the permanent waterways (wadis) draining into the Red Sea in the west of the country.
919 The vector breeds in very shallow flat wadis with low discharges of up to 1 $m^3.sec^{-1}$ (Garms and Kerner,
920 1982). It is a unique species *S. rasyani*, a member of the *S. damnosum* complex (Garms et al., 1988).
921 Although planned, to our knowledge, there has been no vector control but sporadic ivermectin
922 distribution was begun in the early 1990s. Since 2011 civil strife and wars have interrupted the national
923 campaign. The disease in Yemen is characterised by high rates of the hyperreactive clinical manifestation
924 known as sowda (Anderson et al., 1973; Büttner et al., 1982; Büttner and Racz, 1983). Mahdy et al. (2018)
925 reported an overall seroprevalence rate of 18.5% during their surveys in 2017. According to WHO
926 (2018a,b) in Yemen in 2017 of about 6.3 million people in 33 districts were requiring MDA.

927

928 4.3.3. Americas (OEPA)

929 In the continent of America onchocerciasis was restricted to six countries of central and south
930 America: Brazil, Colombia, Ecuador, Guatemala, Mexico and Venezuela (Fig. 4). Differing from Africa with
931 its prevalence in large parts of 31 countries, in the Americas the occurrence of onchocerciasis was or is
932 confined to limited foci. Accordingly, the combat against onchocerciasis was different and an elimination
933 of the infection appears to have been or will be feasible by mass drug administration with ivermectin.

934 A variety of vectors is or was responsible for transmission in central and southern America. Members
935 of the *S. ochraceum* and *S. metallicum* complexes were involved in Mexico, with the former most active in
936 transmission in Guatemala (Garms, 1975b; Rodríguez-Pérez et al., 2015).
937 A detailed review of the potential importance of further anthropophilic *Simulium* species as vectors of *O.*
938 *volvulus* in Guatemala has been presented by Takaoka (2015).
939 In 1993 the *Onchocerciasis Elimination Program for the Americas* (OEPA), a regional initiative and
940 international partnership, was launched. Sauerbrey et al. (2018) reported on the successful progress
941 toward elimination of onchocerciasis in the Americas. From 1989 to 2016, more than 11 million ivermectin
942 treatments, given twice or four times per year, have been given in the Americas, eliminating transmission in
943 11 of 13 foci. The number of people at risk of onchocerciasis decreased from >530 thousand to about 30
944 thousand. Nodulectomy campaigns, e.g. in Mexico and Guatemala, probably helped the success of the MDA
945 (Figueroa Marroquin,1975).

946 Onchocerciasis was eliminated in Columbia in 2010, in Guatemala 2011, in Ecuador 2012, in Mexico
947 2014 and in Venezuela in 2017 apart from a focus in the South. One focus also exists in the north of Brazil.
948 In the remaining Amazonas focus that straddles the Venezuela-Brazil border the main vectors are
949 members of the *S. oyapockense* and *S. guianense* species complexes and *S. incrustatum* (Shelley et al. 2010).

The OEPA's success influenced programmes in Africa, especially in Sudan and Uganda, which moved from a control to an elimination strategy in 2006 and 2007, respectively. The successes in the Americas have also influenced WHO guidelines for onchocerciasis transmission elimination. With four of the six originally endemic American countries now having eliminated onchocerciasis transmission, and 95% of ivermectin treatments in the region halted, the regional focus is now on the remaining active transmission zone on the border between Venezuela and Brazil.

5. Future perspective

Recent publications report and discuss the success of elimination or close to elimination of onchocerciasis in limited foci in Africa - in Sudan, Mali, Senegal, Burundi, Chad, Malawi and Nigeria (Tekle et al., 2012; Zarroug et al., 2014, 2016; Walker et al., 2017; Rebollo et al., 2018; Richards et al., 2020). This success is completely or mainly based on MDA, of ivermectin. Exceptions are Bioko, Equatorial Guinea, where vector control was successful, and Uganda where onchocerciasis was eliminated from several isolated foci by combinations of control of the vector *S. neavei* by ground larviciding with temephos and MDA (Katabarwa et al 2018, 2020a,b; Michael et al., 2020).

The priority is given to treatment with ivermectin. Recently, attention, however, is drawn to the problems of poor coverage and inadequate compliance to MDA (Agyemang et al., 2018; Dissak-Delon et al., 2019). Correspondingly, Verver et al. (2018) discussed why a wide-reaching elimination of onchocerciasis cannot be guaranteed by 2025 and proposed a long-term biannual or quarterly MDA combined with vector control activities as complementary approaches (Routledge et al., 2018) for high-endemicity areas to accelerate progress toward elimination. The proof-of-principle in distinct foci in Mali, Senegal and Sudan indicate a possibility to eliminate onchocerciasis with annual or 6-monthly ivermectin treatment in some endemic foci in Africa. Correspondingly, the published *WHO 2030 goals* for onchocerciasis were influenced by the cited models (EPIONCHO and ONCHOSIM) on the impact of biannual or quarterly ivermectin treatment frequency and in addition complementary vector control (NTD Modelling Consortium Onchocerciasis Group, 2019; Gates Open Research 2019; Hassan and Shaban, 2020).

Anthelminthic drug alternatives to ivermectin, include the aforementioned Moxidectin (Awadzi et al. 2014, Opoku et al., 2018) and novel anti-*Wolbachia* agents like the thienopyrimidine/quinazoline scaffold AWZ1066 (Hong et al., 2019).

The timelines of onchocerciasis from control to elimination and eradication were discussed by Kim et al. (2015). They estimated that the elimination scenario will endure until 2028 in all endemic countries except four (Republic of Congo, Central African Republic, South Sudan, Gabon) but CDTI was predicted to continue beyond 2045 in countries with operational challenges, with around 1.15 billion treatments. The elimination of transmission (EOT) of onchocerciasis for the majority of foci in the 34 countries in Africa has been projected in several publications to be between 2025 and 2045 (Dadzie et al., 2018; Gebrezgabiher et al., 2019; Kim et al., 2015).

One major problem is that an elimination of onchocerciasis with ivermectin treatment alone has not so far appeared to be feasible in many African countries where onchocerciasis was endemic over millions of square kilometres spanning more than 30 countries. In addition, the vectors are highly efficient and with much higher endemicity levels migrating over hundreds of kilometres (Dadzie et al., 2003) threatening re-emergence of infected vectors and of onchocerciasis in their wake. Thus, exemplarily, on Bioko where the unique endemic vector (the Bioko form of *S. yahense*) was rendered extinct (Traore et al 2009) some vectors may have returned. These are *S. squamosum* rather than *S. yahense* (D. Boakye, pers, comm 2019) and it is unknown if they brought any *O. volvulus* with them.

Nevertheless, given that after nearly 15 years without any transmission on the island very few onchocercal cases remained (Hernández-González et al., 2016; Moya et al., 2016; Herrador et al., 2018; Ta et al., 2018), prospects for confirming elimination are good. The interruption of transmission was considered to have been permanent, but the Bioko case is salutary and illustrates that, however good planning and forecasts can be, there is room for the unexpected to affect our perspectives. In contrast, in the Americas, onchocerciasis elimination with ivermectin treatment has been considered feasible, since most onchocerciasis foci in the Americas were small and circumscribed, and most vector species are relatively inefficient. Thus, interruption of the transmission was feasible by 6-monthly or even 3-monthly ivermectin treatments (Sauerbrey et al., 2018).

Planning MDA programmes is now often based on the outputs of mathematical models such as ONCHOSIM (Plaisier et al 1990) or EPIONCHO (Basáñez et al. 2016) but these models skimped on details of blackfly biology. Only recently have models begun to model vector biology explicitly and started to take account of future uncertainties regarding climate change (Cheke et al., 2015) and the likelihood of needing to supplement MDA with vector control (Routledge et al., 2018). Such vector control in isolated foci could include ground larviciding, slash-and-clear vegetation destruction and killing host-seeking adult female flies in traps such as the Esperanza window trap (Rodriguez-Pérez, 2013; Toé et al., 2014; Hendy et al., 2017; NTD Modelling Consortium Onchocerciasis Group, 2019; NTD Modelling Consortium, Gates Open Research, 2019). These could be supplemented by deploying traps to catch ovipositing female flies such as "Bellec plates" placed beside breeding sites (Bellec, 1976; Cheke et al., 1982).

Difficulties surrounding the elimination of the transmission of onchocerciasis were reviewed by Cheke (2017), who drew attention to cases of successful control where transmission had probably been eliminated in contrast to areas where such interruptions were likely to be only temporary. These included areas in Africa with >55% prevalence, where mass drug administration (MDA) alone was thought of as unlikely to succeed.

In summary, anthelminthic MDA complemented by appropriate vector control measures may increasingly lead to control and hopefully eradication of onchocerciasis which may be fulfilled in mid-century.

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References

Abegunde, A.T., Ahuja, R.M., Okafor, N.J. 2016. Doxycycline plus ivermectin versus ivermectin alone for treatment of patients with onchocerciasis. Cochrane Database Syst Rev. 1, CD011146. Review

Adjobimey, T., Hoerauf, A. 2010. Induction of immunoglobulin G4 in human filariasis: An indicator of immunoregulation. Induction of immunoglobulin G4 in human filariasis: an indicator of immunoregulation. Ann. Trop. Med. Parasitol. 104, 455-464.

Abraham, D., Leon, O., Schnyder-Candrian, et al., 2004. Immunoglobulin E and eosinophil-dependent protective immunity to larval *Onchocerca volvulus* in mice immunized with irradiated larvae. Infect. Immun. 72, 810-817.

Achukwi, M.D., Harnett, W., Enyong, P., et al., 2007. Successful vaccination against *Onchocerca ochengi* infestation in cattle using live *Onchocerca volvulus* infective larvae. Parasite Immunol. 29, 11311-11316.

Adler, P. H., Cheke, R.A., Post, R.J. 2010.) Evolution, epidemiology, and population genetics of black flies (Diptera: Simuliidae). Infection, Genetics, Evolution 10: 846-865.

Adler, P.H. 2019. World blackflies (Diptera: Simuliidae): a comprehensive revision of the taxonomic and geographical inventory. https://biomia.sites.clemson.edu/pdfs/blackflyinventory.pdf

Agyemang, A.N.O., Badu, K., Baffour-Awuah, S., et al., 2018. Evaluation of onchocerciasis control in the Upper Denkyira East municipal in the forest area of Ghana: Responses of participants and distributors to the CDTI programme. Acta Trop. 185, 357-362.

Akama, T., Freund, Y.R., Berry, P.W., et al., 2020. Macrofilaricidal benzimidazole-benzoxaborole hybrids as an approach to the treatment of river blindness: part 1. amide linked analogs. ACS Infect. Dis. 6, 173-179.

Albiez, E.J., Ganley, J.P., Büttner, D.W. 1981. Ocular onchocerciasis in a hyperendemic village in the rain forest of Liberia. Trop. Med. Parasitol. 32, 25-28.

Albiez, E.J., Büttner, D.W., Duke, B.O. 1988a. Diagnosis and examination of nodules in human onchocerciasis. Trop. Med. Parasitol. 39 Suppl 4, 331-346. Review.

Albiez, E.J., Newland, H.S., White, A.T., et al., 1988b. Chemotherapy of onchocerciasis with high doses of diethylcarbamazine or a single dose of ivermectin: microfilaria levels and side effects. Trop. Med. Parasitol. 39, 19-24.

Alhassan, A., Osei-Atweneboana, M.Y., Kyeremeh, K.F., et al., 2016. Comparison of a new visual isothermal nucleic acid amplification test with PCR and skin snip analysis for diagnosis of onchocerciasis in humans. Mol . Biochem. Parasitol. 210, 10-12.

Al-Kubati, A.S., Mackenzie, C.D., Boakye, D., et al., 2018. Onchocerciasis in Yemen: moving forward towards an elimination program. Int Health. 10, Suppl. 1, i89-i96.

Allen, J.E., Sutherland, T.E. 2014. Host protective roles of type 2 immunity: parasite killing and tissue repair, flip sides of the same coin. Semin. Immunol. 26, 329-340. Review.

Amazigo, U., 2008. The African Programme for Onchocerciasis Control (APOC). Ann. Trop. Med. Parasitol. 102, Suppl 1, 19-22.

Anderson, J., Fuglsang, H., Al-Zubaidy, A. 1973. Onchocerciasis in Yemen with special reference to sowda. Trans. Roy. Soc. trop. Med. Hyg. 67, 30-31.

Andrews, J.A., Bligh, W.J., Chiodini, P.L., et al., 2008. The role of a recombinant hybrid protein based Elisa for the serodiagnosis of *Onchocerca volvulus*. J. Clin. Pathol. 61, 347-351.

Anon. 2015. Guidelines for onchocerciasis elimination in Ethiopia. Ministry of Health of the Federal Democratic Republic of Ethiopia. Addis Ababa, Ethiopia. 90 pages. Available from https://www.cartercenter.org/resources/pdfs/news/health_publications/river_blindness/Onchocerciasis-Elimination-Certification-Guidelines-Ethiopia.pdf.

Awadzi, K., Boakye, D.A., Edwards, G., et al., 2004. An Investigation of persistent microfilaridermias despite multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana. Ann. Trop. Med. Parasitol. 98, 231–249.

Awadzi, K, Opoku, N.O., Attah, S.K., et al., 2014. A randomized, single-ascending-dose, ivermectin-controlled, double-blind study of moxidectin in *Onchocerca volvulus* infection. PLoS Negl. Trop. Dis. 8, e2953.

1077 Awadzi, K., Opoku, N.O., Attah, S.K., et al. 2015. Diagnosis of *O. volvulus* infection via skin exposure to
1078 diethylcarbamazine: clinical evaluation of a transdermal delivery technology-based patch. Parasit.
1079 Vectors 8, 515.
1080 Aziz. M.A., Diallo, S., Diop, I.M., et al., 1982. Efficacy and tolerance of ivermectin in human onchocerciasis.
1081 Lancet. 2, 171-173.
1082 Bain, O., Philippon, B., Séchan, Y., et al., 1976. Correlation between the number of microfilaria ingested
1083 and the thickness of the peritrophic membrane of the vector in onchocercosis of the African
1084 savannah. C. R. Acad Hebd Seances Acad. Sci. D. 283, 391-392.
1085 Bain, O. 2002. Evolutionary relationships among filarial nematodes. pp. 21–29 in Klei, T.R. and Rajan, T.V.
1086 (Eds). The Filaria. Boston, Dordrecht and London, Kluwer Academic Publishers
1087 Baker, R.H.A., Abdelnur, O.M. 1986. Localised onchocerciasis vector control in the Bahr el Ghazal Region of
1088 South-Western Sudan. II. Control. Trop. Med. Parasitol. 37, 135-142.
1089 Baker, R.H., Guillet, P., Sékétéli, A., et al., 1990. Progress in controlling the reinvasion of windborne vectors
1090 into the western area of the Onchocerciasis Control Programme in West Africa. Philos. Trans. R. Soc.
1091 Lond. B Biol. Sci. 328, 731-747.
1092 Bakowski, M.A., McNamara, C.W. 2019. Advances in antiwolbachial drug discovery for treatment of
1093 parasitic filarial worm infections. Trop. Med. Infect. Dis. 4, 108.
1094 Bandi, C., Slatko, B., O'Neill, S.L. 1999. *Wolbachia* genomes and the many faces of symbiosis. Parasitol.
1095 Today. 15, 428-429.
1096 Bandi, C., Trees, A.J., Brattig, N.W. 2001. *Wolbachia* in filarial nematodes: evolutionary aspects and
1097 implications for the pathogenesis and treatment of filarial diseases. Vet. Parasitol.,98, 215–238.
1098 Review
1099 Bartlett, A., Bidwell, D.E., Voller, A. 1975. Preliminary studies on the application of enzyme immunoassay
1100 in the detection of antibodies in onchocerciasis. Tropenmed. Parasitol. 26, 370-374.
1101 Bartlett, A., Turk, J., Ngu, J., et al., 1978. Variation in delayed hypersensitivity in onchocerciasis. Trans. R.
1102 Soc. Trop. Med. Hyg. 72, 372-377.
1103 Basáñez, M.G., Walker, M., Turner, H.C., et al., 2016. River blindness: mathematical models for control and
1104 elimination. Adv. Parasitol. 94:247–341.
1105 Bellec, C. 1976. Captures d'adultes des *Simulium damnosum* Theobald, 1903 (Diptera: Simuliidae) à l'aide
1106 de plaques d'aluminium, en Afrique de l'Ouest. Cahiers O.R.S.T.O.M. Série Entomologie Médicale et
1107 Parasitoligie 14, 209-217.
1108 Bennuru, S., Cotton, J.A., Ribeiro, J.M., et al., 2016. Stage-specific transcriptome and proteome analyses of
1109 the filarial parasite *Onchocerca volvulus* and its *Wolbachia* endosymbiont. mBio 7, e02028- e02116.
1110 Bennuru, S, O'Connell, E.M., Drame, P.M., et al., 2018. Mining filarial genomes for diagnostic and
1111 therapeutic targets. Trends Parasitol. 34, 80-90.
1112 Bennuru, S., Oduro-Boateng, G., Osigwe, C., et al., 2020. Integrating multiple biomarkers to increase
1113 sensitivity for the detection of *Onchocerca volvulus* infection. J. Infect. Dis . 221, 1805-1815.
1114 Blacklock, D.B., 1927. The insect transmission of *Onchocerca volvulus* (Leuckart, 1893). The cause of worm
1115 nodules in man in Africa. Br. Med. J. 1; 3446, 129-133.
1116 Boakye, D., Back, C., Fiasorgbor, G.K., et al., 1998. Sibling species distributions of the *Simulium damnosum*
1117 complex in the west African Onchocerciasis Control Programme area during the decade 1984-93,
1118 following intensive larviciding since 1974. Med. Vet. Entomol . 12, 345-58.
1119 Bockarie, M.J., Kelly-Hope, L.A., Rebollo, M., et al., 2013. Preventive chemotherapy as a strategy for
1120 elimination of neglected tropical parasitic diseases: endgame challenges. Philos. Trans. R. Soc. Lond. B
1121 Biol, Sci. 368, 20120144.
1122 Bourguinat, C., Pion, S.D., Kamgno, J., et al., 2007. Genetic selection of low fertile *Onchocerca volvulus* by
1123 ivermectin treatment. Plos Negl. Trop. Dis. 1:e72
1124 Boussinesq, M., Fobi, G., Kuesel, A.C. 2018. Alternative treatment strategies to accelerate the elimination of
1125 onchocerciasis. Int. Health. 10(suppl_1), i40-i48.
1126 Bradley, J.E., Helm, R., Lahaise, M., et al., 1991. cDNA clones of *Onchocerca volvulus* low molecular weight
1127 antigens provide immunologically specific diagnostic probes. Mol. Biochem. Parasitol. 46, 219-227.
1128 Bradley, J.E., Unnasch, T.R. 1996. Molecular approaches to the diagnosis of onchocerciasis. Adv. Parasitol.
1129 37, 57-106. Review.
1130 Brattig, N.W., Tischendorf, F.W., Albiez, E.J., et al., 1987. Distribution pattern of peripheral lymphocyte
1131 subsets in localized and generalized form of onchocerciasis. Clin. Immunol. Immunopathol. 44, 149-
1132 159.
1133 Brattig, N.W., Tischendorf, F.W., Strote, G., et al., 1991. Eosinophil-larval-interaction in onchocerciasis:
1134 heterogeneity of in vitro adherence of eosinophils to infective third and fourth stage larvae and
1135 microfilariae of *Onchocerca volvulus*. Parasite Immunol. 13, 13-22.

Brattig, N.W., Krawietz, I., Abakar, A.Z., et al., 1994. Strong IgGisotypic antibody response in sowdah type onchocerciasis. J. Infect. Dis. 170, 955-961.
Brattig, N., Nietz, C., Hounkpatin, S., et al., 1997. Differences in cytokine responses to *Onchocerca volvulus* extract and recombinant Ov33 and OvL3-1 proteins in exposed subjects with various parasitologic and clinical states. J. Infect. Dis. 176, 838-842.
Brattig, N.W., Rathjens, U., Ernst, M., et al., 2000. Lipopolysaccharide-like molecules derived from *Wolbachia* endobacteria of the filaria *Onchocerca volvulus* are candidate mediators in the sequence of inflammatory and antiinflammatory responses of human monocytes. Microbes Infect. 2, 1147-1157.
Brattig, N.W., Büttner, D.W., Hoerauf, A. 2001. Neutrophil accumulation around *Onchocerca* worms and chemotaxis of neutrophils are dependent on *Wolbachia* endobacteria. Microbes Infect. 3, 439-446.
Brattig, N.W., Lepping, B., Timmann, C., et al., 2002. *Onchocerca volvulus*-exposed persons fail to produce interferon-gamma in response to *O. volvulus* antigen but mount proliferative responses with interleukin-5 and IL-13 production that decrease with increasing microfilarial density. J. Infect. Dis. 185, 1148-1154.
Brattig, N.W. 2004a. Pathogenesis and host responses in human onchocerciasis: impact of *Onchocerca* filariae and *Wolbachia* endobacteria. Microbes Infect. 6, 113-128. Review.
Brattig, N.W., Bazzocchi, C., Kirschning, C.J., et al., 2004b. The major surface protein of *Wolbachia* endosymbionts in filarial nematodes elicits immune responses through TLR2 and TLR4. J. Immunol. 173, 437-445.
Brumpt, E., 1919. Une nouvelle filaire pathogène parasite de l'homme (*Onchocerca caecutiens*, n. sp.). Bull. Soc. Pathol. Exot. Filiales 12, 464–473
Burbelo, P.D., Leahy, H.P., Iadarola, M.J., Nutman, T.B. 2009. A four-antigen mixture for rapid assessment of *Onchocerca volvulus* infection. PLoS Negl Trop Dis. 3, e438.
Burchard, G.D., Büttner, D.W., Bierther, M. 1979. Electron microscopical studies on onchocerciasis. III. The onchocerca-nodule. Tropenmed. Parasitol. 30, 103-112.
Büttner DW, von Laer G, Mannweiler E., et al., 1982. Clinical, parasitological and serological studies on onchocerciasis in the Yemen Arab Republic. Tropenmed Parasitol. 33, 201-212.
Büttner DW, Rácz P. 1983. Macro- and microfilariae in nodules from onchocerciasis patients in the Yemen Arab Republic. Tropenmed Parasitol. 34, 113-121.
Büttner, D.W. 1984. Onchocerciasis. Internist (Berl). 25, 229-235. Review
Caballero, C. E.., Barrera, A. 1958. Estudios helmintológicos de la region onchocercosa de Mexico y de la Repùblica de Guatemala. Nematodeda Iia Parte. Filaroidea V. Hallozgo de un nodulo oncocerciso en un mono arana *Ateles geoffroyi vellerosus Gray*, del Estado de Chiapas. Re´v. Lat. Amer. Microbiol. 7, 79-94
Calamari, D., Yameogo, L., Hougard, J.M., et al., 1998. Environmental assessment of larvicide use in the Onchocerciasis Control Programme. Parasitology Today 14, 485-489.
Campbell, W.C., Fisher, M.H., Stapley, E.O., et al., 1983. Ivermectin: a potent new antiparasitic agent. Science. 221, 823-828.
Campbell, W.C. 2016. Ivermectin: A Reflection on Simplicity (Nobel Lecture). Angew Chem Int Ed Engl. 55, 10184-10189.
Campillo, J.T., Chesnais, C.B., Pion, S.D.S., et al., 2020. Individuals living in an onchocerciasis focus and treated three-monthly with ivermectin develop fewer new onchocercal nodules than individuals treated annually. Parasit. Vectors. 13, 258.
Cantey, P.T., Roy, S.L., Boakye, D., et al., 2018. Transitioning from river blindness control to elimination: steps toward stopping treatment. Int. Health. 10 (suppl 1); i7-i13.
Centers for Disease Control and Prevention (CDC).2013. Progress toward elimination of onchocerciasis in the Americas - 1993-201. MMWR Morb Mortal Wkly Rep. 62, 405-408.
Cheke, R. A., Garms, R., Kerner, M. 1982. The fecundity of *Simulium damnosum* s.l. in northern Togo and Infections with *Onchocerca* spp. Ann. Trop. Med. Parasit. 76: 561-568.
Cheke, R.A., Garms, R. 1983. Reinfestations of the southeastern flank of the Onchocerciasis Control Programme area by windborne vectors. Phil. Trans. R. Soc. Lond. B 302, 471-484.
Cheke, R.A., Fiasorgbor, G.K., et al., 2008. Elimination of the Djodji form of the blackfly *Simulium sanctipauli* sensu stricto as a result of larviciding by the WHO Onchocerciasis Control Programme in West Africa. Med. Vet. Entomol. 22, 172-174.
Cheke, R.A., Garms, R. 2013. Indices of onchocerciasis transmission by different members of the *Simulium damnosum* complex conflict with the paradigm of forest and savanna parasite strains. Acta Trop. 125, 43-52.
Cheke, R.A., Basáñez, M.G., Perry, M., et al., 2015. Potential effects of warmer worms and vectors on onchocerciasis transmission in West Africa. Philos. Trans. R. Soc. Lond. B Biol .Sci. 370, 1665.

1195 Cheke, R.A. 2017. Factors affecting onchocerciasis control: lessons for infection control. Expert Review
1196 Anti-infective Therapy 15: 377 - 386. Review
1197 Cheke, R.A., Little, K.E., Young, S., et al., 2020. Taking the strain out of onchocerciasis? A reanalysis of
1198 blindness and transmission data does not support the existence of a savannah blinding strain of
1199 onchocerciasis in West Africa. Adv. Parasitol. (in review).
1200 Choi ,Y.J., Tyagi, R., McNulty, S.N., et al., 2016. Genomic diversity in *Onchocerca volvulus* and its
1201 *Wolbachia* endosymbiont. Nat. Microbiol. 2:16207.
1202 Colebunders, R., Nelson Siewe, F.J., Hotterbeekx, A. 2018. Onchocerciasis-associated epilepsy, an
1203 additional reason for strengthening onchocerciasis elimination programs. Trends Parasitol. 34, 208-
1204 216. Review.
1205 Comandatore, F., Cordaux, R., Bandi, C., et al., D. 2015. Supergroup C *Wolbachia*, mutualist symbionts of
1206 filarial nematodes, have a distinct genome structure. Open Biol. 5, 150099.
1207 Connor, D.H., Gibson, D.W,, Neafie, R.C., et al., 1983. Sowda - onchocerciasis in north Yemen: a
1208 clinicopathologic study of 18 patients. Am. J Trop. Me.d Hyg. 32, 123-37.
1209 Cotton, J.A., Bennuru, S., Grote, A., et al., 2016. The genome of *Onchocerca volvulus*, agent of river
1210 blindness. Nat. Microbiol. 2:16216.
1211 Crainey, J.L., Wilson, M.D., Post, R.J. 2010. Phylogenetically distinct *Wolbachia* gene and pseudogene
1212 sequences obtained from the African onchocerciasis vector *Simulium squamosum*. Int. J. Parasitol 40,
1213 569–578.
1214 Crainey, J.L., da Silva, T.R.R., Encinas, F., et al., 2016. The mitogenome of *Onchocerca volvulus* from the
1215 Brazilian Amazonia focus. Mem. Inst. Oswaldo Cruz. 111, 79-81.
1216 Crainey, J.L., Hurst, J., Lamberton, P.H.L., et al., 2017. The genomic architecture of novel *Simulium*
1217 *damnosum Wolbachia* prophage sequence elements and implications for onchocerciasis epidemiology.
1218 *Frontiers in Microbiology* 8: 852-869.
1219 Crisp, G. 1956. *Simulium* and onchocerciasis in the northern territories of the Gold Coast. London,
1220 H.K.Lewis and Co. Ltd., pp. 171.
1221 Crosskey, R.W.1990. The natural history of blackflies. John Wiley and Sons, Ltd, Chichester, UK, 711 pp.
1222 Crump A, Morel CM, Omura S., 2012. The onchocerciasis chronicle: from the beginning to the end? Trends
1223 Parasitol. 28, 280-288.
1224 Cupp, E.W., Sauerbrey, M., Richards, F. 2011. Elimination of human onchocerciasis: history of progress and
1225 current feasibility using ivermectin (Mectizan(®)) monotherapy. Acta Trop. 120 Suppl 1, S100-108.
1226 Dadzie, Y., Neira, M., Hopkins, D. 2003. Final report of the Conference on the eradicability of
1227 onchocerciasis. Filaria J. 2, 2.
1228 Dadzie, Y., Amazigo, U.V., Boatin, B.A., et al., 2018. Is onchocerciasis elimination in Africa feasible by
1229 2025: a perspective based on lessons learnt from the African control programmes. Infect. Dis.
1230 Poverty. 7, 63.
1231 Darge, K., Büttner, D.W. 1995. Ivermectin treatment of hyperreactive onchodermatitis (sowda) in Liberia.
1232 Trop Med Parasitol. 46, 206-212.
1233 Davies, J.B. 1994. Sixty years of onchocerciasis vector control: a chronological summary with comments on
1234 eradication, reinvasion, and insecticide resistance. Annu. Rev. Entomol. 39, 23-45.
1235 Demanou, M., Enyong, P., Pion, S.D.S., et al., 2003. Experimental studies on the transmission of *Onchocerca*
1236 *volvulus* by its vector in the Sanaga valley (Cameroon): *Simulium squamosum* B. Intake of microfilariae
1237 and their migration to the haemocoel of the vector. Ann. Trop. Med. Parasitol. , 97, 381–402.
1238 Denery, J.R., Nunes, A.A., Hixon, M.S., et al., 2010. Metabolomics-based discovery of diagnostic biomarkers
1239 for onchocerciasis. PLoS. Negl. Trop. Dis. 4, pii: e834.
1240 De Sole, G., Remme, J., Awadzi, K., et al., 1989. Adverse reactions after large-scale treatment of
1241 onchocerciasis with ivermectin: combined results from eight community trials. Bull. World Health
1242 Organ. 67, 707-719.
1243 De Sole, G., Baker, R., Dadzie, K. Y., et al., 1991. Onchocerciasis distribution and severity in five West
1244 African countries. Bull. World Health Organ. 69, 689-698.
1245 Diawara, L., Traore, M.O., Badji, A., et al., 2009. Feasibility of onchocerciasis elimination with ivermectin
1246 treatment in endemic foci in Africa: first evidence from studies in Mali and Senegal. PLoS Negl. Trop.
1247 Dis. 3, 497.
1248 Dissak-Delon, F.N., Kamga, G.R., Humblet, P.C., et al., 2019. Docommunities really "direct" in community-
1249 directed interventions? a qualitative assessment of beneficiaries' perceptions at 20 years of
1250 community directed treatment with ivermectin in Cameroon. Trop. Med. Infect. Dis. 4, 105.
1251 Ditgen, D., Anandarajah, E.M., Meissner, K.A., et al., 2014. Harnessing the helminthsecretome for
1252 therapeutic immunomodulators. Biomed. Res. Int. 964350. Review.

1253 Doetze, A., Satoguina, J., Burchard, G., et al., 2000. Antigen-specificcellular hyporesponsiveness in a chronic
1254 human helminth infection is mediated by T(h)3/T(r)1-type cytokines IL-10 and transforming growth
1255 factor-beta but not by a T(h)1 to T(h)2 shift. Int Immunol. 12, 623-630.
1256 Donelson, J.E., Duke, B.O.L., Moser, D., et al., 1988. Construction of *Onchocerca volvulus* cDNA libraries and
1257 partial characterization of the cDNA for a major antigen. Mol. Biochem. Parasitol. 31, 241-250.
1258 Druet-Cabanac, M., Preux, P.M., Bouteille, B., et al., 1999. Onchocerciasis and epilepsy: a matched case-
1259 control study in the Central African Republic. Am. J. Epidemiol. 149, 565-570.
1260 Duke, B.O.L, Lewis, D.J., Moore, P.J. 1966. *Onchocerca-Simulium* complexes. I. Transmission of forest and
1261 Sudan-savanna strains of *Onchocerca volvulus*, from Cameroon, by *Simulium damnosum* from various
1262 West African bioclimatic zones. Ann. Trop. Med. Parasitol. 60:318-326.
1263 Duke, B.O.L. 1967a. *Onchocerca-Simulium* complexes. IV. Transmission of a variant of the forest strain of
1264 *Onchocerca volvulus.* Ann. Trop. Med. Parasitol. 61, 326-331.
1265 Duke, B.O.L. 1967b. Infective filaria larvae other than *Onchocerca volvulus* in *Simulium damnosum.* Ann
1266 Trop. Med. Parasitol. 61, 700-705.
1267 Duke, B.O.L. 1970. *Onchocerca-Simulium* complexes. VI. Experimental studies on the transmission of
1268 Venezuelan and West African strains of *Onchocerca volvulus* by *Simulium metallicum* and *Simulium*
1269 *exiguum* in Venezuela. Ann. Trop. Med. Parasitol. 64, 421-431.
1270 Duke, B.O.L. 1972. Onchocerciasis. Br. Med. Bull. 28, 66-71. Review.
1271 Duke, B.O.L. 1980. Observations on *Onchocerca volvulus* in experimentally infected chimpanzees
1272 (*Pan troglotydes*). Tropenmed. Parasit. 31. 41-54.
1273 Duke, B.O.L. 1990. Human onchocerciasis--an overview of the disease. Acta Leiden. 59, 9-24. Review
1274 Duke, B.O.L. 1998. Onchocerciasis, epilepsy and hyposexual dwarfism. Trans. R. Soc. Trop. Med. Hyg. 92,
1275 236.
1276 Eberle, R., Brattig, N.W., Trusch, M., et al., 2015. Isolation, identification and functional profile of excretory-
1277 secretory peptides from *Onchocerca ochengi*. Acta Trop. 142, 156-166.
1278 Ehrens, A., Lunde, C.S., Jacobs, R.T., et al., 2020. *In vivo* efficacy of the boron-pleuromutilin an11251 against
1279 *Wolbachia* of the rodent filarial nematode *Litomosoides sigmodontis.* PLoS Negl. Trop. Dis. 14,
1280 e0007957.
1281 Eisenbarth, A., Achukwi, M.D., Renz, A. 2016. Ongoing transmission of *Onchocerca volvulus* after 25 years
1282 of annual ivermectin mass treatments in the Vina du Nord river valley, in North Cameroon. PLoS Negl.
1283 Trop. Dis. 10, e0004392.
1284 Erttmann, K.D., Unnasch, T.R., Greene, B.M., et al., 1987. A DNA sequence specific for forest form
1285 *Onchocerca volvulus.* Nature 327, 415–417.
1286 Fain, A., Wery, M., Tilkin, J. 1981. Transmission of *Onchocerca volvulus* by *Simulium albivirgulatum* in the
1287 endemic area for onchocercosis of the Central Basin, Zaire. Ann. Soc. Belg. Med. Trop. 61, 307-309.
1288 Figueroa Marroquin, H., Garcia Guillioli, C. 1971. Present status of Robles' disease in Guatemala. Rev.
1289 Invest. Salud Publica. 31, 17-25
1290 Figueroa Marroquin, H. 1975. Die Robles‘ Krankheit (Onchocerciasis americana) und ihre Bedeutung in
1291 Guatemala. In: VIII. Tagung der Deutschen Tropenmedizinischen Gesellschaft anlässlich des 75-
1292 jährigen Bestehens des Bernhard-Nocht-Instituts für Schiffs- und Tropenkrankheiten. Hamburg, 9.-
1293 11. Oktober 1975
1294 Fischer, P., Garms, R., Büttner, D.W., et al., 1997. Reduced prevalence of onchocerciasis in Uganda
1295 following either deforestation or vector control with DDT. East Afr. Med. J. 74, 321-325.
1296 Frempong, K.K., Walker, M., Cheke, R.A., et al., 2016. Does increasing treatment frequency address s
1297 uboptimal responses to ivermectin for the control and elimination of river blindness? Clin. Infect. Dis.
1298 62, 1338-1347.
1299 Frentzel-Beyme, R. 1973. The prevalence of onchocerciasis and blindness in the population of the Bong-
1300 Range, Liberia. Z. Tropenmed. Parasit. 24, 339-357.
1301 Frentzel-Beyme, R.R. 1975a. The geographical distribution of *Onchocerca volvulus* infection in Liberia.
1302 Tropenmed. Parasitol. 26, 70-87.
1303 Frentzel-Beyme, R.R. 1975b. Visual impairment and incidence of blindness in Liberia and their relation to
1304 onchocerciasis. Tropenmed. Parasitol.26: 469-488.
1305 Fülleborn, F. 1908. Ueber *Filaria volvulus Leuckart*. Arch. f. Schiffs- und Tropen-Hygiene, Beiheft 7 (Bd.
1306 XII.), 17 pp.
1307 Fülleborn, F. 1924. The ‘‘blinding filarial’’ of Guatemala (*Onchocerca caecutiens*, Brumpt 1919). In
1308 Proceedings of the International Conference on Health Problems in Tropical Countries, pp. 241–255.
1309 Gallin, M.Y., Jacobi, A.B., Büttner, D.W., et al., 1995. Human autoantibody to defensin: disease association
1310 with hyperreactive onchocerciasis (sowda). J. Exp. Med. 182, 41-47.
1311 Gardon, J., Gardon-Wendel, N., Demanga-Ngangue, et al., 1997. Serious reactions after mass treatment of
1312 onchocerciasis with ivermectin in an area endemic for *Loa loa* infection. Lancet 350, 18-22.

Garms, R., Post, A. 1966. Die Verbreitung von *Simulium damnosum* in Guinea/Westafrika. Z. Tropenmed. Parasitol. 17, 443-466.
Garms, R. 1972. Vorkommen phoretischer Simulien in Liberia. Z. Tropenmed. Parasitol. 23, 302-307.
Garms, R., Vajime, C.G. 1975a. On the ecology and distribution of the species of the *Simulium damnosum* complex in different bioclimatic zones of Liberia and Guinea. Tropenmed. Parasitol. 26, 375-380.
Garms, R. 1975b. Observations on filarial infections and parous rates of anthropophilic blackflies in in Guatemala, with reference to the transmission of *Onchocerca volvulus*. Tropenmed. Parasitol. 26, 169-182.
Garms, R. 1978. Use of morphological characters in the study of *Simulium damnosum* s.l. populations in West Africa. Tropenmed. Parasitol. 29, 483-491.
Garms, R., Ochoa J.O. 1979a. Further studies on the relative importance of Guatemalan blackfly species as vectors of *Onchocerca volvulus*. Tropenmed. Parasitol. 30, 120-128.
Garms, R., Walsh, J.F., Davies, J.B. 1979b. Studies on the reinvasion of the Onchocerciasis Control Programme in the Volta River Basin by *Simulium damnosum* s.l. with emphasis on the south-western areas. Tropenmed. Parasitol. 30, 345-362.
Garms, R., Cheke, R.A., Vajime, C.G., et al., 1982, The occurrence and movements of different members of the *Simulium damnosum* complex in Togo and Benin. Z. Angew. Zool., 69, 219-236.
Garms, R., Kerner, M. 1982. Anthropophily of *Simulium damnosum* s.l. and its rôle as a vector of human onchocerciasis in the Yemen Arab Republic. Tropenmed. Parasitol. 33, 175-180.
Garms, R., Cheke , R.A. 1985, Infections with *Onchocerca volvulus* in different members of the *Simulium damnosum* complex in Togo and Benin. Z. Angew. Zool. 72, 479-495.
Garms, R. 1987. Occurrence of the savanna species of the *Simulium damnosum* complex in Liberia. Trans. R. Soc. Trop. Med. Hyg. 81, 518.
Garms, R., Kerner M, Meredith, S.E.O. 1988. *Simulium* (*Edwardsellum*) *rasyani* n.sp., the Yemen species of the *Simulium damnosum* complex. Trop. Med. Parasitol. 39, 239-244.
Garms, R., Cheke, R.A., Sachs, R. 1991. A temporary focus of savanna species of the *Simulium damnosum* complex in the forest zone of Liberia. Trop. Med. Parasitol. 42, 181-187.
Garms, R, Yocha, J., Kipp, W. 1994. Decline of *Simulium neavei* and its associated crabs in the onchocerciasis foci of the Ruwenzori area, West Uganda, during the past 20 years. Brit. Simuliid Group Bull. 3, 11-12.
Garms, R., Lakwo, T.L., Ndyomugyenyi, R., et al., 2009. The elimination of the vector *Simulium neavei* from the Itwara onchocerciasis focus in Uganda by ground larviciding. Acta Trop 111, 203–210.
Garms, R., Badu, K.,Owusu-Dabo, E., et al., 2015. Assessments of the transmission of *Onchocerca volvulus* by *Simulium sanctipauli* in the Upper Denkyira District, Ghana, and the intermittent disappearance of the vector. Parasitol. Res 114, 1129–1137.
Garraud, O., Nkenfou, C., Bradley, J.E., et al., 1996. Differential regulation of antigen-specific IgG4 and IgE antibodies in response to recombinant filarial proteins. Int. Immunol. 8, 1841-1848.
Gasparini, G. 1962. "Sowda" a new disease or an unpublished type of onchocerciasis? Arch. Ital. Sci. Med. Trop. Parasitol. 43, 635-646.
Gebrezgabiher, G., Mekonnen, Z., Yewhalaw, D., et al., 2019.Reaching the last mile: main challenges relating to and recommendations to accelerate onchocerciasis elimination in Africa. Infect. Dis. Poverty. 8, 60. Review.
George, P.J., Hess, J.A., Jain, S., et al., 2019. Antibody responses against the vaccine antigens Ov-103 and Ov-ral-2 are associated with protective immunity to *Onchocerca volvulus* infection in both mice and humans. PLoS. Negl. Trop. Dis. 13, e0007730.
Globisch, D., Moreno, A.Y., Hixon, M.S., et al., 2013. *Onchocerca volvulus*-neurotransmitter tyramine is a biomarker for river blindness. Proc. Natl. Acad. Sci. U.S.A. 110, 4218-4223.
Gonzalez-Moa, M.J., Van Dorst, B., Lagatie, O., et al., 2018. Proof-of-Concept rapid diagnostic test for onchocerciasis: exploring peptide biomarkers and the use of gold nanoshells as reporter nanoparticles. ACS Infect. Dis. 4, 912-917.
Graham, S.P., Lustigman, S., Trees, A.J., et al., 2000. *Onchocerca volvulus:* Comparative analysis of antibody responses to recombinant antigens in two animal models of onchocerciasis. Exp. Parasitol. 94, 158-162.
Greene, B.M. 1987. Primate models for onchocerciasis research. Ciba Found Symp. 127, 236-243.
Güzelhan, C., Garms, R. 1991. Cytogenetic comparison of *Simulium soubrense* populations in Liberia (Simuliidae, Diptera). Z. angew. Zool. 78, 179-187.
Guillet, P., Escaffre, H., Ouedraogo, M., et al., 1980. Mise en évidence d'une résistance au téméphos dans le complexe *Simulium damnosum* [*S. sanctipauli* et *S. soubrense*] en Côte d'ivoire (Zone du programme de lutte contre l'onchocercose dans la région du Bassin de la Volta). Cahiers. O.R.S.T.O.M., sér. Ent. méd. et Parasitol. 18, 291-299.

1373 Hadis, M., Wilson, M.D., Cobblah, M., et al., 2005. Cytotaxonomic description of *Simulium kaffaense*, a new
1374 member of the *S. damnosum* complex (Diptera: Simuliidae) from south-western Ethiopia. Annals
1375 Trop. Med. Parasitol. 99, 267-291.
1376 Haffner, A., Guilavogui, A.Z., Tischendorf, F.W., et al., 1998. *Onchocerca volvulus*: microfilariae secrete
1377 elastinolytic and males nonelastinolytic matrix-degrading serine and metalloproteases. Exp. Parasitol.
1378 90, 26-33.
1379 Hall, L.R., Pearlman, E. 1999. Pathogenesis of onchocercal keratitis (river blindness). Clin. Microbiol. Rev.
1380 12, 445-453. Review
1381 Hassan, A., Shaban, N. 2020. Onchocerciasis dynamics: modelling the effects of treatment,education and
1382 vector control. J. Biol. Dyn. 14, 245-268.
1383 Hedtke, S.M., Kuesel, A.C., Crawford, K.E., et al., 2020. Genomic epidemiology in filarial nematodes:
1384 transforming the basis for elimination program decisions. Front Genet. 10, 1282. Review.
1385 Hendy, A., Sluydts, V., Tushar, T., et al., 2017. Esperanza Window Traps for the collection of
1386 anthropophilic blackflies (Diptera: Simuliidae) in Uganda and Tanzania. PLoS Negl Trop Dis 11(6):
1387 e0005688.
1388 Henkle-Dührsen K, Kampkötter A. 2001. Antioxidant enzyme families in parasitic nematodes. Mol
1389 Biochem Parasitol. 114, 129-142. Review
1390 Hernández-González, A., Moya, L., Perteguer, M.J., et al., 2016. Evaluation of onchocerciasis seroprevalence
1391 in Bioko Island (Equatorial Guinea) after years of disease control programmes. Parasit. Vectors 9, 509.
1392 Herrador, Z., Garcia, B., Ncogo, P., et al., 2018. Interruption of onchocerciasis transmission in Bioko
1393 Island: Accelerating the movement from control to elimination in Equatorial Guinea. PLoS Negl. Trop.
1394 Dis. 12, e0006471.
1395 Hertig, M., Wolbach, S.B. Studies on *Rickettsia*-like micro-organisms in Insects. 1924. J. Med. Res. 44, 329-
1396 374.
1397 Hewitson, J.P., Grainger, J.R., Maizels, R.M. 2009. Helminth immunoregulation: The role of parasite
1398 secreted proteins in modulating host immunity. Mol. Biochem. Parasitol. 167, 1-11.
1399 Higazi, T.B., Katholi, C.R., Mahmoud, B.M., et al., 2001. *Onchocerca volvulus*: genetic diversity of parasite
1400 isolates from Sudan. Exp. Parasitol. 97, 24-34.
1401 Higazi, T.B., Zarroug, I.M., Mohamed, H.A., et al., 2013. Interruption of *Onchocerca volvulus* transmission in
1402 the Abu Hamed focus, Sudan. Am. J. Trop. Med. Hyg. 89, 51-57.
1403 Hirai, H., Tada, I., Takahashi, H., et al., 1987. Chromosomes of *Onchocerca volvulus* (Spirurida:
1404 Onchocercidae): a comparative study between Nigeria and Guatemala. J. Helminthol. 61, 43-46.
1405 Hoerauf, A., Volkmann, L., Hamelmann, C., et al., 2000.Endosymbiotic bacteria in worms as targets for a
1406 novel chemotherapy in filariasis. Lancet 355, 1242–1243.
1407 Hoerauf, A., Mand, S., Adjei, O., et al., 2001. Depletion of *Wolbachia* endobacteria in *Onchocerca volvulus* by
1408 doxycycline and microfilaridermia after ivermectin treatment. Lancet 357, 1415-1416.
1409 Hoerauf, A., Kruse, S., Brattig, N.W., et al., 2002. The variant Arg110Gln of human IL-13 is associated with
1410 an immunologically hyper-reactive form of onchocerciasis (sowda). Microbes Infect. 4, 37-42.
1411 Hoerauf, A., Brattig, N. 2002. Resistance and susceptibility in human onchocerciasis - beyond Th1 vs. Th2.
1412 Trends Parasitol. 18, 25-31. Review
1413 Hoerauf, A., Büttner, D.W., Adjei, O., et al., 2003a. Onchocerciasis Brit. Med. J., 326, 207-210. Review.
1414 Hoerauf, A., Mand, S., Volkmann, L., et al., 2003b. Doxycycline in the treatment of human onchocerciasis:
1415 Kinetics of *Wolbachia* endobacteria reduction and of inhibition of embryogenesis in female
1416 *Onchocerca* worms. Microbes Infect. 5, 261-273.
1417 Hoerauf, A., Specht, S., Büttner, M., et al., 2008. *Wolbachia* endobacteria depletion by doxycycline as
1418 antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled
1419 study. Med. Microbiol. Immunol. 197, 295-311.
1420 Hoffmann, A.A., Montgomery, B.L., Popovici, J., I et al., 2011. Successful establishment of *Wolbachia* in
1421 *Aedes* populations to suppress dengue transmission. Nature 476, 454-459.
1422 Hong, W.D., Benayoud, F., Nixon, G.L., et al., 2019. AWZ1066S, a highly specific anti-*Wolbachia* drug
1423 candidate for a short-course treatment of filariasis. Proc. Natl. Acad. Sci. U.S.A. 116, 1414-1419.
1424 Hopkins, A.D. 2016. Neglected tropical diseases in Africa: a new paradigm. Int Health 8 (Suppl 1), i28–i33.
1425 Hotez, P.J., Alvarado, M., Basáñez, M.G., et al., 2014. The global burden of disease study 2010:
1426 interpretation and implications for the neglected tropical diseases. PLoS Negl. Trop. Dis. 8, e2865.
1427 Hotez, P.J., Bottazzi, M.E., Zhan, B., et al., 2015. The Onchocerciasis Vaccine for Africa--TOVA-Initiative.
1428 PLoS Negl. Trop. Dis. 9, e0003422.
1429 Hougard, J. M., Yaméogo, L., Sékétéli, A., et al., 1997. Twenty-two years of blackfly control in the
1430 onchocerciasis control programme in West Africa. Parasitol. Today 13, 425-431.

1431 Jacob, B.G., Loum, D., Lakwo, T.L., et al., 2018. Community directed vector control to supplement mass drug
1432 distribution for onchocercerciasis elimination in the Madi mid-North focus in Northern Uganda. PLOS
1433 Negl.Trop. Dis. 2018.
1434 Jaurigue, J.A., Seeberger, P.H. 2017. Parasite carbohydrate vaccines. Front. Cell. Infect. Microbiol. 7, 248.
1435 Johnson, T.P., Tyagi, R., Lee, P.R., et al., 2017. Nodding syndrome may be an autoimmune reaction to the
1436 parasitic worm *Onchocerca volvulus.* Sci. Transl. Med. 9, 377.
1437 Kahl, J., Brattig, N., Liebau, E. 2018. The untapped pharmacopeic potential of helminths. Trends Parasitol.
1438 34, 828-842. Review.
1439 Kamga, G.-R., Dissak-Delon, F.N., Nana-Djeunga, H.C., et al., 2016. Still mesoendemic onchocerciasis in two
1440 Cameroonian community-directed treatment with ivermectin projects despite more than 15 years of
1441 mass treatment. Parasit. Vectors 9, 581.
1442 Kamga, G.-R., Dissak-Delon, F.N., Nana-Djeunga, H.C., et al., 2017. Important progress towards elimination
1443 of onchocerciasis in the West Region of Cameroon. Parasit. Vectors, 10, 373.
1444 Kashan, A., Garms, R. 1987. Cytotaxonomy of the *Simulium sanctipauli* sub-complex in Liberia. Trop.
1445 Med. Parasit. 38, 289-293.
1446 Katabarwa, M.N., Eyamba, A., Nwane, P., et al., 2013. Fifteen years of annual mass treatment of
1447 onchocerciasis with ivermectin have not interrupted transmission in the West region of Cameroon. J.
1448 Parasitol. Res. 2013, 420928.
1449 Katabarwa, M., Lakwo, T., Habomugisha, P., et al., 2014a. Transmission of *Onchocerca volvulus* by *Simulium*
1450 *neavei* in Mount Elgon focus of eastern Uganda has been interrupted. Am. J. Trop. Med. Hyg. 90, 1159–
1451 1166.
1452 Katabarwa, M.N., Endeshaw, T., Taye, A., et al., 2014b. The disappearance of onchocerciasis without
1453 intervention in Tigray Region in northwest Ethiopia. Pathog. Glob. Health..108, 123.
1454 Katabarwa, M.N., Katamanywa, J., Lakwo, T., et al., 2016. The Imaramagambo onchocerciasis focus in
1455 southwestern Uganda: interruption of transmission after disappearance of the vector *Simulium neavei*
1456 and its associated freshwater crabs. Am. J. Trop. Med. Hyg. 95, 417- 425.
1457 Katabarwa, M.N., Lakwo, T., Habomugisha, P., et al., 2018. After 70 years of fighting an age-old scourge,
1458 onchocerciasis in Uganda, the end is in sight. Int. Health 10 (suppl 1), i79-i88.
1459 Katabarwa, M.N., Habomugisha, P., Khainza, A., et al., 2020a. Historical Elimination of Onchocerciasis from
1460 Victoria Nile focus in central Uganda verified using Who criteria. Am. J. Trop. Med. Hyg. 2020 Mar 30.
1461 Katabarwa, M.N., Zarroug, I.M.A., Negussu, N., et al., 2020b. The Galabat-Metema cross-border
1462 onchocerciasis focus: The first coordinated interruption of onchocerciasis transmission in Africa.
1463 PLoS Negl. Trop. Dis. 14, e0007830
1464 Katawa, G., Layland, L.E., Debrah, A.Y., et al., 2015. Hyperreactive onchocerciasis is characterized by a
1465 combination of Th17-Th2 immune responses and reduced regulatory T cells. PLoS Negl. Trop. Dis. 9,
1466 e3414.
1467 Kazura, J.W. 2016. Onchocerciasis elimination from Africa: One step in Northern Sudan. Am. J. Trop. Med.
1468 Hyg. 95, 983-984.
1469 Kim, Y.E., Remme, J.H., Steinmann, P., et al., 2015. Control, elimination, and eradication of river blindness:
1470 scenarios, timelines, and ivermectin treatment needs in Africa. PLoS Negl. Trop. Dis. 9, e0003664.
1471 Knight, A. 2008. The beginning of the end for chimpanzee experiments? Philos. Ethics Humanit. Med. 3, 16.
1472 Knüttgen, H-J. 1964. Untersuchungen über Vorkommen und Bedeutung der Onchozerkose in Guinea,
1473 Westafrika. Z. Tropenmed. Parasit. 15, 427-435.
1474 Knüttgen, H.J., Büttner, D.W. 1968. Untersuchungen zur Epidemiologie und Bedeutung der Onchozerkose
1475 in Oberguinea. Z. Trop. Med. Parasitol. 19, 1- 42.
1476 Knüttgen, H.J. 1971. Remarks on the epidemiology and importance of onchocerciasis in Upper Guinea.
1477 Ann. Soc. Belg. Med. Trop. 51, 611-614.
1478 Korten, S., Wildenburg, G., Darge, K., et al., 1998. Mast cells in onchocercomas from patients with
1479 hyperreactive onchocerciasis (sowda). Acta Trop. 70, 217-231.
1480 Korten, S., Badusche, M., Büttner, D.W., et al., 2008. Natural death of adult *Onchocerca volvulus* and
1481 filaricidal effects of doxycycline induce local FOXP3+/CD4+ regulatory T cells and granzyme
1482 expression. Microbes Infect. 10, 313-324.
1483 Korten, S., Hoerauf, A., Kaifi, J.T., et al., 2011. Low levels of transforming growth factor-beta (TGF- beta)
1484 and reduced suppression of Th2-mediated inflammation in hyperreactive human onchocerciasis.
1485 Parasitology 138, 35-45.
1486 Kozek, W.J., Figueroa-Marroquin, H.F. 1977. Intracytoplasmic bacteria in *Onchocerca volvulus*. Am. J. Trop.
1487 Med. Hyg. 26:663-678.
1488 Krüger, A., Nurmi, V., Yocha, J., et al., 1999. The *Simulium damnosum* complex in western Uganda and its
1489 role as a vector of *Onchocerca volvulus*. Trop. Med. Int. Health 4, 819-826.

1490 Kuesel, A.C. 2016. Research for new drugs for elimination of onchocerciasis in Africa. Int. J. Parasitol.
1491 Drugs. Drug Resist. 6, 272-286.
1492 Kurtak, D.C., Meyer, R., Ocran, M., et al., 1987. Management of insecticide resistance in control of the
1493 *Simulium damnosum* complex by the Onchocerciasis Control Programme, West Africa: potential use of
1494 negative correlation between organophosphate resistance and pyrethroid susceptibility. Med. Vet.
1495 Entomol. 1, 137–146.
1496 Kutin, K., Kruppa, T.F., Brenya, R., et al., 2004. Efficiency of *Simulium sanctipauli* as a vector of *Onchocerca*
1497 *volvulus* in the forest zone of Ghana. Med. Vet. Ent. 18, 167–173.
1498 Lagatie, O., Merino, M., Batsa Debrah, L., et al., 2016. An isothermal DNA amplification method for
1499 detection of *Onchocerca volvulus* infection in skin biopsies. Parasit. Vectors. 9, 624.
1500 Lagatie, O., Verheyen, A., Van Dorst, B., et al., 2018. Linear epitopes in *Onchocerca volvulus* vaccine
1501 candidate proteins and excretory-secretory proteins. Parasite Immunol. 40, e12587.
1502 Lagatie, O., Verheyen, A., Nijs, E., et al., 2019. Performance evaluation of three serodiagnostic peptide
1503 epitopes and the derived multi-epitope peptide OvNMP-48 for detection of *Onchocerca volvulus*
1504 infection. Parasitol. Res. 118, 2263-2270.
1505 Lakwo,T.L., Garms, R., Wamani, J., et al., 2017. Interruption of the transmission of *Onchocerca volvulus* in
1506 the Kashoya-Kitomi focus, western Uganda by long-term ivermectin treatment and elimination of
1507 he vector *Simulium neavei* by larviciding. Acta Trop. 167, 128-136.
1508 Lamberton, P.H.L., Cheke, R.A., Winskill, P., et al., 2015. Onchocerciasis transmission in Ghana: persistence
1509 under different control strategies and the role of the simuliid vectors. PLoS. Negl.Trop. Dis. 9(4),
1510 e0003688.
1511 Lefoulon, E., Giannelli, A., Makepeace, B.L., et al., 2017. Whence river blindness? The domestication of
1512 mammals and host-parasite co-evolution in the nematode genus *Onchocerca*. Int. J. Parasitol. 47, 457-
1513 470.
1514 Leuckart, R. 1893. *Filaria volvuloxus*. in Manson P., Sir Patrick, 1903: Diseases of the skin in tropical
1515 climates, in Davidson's Textbook of Hygiene and Diseases of warm climates. Tropical Diseases,
1516 LONDON, 628-995.
1517 Lewis, D.J., 1953. *Simulium damnosum* and its relation to onchocerciasis in the Anglo-Egyptian Sudan. Bull.
1518 Entomol. Res. 43, 597–564.
1519 Lewis, D.J., Duke, B.O.L., 1966. *Onchocerca-Simulium* complexes. II. Variation in West African female
1520 *Simulium damnosum*. Ann. Trop. Med. Parasit. 60, 337-346.
1521 Little, M.P., Basáñez, M.-G., Breitling, L.P., et al., 2004. Incidence of blindness during the Onchocerciasis
1522 Control Programme in western Africa, 1971-2002. J. Infect. Dis. 189, 1932-1941.
1523 Lloyd, M.M., Gilbert, R., Taha, N.T., et al., 2015. Conventional parasitology and DNA-based diagnostic
1524 methods for onchocerciasis elimination programmes. Acta Trop. 146, 114- 118.
1525 Lobos, E., Weiss, N., Karam, M., et al., 1991. An immunogenic *Onchocerca volvulus* antigen: a specific and
1526 early marker of infection. Science 251, 1603-1605.
1527 Lont, Y.L., Coffeng, L.E., de Vlas, S.J., et al., 2017. Modelling anti-Ov16 IgG4 antibody prevalence as an
1528 indicator for evaluation and decision making in onchocerciasis elimination programmes. PLoS. Negl.
1529 Trop. Dis. 11, e0005314.
1530 Lucius, R., Büttner, D.W., Kirsten, C., et al., 1986. A study on antigen recognition by onchocerciasis patients
1531 with different clinical forms of disease. Parasitology 92, 569-580
1532 Lucius, R., Schulz-Key, H., Büttner, D.W., et al., 1988. Characterization of an immunodominant *Onchocerca*
1533 *volvulus* antigen with patient sera and a monoclonal antibody. J. Exp. Med. 167, 1505-1510.
1534 Lugga, M.C.L., Chane, F., 2011. Onchocerciasis control in South Sudan. South Sudan Medical Journal 4: 61-
1535 62.
1536 Lustigman, S., James, E.R., Tawe, W., et al., 2002. Towards a recombinant antigen vaccine against
1537 *Onchocerca volvulus.* Trends Parasitol. 18, 135-141. Review.
1538 Lustigman, S., MacDonald, A.J., Abraham, D. 2003. CD4+-dependent immunity to *Onchocerca volvulus* third-
1539 stage larvae in humans and the mouse vaccination model: common ground and distinctions. Int. J.
1540 Parasitol. 33, 1161-1171. Review.
1541 Lustigman, S., Makepeace, B.L., Klei, T.R., et al., 2018. *Onchocerca volvulus*: the road from basic biology to a
1542 vaccine. Trends Parasitol. 2018 Jan;34(1):64-79.
1543 Macfarlane, C.L., Quek, S., Pionnier, N., et al., 2020. The insufficiency of circulating miRNA and DNA as
1544 diagnostic tools or as biomarkers of treatment efficacy for *Onchocerca volvulus.* Sci Rep. 10, 6672.
1545 Mackenzie, C.D., Williams, J.F., Sisley, B.M., et al., 1985. Variations in host responses and the pathogenesis
1546 of human onchocerciasis. Rev. Infect. Dis. 7, 802-808.
1547 Mahdy, M.A.K., Abdul-Ghani, R., Abdulrahman, T.A.A., et al., 2018. *Onchocerca volvulus* infection in the
1548 Tihama region – west of Yemen: continuing transmission in ivermectin-targeted endemic foci and
1549 unveiled endemicity in districts with previously unknown status. PLoS Negl. Trop. Dis. 12, e0006329.

1550 Maizels, R.M., Smits, H.H., McSorley, H.J., 2018. Modulation of host immunity by helminths: the expanding
1551 repertoire of parasite effector molecules. Immunity 49, 801-818.
1552 Makepeace, B.L., Tanya, V.N., 2016. 25 Years of the *Onchocerca ochengi* Model. Trends Parasitol. 32, 966-
1553 978. Review.
1554 Manchang, T.K., Ajonina-Ekoti, I., Ndjonka, D., et al., 2015. Immune recognition of *Onchocerca volvulus*
1555 proteins in the human host and animal models of onchocerciasis. J. Helminthol. 89, 375-386.
1556 Mazzotti, L., 1951. Observations on the use of hetrazan in onchocerciasis in Mexico. Am. J. Trop. Med. Hyg.
1557 31, 628-632.
1558 McCrae, A.W.R. 1978. Intermittent eradication of *Simulium damnosum* Theo. on the Nile from Jinja,
1559 Uganda: 1951-1977. Med. Entom. Centenary Symposium Proceedings, 1978, 133-134.
1560 McMahon, J.P., Highton, R.B., Goiny, H. 1958. The eradication of *Simulium neavei* from Kenya. Bull. World
1561 Health Org. 19, 75-107.
1562 McNulty, S.N., Foster, J.M., Mitreva, M., et al., 2010. Endosymbiont DNA in endobacteria-free filarial
1563 nematodes indicates ancient horizontal genetic transfer. PLoS One. 5, e11029.
1564 McNulty, S.N., Rosa, B.A., Fischer, P.U., et al., 2015. An integrated multiomics approach to identify
1565 candidate antigens for serodiagnosis of human onchocerciasis. Mol. Cell Proteomics. 14, 3224-3233.
1566 Medina-De la Garza, C.E., Brattig, N.W., Tischendorf, F.W., et al., 1990. Serum-dependent interaction of
1567 granulocytes with *Onchocerca volvulus* microfilariae in generalized and chronic hyper-reactive
1568 onchocerciasis and its modulation by diethylcarbamazine. Trans. R. Soc. Trop. Med. Hyg. 84, 701-706.
1569 Meredith, S.E.O., Cheke, R.A., Garms, R., 1983. Variation and distribution of forms of *Simulium soubrense*
1570 and *S. sanctipauli* in West Africa. Ann. Trop. Med. Parasitol. 77, 627-640.
1571 Meyer, C.G., Gallin, M., Erttmann, K.D., et al., 1994. HLA-D alleles associated with generalized disease,
1572 localized disease, and putative immunity in *Onchocerca volvulus* infection. Proc. Natl. Acad. Sci. U S A.
1573 91, 7515-7519.
1574 Michael, E., Smith, M.E., Singh, B.K., et al., 2020. Data-driven modelling and spatial complexity supports
1575 heterogeneity-based integrative management for eliminating *Simulium neavei*-transmitted river
1576 blindness. Sci. Rep. 10, 4235.
1577 Monahan, C.M., Chapman, M.R., French, D.D., et al., 1995. Efficacy of moxidectin oral gel against *Onchocerca*
1578 *cervicalis* microfilariae. J. Parasitol. 81, 117-118.
1579 Morales-Hojas, R., Cheke, R.A., Post, R.J. 2006. Molecular systematics of five *Onchocerca* species
1580 (Nematoda: Filarioidea) including the human parasite, *O. volvulus*, suggest sympatric speciation. J.
1581 Helminthol. 80, 281-290.
1582 Morales-Hojas, R., Cheke, R.A., Post, R.J. 2007. A preliminary analysis of the population genetics and
1583 molecular phylogenetics of *Onchocerca volvulus* (Nematoda: Filarioidea) using nuclear ribosomal
1584 second internal transcribed spacer sequences. Mem. Inst. Oswaldo Cruz, Rio de Janeiro, 102, 879-882.
1585 Moya, L., Herrador, Z., Ta-Tang, T.H., et al., 2016. Evidence for suppression of onchocerciasis transmission
1586 in Bioko Island, Equatorial Guinea. Plos. Negl Trop Dis. 2016;10:e0004829.
1587 Mpagi, J.L., Büttner, D.W., Tischendorf, F.W., et al., 2000. Use of the recombinant *Onchocerca volvulus*
1588 protein Ov20/OvS1 for the immunodiagnostic differentiation between onchocerciasis and
1589 mansonelliasis and for the characterization of hyperreactive onchocerciasis (sowda). Trop. Med. Int.
1590 Health 5, 891-897.
1591 Navarro, M., Camprubí, D., Requena-Méndez, A., et al., 2020. Safety of high-dose ivermectin: a systematic
1592 review and meta-analysis. J. Antimicrob. Chemother. 75, 827-834.
1593 Ndyomugyenyi, R. 1998. The burden of onchocerciasis in Uganda. Ann. Trop. Med. Parasit. 92 (Suppl. 1),
1594 133-137.
1595 Neumann, E., Lucasse, C., Gunders, A. 1964. Experimental onchocercal ocular lesions in the chimpanzee.
1596 Am. J. Ophthalmol. 57, 217-227.
1597 Njume, F.N., Ghogomu, S.M., Shey, R.A., et al., 2019. Identification and characterization of the *Onchocerca*
1598 *volvulus* excretory secretory product Ov28CRP, a putative GM2 activator protein. PLoS Negl Trop Dis.
1599 13, e0007591.
1600 NTD Modelling Consortium Onchocerciasis Group. 2019. The World Health Organization 2030 goals for
1601 onchocerciasis: Insights and perspectives from mathematical modelling: NTD Modelling Consortium
1602 Onchocerciasis Group. Gates Open Res. 3, 1545.
1603 Nutman, T.B., Steel, C., Ward, D.J., et al., 1991. Immunity to onchocerciasis: recognition of larval antigens by
1604 humans putatively immune to *Onchocerca volvulus* infection. J. Infect. Dis. 163, 1128-1133.
1605 O'Day, J., Mackenzie, C.D. 1985. Ocular onchocerciasis. Diagnosis and current clinical approaches. Trop
1606 Doct. 15, 87-94. Review.
1607 O'Hanlon, S.J., Slater, H.C., Cheke, R.A., et al., 2016. Model-based geostatistical mapping of the prevalence of
1608 *Onchocerca volvulus* in West Africa. *PLoS Neglected Tropical Diseases* 10: e0004328.

Omar, M.S., Garms, R. 1975. The fate and migration of microfilariae of a Guatemalan strain of *Onchocerca volvulus* in *Simulium ochraceum* and *S. metallicum*, and the role of the buccopharyngeal armature in the destruction of microfilariae. Tropenmed. Parasitol. 26, 183-190.
Omar, M.S., Garms, R.,1977. Lethal damage to *Simulium metallicum* following high intakes of *Onchocerca volvulus* microfilariae in Guatemala. Tropenmed. Parasitol. 28, 109-119.
Omar, M.S., Franz, M., Büttner, D.W., 1979. Some observations on onchocerciasis including sowda in the Yemen Arab Republic. Tropenmed Parasitol. 30, 113-119.
Ōmura, S. 2016. Splendid gift from the Earth: the origins and impact of the Avermectins (Nobel Lecture). Angew. Chem. Int. Ed. Engl. 55, 10190-10209. Review.
O'Neill, J., 1875. On the presence of a filaria in "Craw craw". Lancet 1, 265-266.
Opoku, N.O., Bakajika, D.K., Kanza, E.M., et al., 2018. Single dose moxidectin versus ivermectin for *Onchocerca volvulus* infection in Ghana, Liberia, and the Democratic Republic of the Congo: a randomised, controlled, double-blind phase 3 trial. Lancet 392, 1207-1216.
Osei-Atweneboana, M.Y., Eng, J.K.L., Boakye, D.A., et al., 2007. Prevalence and intensity of *Onchocerca volvulus* infection and efficacy of ivermectin in endemic communities in Ghana: a two-phase epidemiological study. Lancet 369, 2021-2029.
Osei-Atweneboana, M.Y., Awadzi, K., Attah, S.K., et al., 2011. Phenotypic evidence of emerging ivermectin resistance in *Onchocerca volvulus.* PLoS Negl Trop Dis 5, e998.
Ottesen, E.A., 1995. Immune responsiveness and the pathogenesis of human onchocerciasis. J. Infect Dis. 171, 659-671. Review.
Painter, T.S., Griffen, A.B., 1937. The structure and the development of the salivary gland chromosomes of *Simulium*. Genetics 22, 612-633.
Parsons, A.C., 1908. *Filaria volvulus Leuckart*, its distribution, structure and pathological effects. Parasitology 1, 359-368.
Pearlman, E., 1997. Immunopathology of onchocerciasis: a role for eosinophils in onchocercal dermatitis and keratitis. Chem. Immunol. 66, 6-40. Review.
Pearlman, E., Gillette-Ferguson, I. 2007. *Onchocerca volvulus, Wolbachia* and river blindness. Chem. Immunol. Allergy 92, 254-265. Review.
Philippon, B., Remme, J.H., Walsh, J.F., et al., 1990. Entomological results of vector control in the Onchocerciasis Control Programme. Acta Leiden. 59, 79-94.
Picq, J.J., Coz, J., Jardel, J.P. 1971. A method of evaluating the density of the microfilaria of *Onchocerca volvulus* Leuckart, 1893 in patients with onchocerciasis: technic and reading time of skin biopsies. Bull. World Health Organ. 45, 517-520.
Plaisier, A.P., Van Oortmarssen, G.J., Habbema, J.D.F., et al. 1990. ONCHOSIM: a model and computer simulation program for the transmission and control of onchocerciasis. Comput. Methods Programs Biomed. 31, 43–56.
Plier, D.A., Awadzi, K., Freedman, D.O. 1995. Immunoregulation in onchocerciasis: persons with ocular inflammatory disease produce a Th2-like response to *Onchocerca volvulus* antigen. J. Infect. Dis. 174, 380-386.
Post, R.J. ,1986. The cytotaxonomy of *Simulium sanctipauli* and *Simulium soubrense* (Diptera: Simuliidae). *Genetica* 69, 191-207.
Post, R.J., McCall, P.J., Trees, A.J., et al., 1989. Chromosomes of six species of *Onchocerca* (Nematoda: Filarioidea). Trop. Med. Parasitol. 40, 292-294.
Post, R.J., Cheke, R.A., Boakye, D.A., et al., 2013. Stability and change in the distribution of cytospecies of the *Simulium damnosum* complex (Diptera: Simuliidae) in southern Ghana from 1971 to 2011. Parasites and Vectors 6, 205.
Prince, A.M., Brotman, B., Johnson, E.H. Jr., et al., 1992. *Onchocerca volvulus*: immunization of chimpanzees with X-irradiated third-stage (L3) larvae. Exp. Parasitol. 74: 239-250.
Puente, S., Ramirez-Olivencia, G., Lago, M., et al., 2018. Dermatological manifestations in onchocerciasis: a retrospective study of 400 imported cases. Enferm. Infecc. Microbiol. Clin. 36, 633-639.
Quintana, J.F., Makepeace, B.L., Babayan, S.A., et al., 2015. Extracellular *Onchocerca*-derived small RNAs in host nodules and blood. Parasit. Vectors. 8, 58.
Railliet, A., Henry, A.C., 1910. Remarques a` l'occasion de la note de. M. le Dr. Antoine. Bull. Soc. Pathol. Exot. Filiales 3, 91–93.
Rebollo, M.P., Zoure, H., Ogoussan, K., et al., 2018. Onchocerciasis: shifting the target from control to elimination requires a new first-step-elimination mapping. Int. Health. 10 (suppl_1), i14-i19.
Remme, J., Baker, R.H.A., De Sole, G., et al., 1989. A community trial of ivermectin in the onchocerciasis focus of Asubende, Ghana. I. Effect on the microfilarial reservoir and transmission of *Onchocerca volvulus*. Trop. Med. Parasit. 40, 367-374.

Renz, A., 1987. Studies on the dynamics of transmission of onchocerciasis in a Sudan-savanna area of north Cameroon. III. Infection rates of the *Simulium* vectors and *Onchocerca volvulus* transmission potentials. Ann. Trop. Med. Parasitol. 81, 239-252.

Renz, A., Wenk, P., 1987. Studies on the dynamics of transmission of onchocerciasis in a Sudan savanna area of North Cameroon. I. Prevailing *Simulium* vectors, their biting rates and age-composition at different distances from their breeding sites. Ann. Trop. Med. Parasitol. 81, 215-228.

Richard-Lenoble, D., al Qubati, Y., Toe, L., et al., 2001. Human onchocerciasis and "sowda" in the Republic of Yemen. Bull. Acad. Natl. Med. 185, 1447-1459.

Richards, F.O., Eigege, A., Umaru, J., et al., 2020. The interruption of transmission of human onchocerciasis by an annual mass drug administration program in plateau and Nasarawa States, Nigeria. Am. J. Trop. Med. Hyg. 102, 582-592.

Robles, R., 1917. Enfermedad nueva en Guatemala. La Juventud Médica 17, 97–115.

Rodríguez-Pérez, M.A., Adeleke, M.A., Burkett-Cadena, N.D., et al., 2013. Development of a novel trap for the collection of black flies of the *Simulium ochraceum* complex. PLOS One. 2013;8(10):e76814. Epub 2013/10/12. pmid:24116169;

Rodríguez-Pérez, M.A., Fernández-Santos, N.A., Orozco-Algarra, M.E., et al., 2015. Elimination of onchocerciasis from Mexico. PLoS Negl Trop Dis. 9, e0003922.

Rolland, A., Prost, A., Thylefors, B., 1980. Review, after 3 years of the treatment with suramin, of a village suffering from onchocerciasis under entomological protection. Rev. Int. Trach. Pathol. Ocul. Trop. Subtrop. 57, 99-106.

Routledge, I., Walker, M., Cheke, R.A., et al., 2018. Modelling the impact of larviciding on the population dynamics and biting rates of *Simulium damnosum* (*s.l.*): implications for vector control as a complementary strategy for onchocerciasis elimination in Africa. *Parasites and Vectors* 11: 316.

Rubio de Krömer, M.T., Medina-De la Garza, C.E., Brattig, N.W., 1995. Differences in eosinophil and neutrophil chemotactic responses in sowda and generalized form of onchocerciasis. Acta Trop. 60, 21-33.

Ruiz Reyes, F. 1951. Treatment of onchocerciasis with diethylcarbamazine. Rev. Asoc. Medica. Mex. 31, 495-504.

Saint André A.v., Blackwell, N.M., Hall, L.R., et al., 2002. The role of endosymbiotic *Wolbachia* bacteria in the pathogenesis of river blindness. Science 295, 1892-1895.

Samba, E.M., 1994 The onchocerciasis control programme in West Africa. An example of effective public health management, WHO 1994 (1994, Public Health in Action 1), Geneva.

Sauerbrey, M., Rakers, L.J., Richards, F.O., 2018. Progress toward elimination of onchocerciasis in the Americas. Int. Health. 10(suppl_1), i71-i78.

Schönemeyer, A., Lucius, R., Sonnenburg, B., et al., 2001. Modulation of human T cell responses and macrophage functions by onchocystatin, a secreted protein of the filarial nematode *Onchocerca volvulus.* J. Immunol. 167, 3207-3215.

Schulz-Key, H., Karam, M. 1986. Periodic reproduction of *Onchocerca volvulus*. Parasitol Today. 2, 284-286.

Seeber, F., Brattig, N., Soboslay, P.T., et al., 1993. Characterization of a recombinant T cell and B cell reactive polypeptide of *Onchocerca volvulus*. J Immunol. 150, 2931-294.

Shelley AJ, Hernández LM, Maia-Herzog M, et al. 2010.The blackflies (Diptera: Simuliidae) of Brazil. In: Arias JR, Golovatch S, Wantzen KM, et al., editors, Aquatic Biodiversity in Latin America (ABLA). Vol.6. Sofia-Moscow: Pensoft; 821 pp.

Shey, R.A., Ghogomu, S.M., Esoh, K.K., et al., 2019. In-silico design of a multi-epitope vaccine candidate against onchocerciasis and related filarial diseases. Sci Rep. 9, 4409

Siddiqui, M.A., al-Khawajah, M.M. 1991. The black disease of Arabia, Sowda-onchocerciasis. New findings. Int. J. Dermatol. 30, 130-133

Sironi, M., Bandi, C., Sacchi, L., et al., 1995. Molecular evidence for a close relative of the arthropod endosymbiont *Wolbachia* in a filarial worm. Mol. Biochem. Parasitol. 74:223–227.

Slatko, B.E., O'Neill, S.L., Scott, A.L., et al., 1999. The *Wolbachia* Genome Consortium. Microb. Comp. Genomics 4, 161-165.

Slatko, B.E., Taylor, M., Foster, J.M. 2010. The *Wolbachia* endosymbiont as an anti-filarial nematode target. Symbiosis 51, 55–65.

Smith, M.E., Bilal, S., Lakwo, T.L., et al., 2019. Accelerating river blindness elimination by supplementing MDA with a vegetation "slash and clear" vector control strategy: a data-driven modeling analysis. Sci Rep. 2019 Oct 24;9(1):15274.

Soboslay, P.T., Dreweck, C.M., Taylor, H.R., et al., 1991. Experimental onchocerciasis in chimpanzees. Cell-mediated immune responses, and production and effects of IL-1 and IL-2 with *Onchocerca volvulus* infection. J. Immunol. 147:346-53.

1727 Soboslay, P.T., Lüder, C.G., Riesch, S., et al., 1999. Regulatory effects of Th1-type (IFN-gamma, IL-12) and
1728 Th2-type cytokines (IL-10, IL-13) on parasite-specific cellular responsiveness in *Onchocerca volvulus*-
1729 infected humans and exposed endemic controls. Immunology 97, 219-225.
1730 Steel, C., Golden, A., Stevens, E., et al., 2015. Rapid point-of-contact tool for mapping and integrated
1731 surveillance of *Wuchereria bancrofti* and *Onchocerca volvulus* infection. Clin. Vaccine Immunol. 22,
1732 896-901.
1733 Steisslinger, V., Korten, S., Brattig, N.W., et al., 2015. DNA vaccine encoding the moonlighting protein
1734 *Onchocerca volvulus* glyceraldehyde-3-phosphate dehydrogenase (Ov-GAPDH) leads to partial
1735 protection in a mouse model of human filariasis. Vaccine 33, 5861-5867.
1736 Strote, G., Brattig, N.W., Tischendorf, F.W., 1990. Ultrastructural study of the interaction between
1737 eosinophilic granulocytes and third and fourth stage larvae of *Onchocerca volvulus*. Acta Trop. 48, 1-8.
1738 Ta, T.-H., Moya, L., Nguema, J., et al., 2018. Geographical distribution and species identification of human
1739 filariasis and onchocerciasis in Bioko Island, Equatorial Guinea. Acta Tropica 180, 12–17.
1740 Takaoka, H., 2015. Review of the biology and ecology of adult blackflies in relation to the transmission of
1741 onchocerciasis in Guatemala. Trop. Med. Health. 43 (Suppl), 71-85.
1742 Tamarozzi, F., Turner, J.D., Pionnier, N., et al., 2016. *Wolbachia* endosymbionts induce neutrophil
1743 extracellular trap formation in human onchocerciasis. Sci. Rep. 6, 35559.
1744 Taylor, C.M., Wang, Q., Rosa, B.A., et al., 2013. Discovery of anthelmintic drug targets and drugs using
1745 chokepoints in nematode metabolic pathways. PLoS. Pathog. 9, e1003505.
1746 Taylor, H.R., Trpis, M., Cupp, E.W., et al., 1988. Ivermectin prophylaxis against experimental *Onchocerca*
1747 *volvulus* infection in chimpanzees. Am. J. Trop. Med. Hyg. 39, 86-90.
1748 Taylor, M.J., Hoerauf, A. 1999. *Wolbachia* bacteria of filarial nematodes. Parasitol. Today 15: 437-442.
1749 Review.
1750 Taylor, M.J., Hoerauf, A., 2001. A new approach to the treatment of filariasis. Curr. Opin. Infect. Dis. 14,
1751 727-731. Review.
1752 Taylor, M.J., Awadzi, K., Basáñez, M.-G., et al., 2009. Onchocerciasis control: vision for the future from a
1753 Ghanaian perspective. Parasit. Vectors. 2, 7.
1754 Taylor, M.J., Hoerauf, A., Bockarie, M. 2010. Lymphatic filariasis and onchocerciasis. Lancet 376, 1175-
1755 1185. Review.
1756 Taylor, M.J., Hoerauf, A., Townson, S., et al., 2014. Anti-*Wolbachia* drug discovery and development: safe
1757 macrofilaricides for onchocerciasis and lymphatic filariasis. Parasitology 141, 119-127. Review.
1758 Taylor, M.J., von Geldern, T.W., Ford, L., et al., 2019. Preclinical development of an oral anti-*Wolbachia*
1759 macrolide drug for the treatment of lymphatic filariasis and onchocerciasis. Sci. Transl. Med. 11, 483.
1760 Tekle, A.H., Elhassan, E., Isiyaku, S., et al., 2012. Impact of long-term treatment of onchocerciasis with
1761 ivermectin in Kaduna State, Nigeria: first evidence of the potential for elimination in the operational
1762 area of the African Programme for Onchocerciasis Control. Parasit. Vectors. 5, 28.
1763 Tekle, A.H., Zouré, H.G., Noma, M., et al., 2016. Progress towards onchocerciasis elimination in the
1764 participating countries of the African Programme for Onchocerciasis Control: epidemiological
1765 evaluation results. Infect. Dis. Poverty 5, 66.
1766 Timmann, C., Abraha, R.S., Hamelmann, C., et al., 2003. Cutaneous pathology in onchocerciasis associated
1767 with pronounced systemic T-helper 2-type responses to *Onchocerca volvulus*. Br. J. Dermatol. 149,
1768 782-787.
1769 Timmann, C., van der Kamp, E., Kleensang, A., et al., 2008. Human genetic resistance to *Onchocerca*
1770 *volvulus*: evidence for linkage to chromosome 2p from an autosome-wide scan. J. Infect. Dis. 198, 427-
1771 433.
1772 Tischendorf, F.W., Brattig, N.W., 1992. Cationic lysosomal proteins and reactive oxygen metabolites of
1773 eosinophilic effector cells in generalized and localized onchocerciasis. Trop. Med. Parasit. 43, 208-209.
1774 Titanji, V.P., Nde, P.N., Ghogoinu, S.M., et al., 1996. The roles of IgG and defined antigensin cytoadherence
1775 and cytotoxicity reactions to onchocercal microfilariae. Afr. J. Health Sci. 3, 33-36.
1776 Toé, L.D., Koala, L., Burkett-Cadena, N.D., et al., 2014. Optimization of the Esperanza window trap for the
1777 collection of the African onchocerciasis vector *Simulium damnosum sensu lato*. Acta Tropica 137, 39–
1778 3. Epub 2014/05/06. pmid:24794201.
1779 Traore, M.O., Sarr, M.D., Badji, A., et al., 2012. Proof-of-principle of onchocerciasis elimination with
1780 ivermectin treatment in endemic foci in Africa: final results of a study in Mali and Senegal. PLoS. Negl.
1781 Trop. Dis. 6, e1825.
1782 Traoré, S., Wilson, M.D., Sima, A., et al., 2009. The elimination of the onchocerciasis vector from the island
1783 of Bioko as a result of larviciding by the WHO African Programme for Onchocerciasis Control. Acta
1784 Trop. 111, 211-218.
1785 Trees, A.J., Graham, S.P., Renz, A., et al., 2000. *Onchocerca ochengi* infections in cattle as a model for human
1786 onchocerciasis: recent developments. Parasitology 120 Suppl:S 133-142. Review.

1787 Trpis, M., Wergin. W.P., Murphy, C.A., 2006. Development of *Onchocerca volvulus* (Filarioidea:
1788 Onchocercidae) in the West African black fly *Simulium yahense* (Diptera: Simuliidae) in Liberia. J.
1789 Parasitol. 87: 1265-1272.
1790 Turaga, P.S., Tierney, T.J., Bennett, K.E., et al., 2000. Immunity to onchocerciasis: cells from putatively
1791 immune individuals produce enhanced levels of interleukin-5, gamma interferon, and granulocyte-
1792 macrophage colony-stimulating factor in response to *Onchocerca volvulus* larval and male worm
1793 antigens. Infect. Immun. 68, 1905-1911.
1794 Unnasch, T.R., Golden, A., Cama, V., et al., 2018. Diagnostics for onchocerciasis in the era of elimination. Int.
1795 Health. 10, Suppl. 1, i20-i26.
1796 Unnasch, T.R., Williams, S.A. 2000. The genomes of *Onchocerca volvulus*. Int. J. Parasitol. 30, 543-552.
1797 Review.
1798 Vajime, C.G., Dunbar, R.W., 1975. Chromosomal identification of eight species of the subgenus
1799 *Edwardsellum* near and including *Simulium* (Edwardsellum) *damnosum* Theobald (Diptera:
1800 Simuliidae). Tropenmed. Parasitol. 26, 111-138.
1801 Van Den Berghe, L., Chardome, M., Peel, E., 1964. The filarial parasite of the eastern gorilla in the Congo.
1802 J. Helminth. 38, 349-368.
1803 Van Someren, V.D., McMahon, J., 1950. Phoretic association between *Afronurus* and *Simulium* species, and
1804 the discovery of the early stages of *Simulium neavei* on freshwater crabs. Nature 166, 350-351.
1805 Van Voorhis, W.C., Hooft van Huijsduijnen, R., Wells, T.N.C. 2015. Profile of William C. Campbell, Satoshi
1806 Ōmura, and Youyou Tu, 2015 Nobel Laureates in Physiology or Medicine. Proc. Natl. Acad. Sci. U S A.
1807 112, 15773-15776.
1808 Verver, S., Walker, M., Kim, Y.E., et al., 2018. How can onchocerciasis elimination in Africa be accelerated?
1809 Modeling the impact of increased ivermectin treatment frequency and complementary vector control.
1810 Clin. Infect. Dis. 66 (suppl_4) S267-S274.
1811 Vinkeles Melchers, N.V.S., Coffeng, L.E., Boussinesq, M., et al., 2020. Projected number of people with
1812 onchocerciasis-loiasis Coinfection in Africa, 1995 to 2025. Clin. Infect. Dis. 70, 2281-2289.
1813 Vlaminck, J., Fischer, P.U., Weil, G.J., 2015. Diagnostic tools for onchocerciasis elimination programs.
1814 Trends Parasitol. 31, 571-582.
1815 Von Geldern, T.W., Morton, H.E., Clark, R.F., et al., 2019. Discovery of ABBV-4083, a novel analog of Tylosin
1816 A that has potent anti-*Wolbachia* and anti-filarial activity. PLoS. Negl. Trop. Dis. 13, e0007159.
1817 Waddy, B.B., 1969. Prospects for the control of onchocerciasis in Africa with special reference to the Volta
1818 River Basin. Bull. WHO 40, 843-858.
1819 Wahl, G., Enyong, P., Ngosso, A., et al., 1998. *Onchocerca ochengi*: epidemiological evidence of cross-
1820 protection against *Onchocerca volvulus* in man. Parasitology 116, 349-362.
1821 Walker, M., Specht, S., Churcher, T.S., et al., 2015. Therapeutic efficacy and macrofilaricidal activity of
1822 doxycycline for the treatment of river blindness. Clin. Infect. Dis 60, 1199– 1207.
1823 Walker, M., Stolk, W.A., Dixon, M.A., et al., 2017. Modelling the elimination of river blindness using long-
1824 term epidemiological and programmatic data from Mali and Senegal. Epidemics 18, 4-15.
1825 Walsh, J.F., Davies, J.B., Le Berre, R., et al., 1978. Standardization of criteria for assessing the effect of
1826 *Simulium* control in onchocerciasis control programmes. Trans. Roy. Soc. Trop. Med. Hyg., 72, 675-
1827 676.
1828 Walsh, J.F., Davies, J.B., Le Berre, R., 1979. Entomological aspects of the first five years of the
1829 Onchocerciasis Control Programme in the Volta River Basin. Tropenmed. Parasit. 30, 328-344.
1830 Walsh, J.F., 1990. Review of vector control prior to the OCP. Acta Leidensia 59, 61-78.
1831 Wanji, S., Kengne-Ouafo, J.A., Esum, M.E., et al., 2015a. Situation analysis of parasitological and
1832 entomological indices of onchocerciasis transmission in three drainage basins of the rain forest of
1833 South West Cameroon after a decade of ivermectin treatment. Parasit. Vectors, 8, 202.
1834 Wanji, S., Kengne-Ouafo, J.A., Esum, M.E., et al., 2015b. Relationship between oral declaration on adherence
1835 to ivermectin treatment and parasitological indicators of onchocerciasis in an area of persistent
1836 transmission despite a decade of mass drug administration in Cameroon. Parasit. Vectors 8, 667.
1837 Wegesa, P., 1970. *Simulium nyasalandicum* (Amani form) and *S. adersi*, two new potential vectors of
1838 *Onchocerca volvulus* in the Eastern Usambaras, North Eastern Tanzania, E. Afr. Med. J. 47, 364-367.
1839 Weil, G.J., Steel, C., Liftis, F., et al., 2000. A rapid-format antibody card test for diagnosis of onchocerciasis.
1840 J. Infect. Dis. 183, 1796-1799.
1841 Weller, P.F., Spencer, L.A., 2017. Functions of tissue-resident eosinophils. Nat. Rev. Immunol. 17, 746-760.
1842 White, G.B., 1977. Man-biting species of *Chrysops* Meigen, *Culicoides* Latreille and *Simulium* Latreille in
1843 Ethiopia, with discussion of their vector potentialities. Trans. Roy. Soc. Trop. Med. Hyg. 71, 161-175.
1844 WHO/ONCHO/69.75 Joint US-AID/OCCGE/WHO Technical Meeting on the Feasibility of onchocerciasis
1845 control. Tunis, 1-8 July 1968, Report.
1846 WHO/OCP/73.1., 1973. Onchocerciasis control in the Volta River basin area. Report of the Preparatory Assistance

ission to the Governements of Dahomey, Ghana, Ivory Coast, Mali, Niger, Togo, Upper Volta, and Annexes, PAG Report Geneva 1973. https://apps.who.int/iris/handle/10665/326101.
WHO, 1995. Onchocerciasis and its control, report of a WHO Expert Committee on Onchocerciasis Control. Geneva: World Health Organization; Technical Report Series No.: 852. https://apps.who.int/iris/handle/10665/37346.
WHO, 2002. Success in Africa: the Onchocerciasis Control Programme in West Africa, 1974-2002. WHO, Geneva.
WHO, 2017. Progress report on the elimination of human onchocerciasis, 2016-2017. Weekly epidemiological record no 45, 92, 681-700.
WHO, 2018a. Progress report on the elimination of human onchocerciasis, 2017-2018. Weekly epidemiological record no 47, 93, 633–648; https://apps.who.int/iris/bitstream/handle/10665/275983/WER9347.pdf?ua=1.
WHO, 2018b. Onchocerciasis elimination mapping of endemic countries is key to defeating river blindness. https://www.who.int/neglected_diseases/news/Onchocerciasis-elimination-mapping-of-endemic-countries-is-key/en/.
WHO, 2019a; https://www.who.int/news-room/fact-sheets/detail/onchocerciasis.
WHO, 2019b: https://www.who.int/neglected_diseases/news/half-million-Yemenis-treated-for-onchocerciasis/en/.
WHO fact sheets, 2020: https://www.who.int/news-room/fact-sheets/detail/onchocerciasis
WHO, 2020. Onchocerciasis; https://www.who.int/onchocerciasis/en/.
Wilson, E.J., Wormall, A., 1949. Studies on suramin (Antrypol: Bayer 205). 7. Further observations on the combination of the drug with proteins. Biochem. J. 45, 224-231.
Wilson, M.D., Cheke, R.A., Flasse, S.P.J., et al., 2002. Deforestation and the spatio-temporal distribution of avannah and forest members of the *Simulium damnosum* complex in southern Ghana and south-western Togo. Trans. Roy. Soc. Trop. Med. Hyg. 96, 632-639.
Yaméogo, L., Crosa, G., Samman, J., et al., 2001. Long-term assessment of insecticides treatments in West Africa: aquatic entomofauna. Chemosphere 44, 1759-1773.
Yen, J.H., 1975. Transovarial transmission of *Rickettsia*-like microorganisms in mosquitoes. Ann. N. Y. Acad. Sci. 266, 152-161.
Zimmerman, P.A., Dadzie, K.Y., De Sole, G., et al., 1992. *Onchocerca volvulus* DNA probe classification correlates with epidemiologic patterns of blindness. J. Infect. Dis. 165, 964-968.
Zarroug, I.M.A., Elaagip, A.H., Abuelmaali, S.A., et al., 2014. The impact of Merowe Dam on *Simulium hamedense* vector of onchocerciasis in Abu Hamed focus - Northern Sudan. Parasit. Vectors 7, 168.
Zarroug, I.M.A., Hashim, K., El Mubarak, W.A., et al., 2016. The first confirmed elimination of an onchocerciasis focus in Africa: Abu Hamed, Sudan. Am. J. Trop. Med. Hyg. 95, 1037–1040.
Zimmerman, P.A., Guderian, R.H., Aruajo, E., et al., 1994. Polymerase chain reaction-based diagnosis of *Onchocerca volvulus* infection: improved detection of patients with onchocerciasis. J. Infect Dis. 165, 964-968.
Zouré, H.G.M., Noma, M., Tekle, A.H. et al., 2014. The geographic distribution of onchocerciasis in the 20 participating countries of the African Programme for Onchocerciasis Control: (2) pre-control endemicity levels and estimated number infected. Parasit. Vectors 7, 326.

Legends

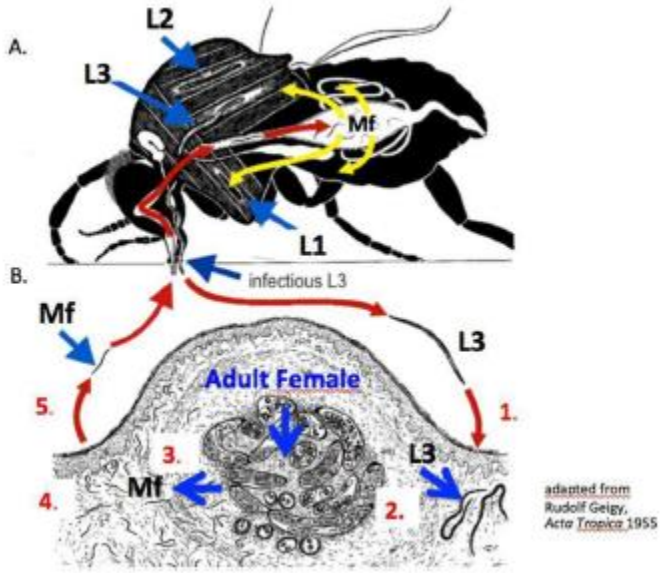

Figure 1. *Onchocerca volvulus* life cycle: B. Infection: (1.) infective third-stage larva (L3) of *O. volvulus* is transmitted by the vector *Simulium* (A.);(2.) a histological section through an onchocercoma in the human host comprising a coiled adult female developed from a fourth-stage larva; (3.) microfilariae produced by the adult female worm which (4.) migrate from the onchocercoma into the skin (5.) to be taken up by the pool-feeding *Simulium*. (A.) In the vector a microfilaria develops into a first stage "sausage" form larva (L1), moults into the second-stage larva (L2) and then moults again to become a third-stage infective larva (L3) which is transmitted into the skin of the human host when the vector pool feeds (1.) (figure modified from Rudolf Geigy, *Acta Tropica* Supplement 6, Geigy and Herbig, *Erreger und Überträger tropischer Krankheiten*, 1955).

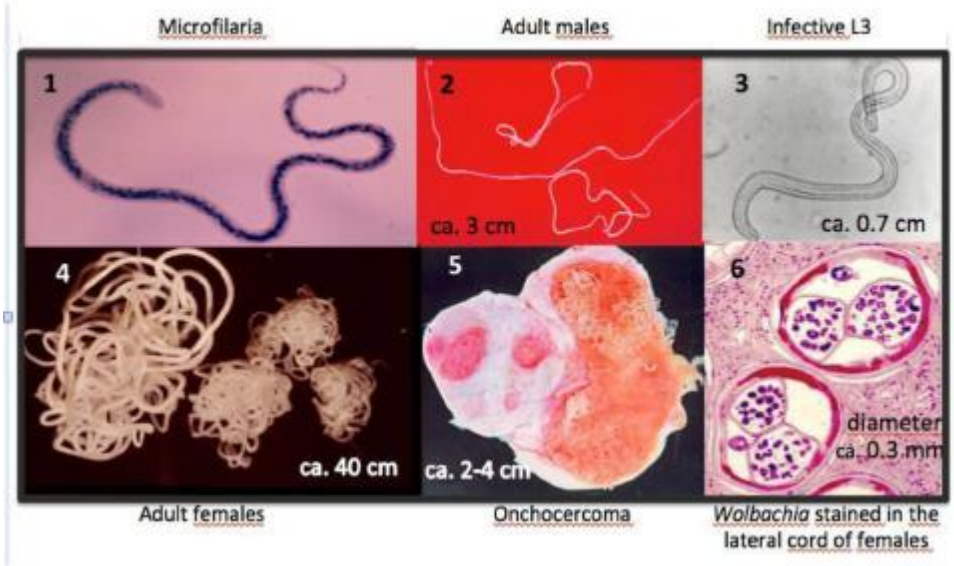

Figure 2. Stages of the *Onchocerca volvulus*: (1.) microfilaria (about 0.2-0.3 mm long), (2.) adult males (1.5-4.5 cm), (3.) infective third-stage larva (0.7-0.8 mm); (4.) adult females (30-60 cm), (5.) an onchocercoma with cut adult females, (6.) sections through a nodule showing adult females (ca. 0.3 mm in diameter) showing two uterus branches with cut microfilariae, cut intestine and lateral cords containing endobacterial *Wolbachia* stained red (photo Brattig et al. 2001; D.W. Büttner, Liberia 1991; N.W. Brattig, BNITM, 2000).

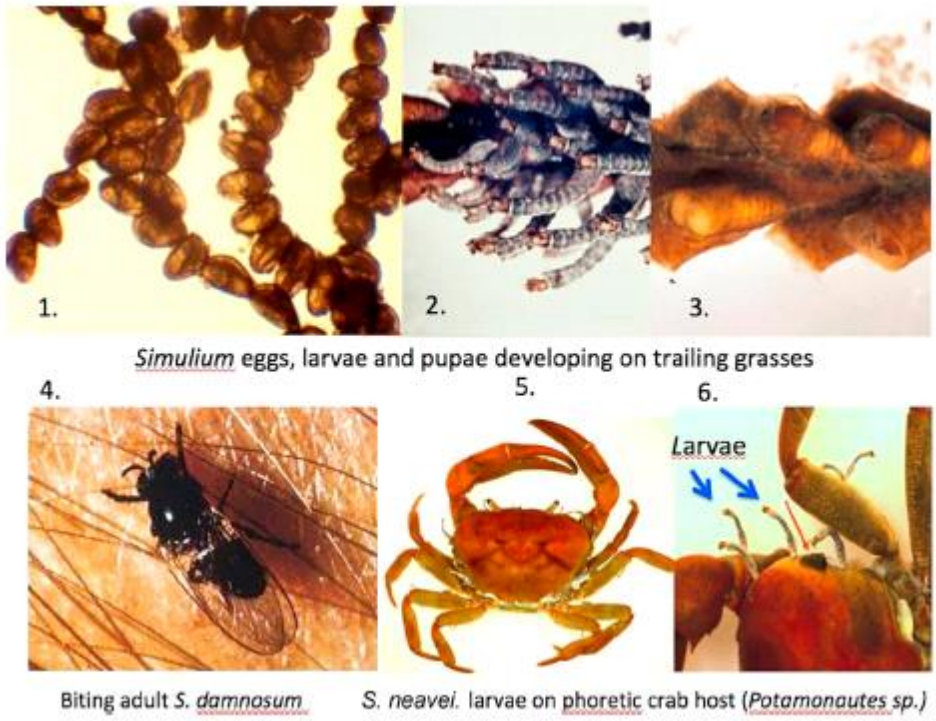

Figure 3. *Simulium damnosum* s.l. stages: (1.) Masses of eggs Niger, Guinea, photo R. Garms, 1963), (2.) larvae on trailing vegetation and (3.) pupae, St. Paul River Liberia (photo R. Garms, 1983). (4.) Adult *Simulium* s.l., photo R. Garms, Liberia, 1983), (5.) Drop of blood after pool-feeding by a *Simulium* (photo R. Gams, Guatemala, 1974).

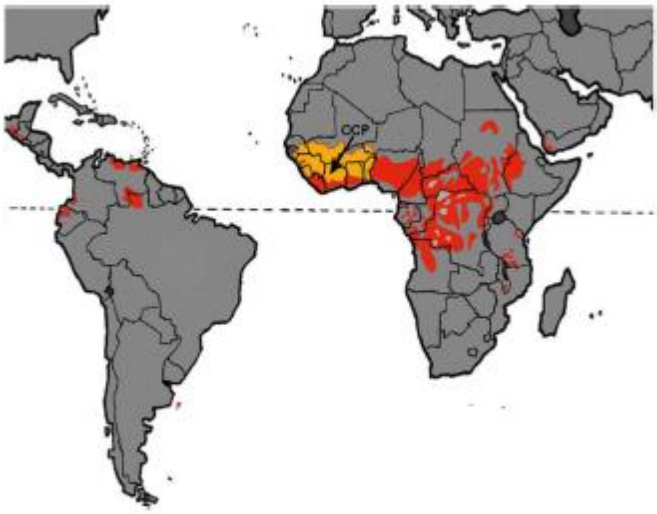

Figure 4. Prevalence of onchocerciasis (marked red) in 30 sub-saharan African countries, in Yemen (Arabian Peninsula) and in 6 countries of central and south America. The area of the Onchocerciasis Control Programme (1974-2002) is marked yellow (modified, WHO, 1995).

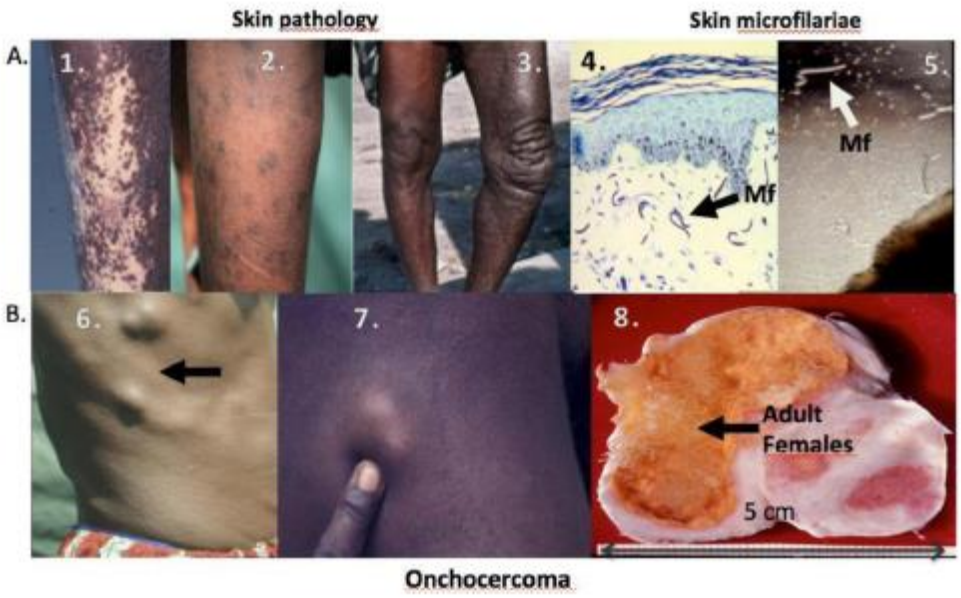

Figure 5. Pathology of onchocerciasis. A. Skin pathology and microfilariae: (1.) depigmentation, (2.) dermatitis, (3.) lichenification and hyperpigmentation (sowda) (Brattig, 2004; photo D.W. Büttner, Liberia 1995), (4.) microfilariae in a histological section of skin (photo D.W. Büttner, Liberia, 1999), (5.) microfilaria released *in vitro* from a skin snip (photo N.W. Brattig, 2000); B. Onchocercomata (6.) nodules in the torso of a man (photo D.W. Büttner, Liberia, 1985), (7.) nodule in the leg of a boy (photo R. Garms, Liberia, 1971), (8.) A bisected onchocercoma with adult females (Brattig, 2004).

Figure 6. Eye pathology (River blindness). (1.) Two onchocercomata in the forehead of a young child which can release microfilariae in the close proximity of the eyes (DW Büttner, Liberia,1993), (2.) cornea opacification,sclerosing keratitis (R. Garms, Kouroussa, Guinea, 1963), (3.) man blinded by onchocerciasis guided by a child (photo R. Garms, Sérékoroba Guinea, 1963). Microfilariae releasing the onchocercoma can infiltrate the eye and can lead to visual impairment and blindness.

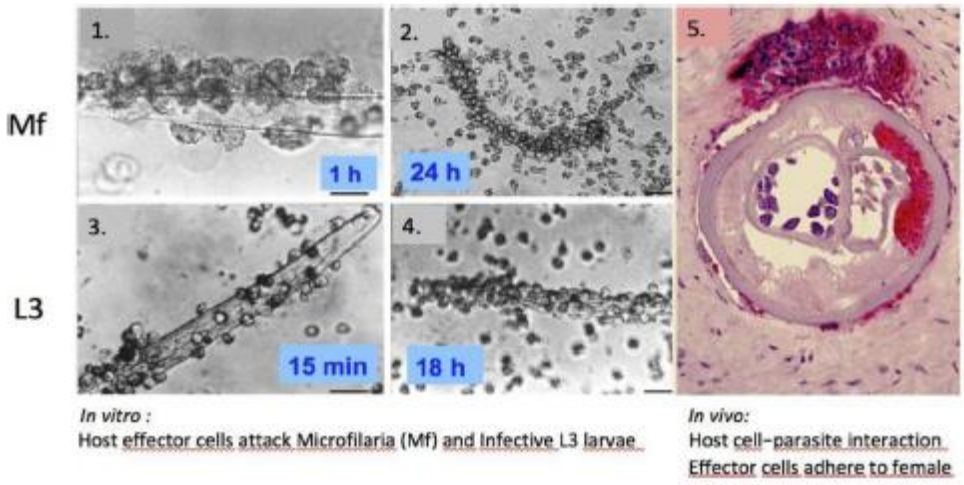

Figure 7. Host-parasite interaction. (1., 2.) time-dependent *in vitro* attack of microfilariae (Mf) by human eosinophilic effector cells (3., 4.) and of infective 3rd stage larvae (L3) (modified figures from Brattig, 2004), (5.) Host neutrophilic granulocytes assembled at the surface of a female in a section of an onchocercoma with *Wolbachia* in the lateral cords of the female; the *Wolbachia* were stained with antibodies against *Wolbachia* heat shock protein 60, the neutrophils with antibodies against defensin (Brattig et al., 2001).

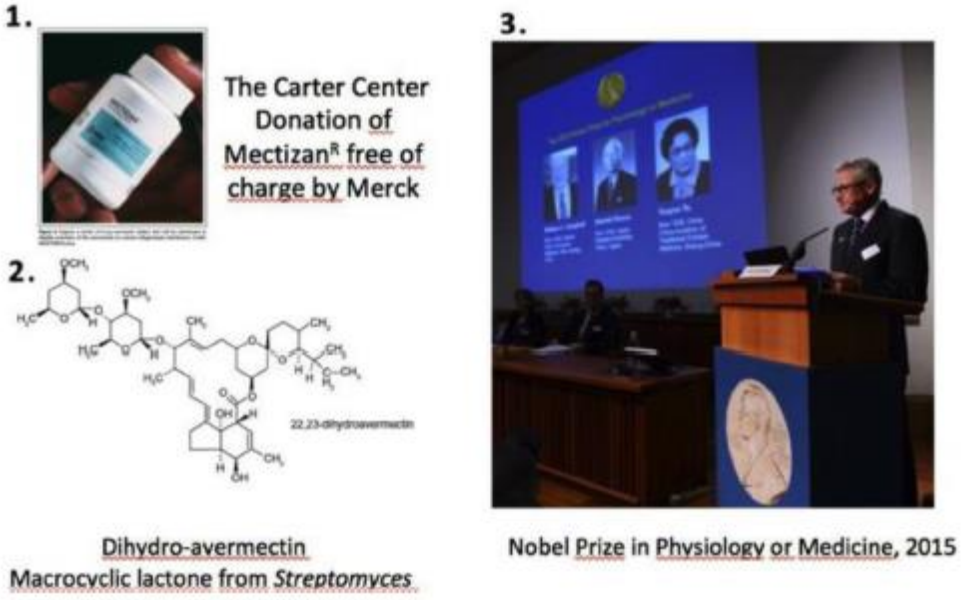

Figure 8. Container with Ivermectin (dihydro-avermectin), the principal drug against onchocerciasis (1.); (2) the chemical formula: a macrocyclic lactone, synthesized by *Streptomyces* sp., administered as *Mectizan*[R] (*Merck Inc*.) is donated free to millions of onchocerciasis patients organized by the Carter Center. (3.) In 2015, the Nobel Prize in Phyiology or Medicine was awarded at the Karolinska Institute to *William C. Campbell* and *Satoshi Ömura* for their discovery of the anti-filarial compound Ivermectin.

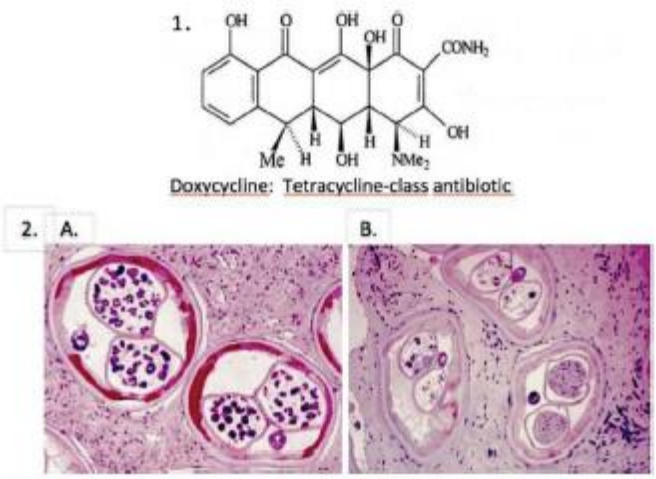

Figure 9. Antibacterial doxycyline, (1.) a tetracycline-class polycyclic antibiotic agent kills *Wolbachia* endobacteriae in *Onchocerca* microfilariae and is introduced for treatment of onchocerciasis in 2003 (Hoerauf et al., 2001; Walker et al., 2015). (2.) Sections through onchocercomata (A.) from an untreated patient which comprise *Wolbachia* stained red in the cords and (B.) females in an onchocercoma from doxycycline-treated patients with depleted *Wolbachia* (Brattig et al., 2001).

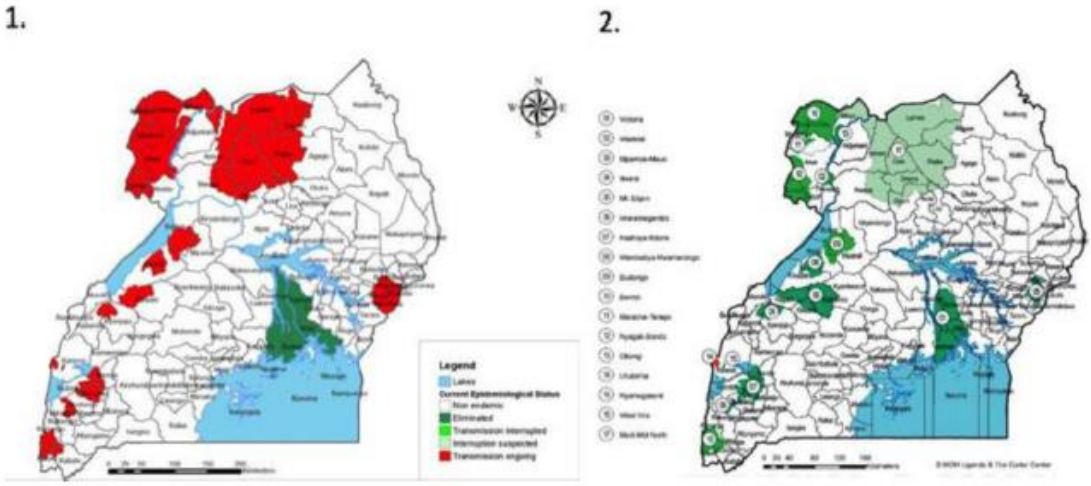

Figure 10. Progress of onchocerciasis elimination in Uganda by 2019. Comparison of transmission in 1992 (1.) and in 2019 (2.) In 1992 (1.), only the historical large Victoria Nile focus (green) had been eliminated after intensive vector control activities. In 2019 (2.), onchocerciasis had been very successfully eliminated from 15 (green) of the original 17 foci, transmission was possible still ongoing in the Madi Mid North focus (focus 17; light green) and still active in the small Lhubiriha focus on the border with D.R. Congo (focus 14; red) (copyright MOH Uganda and The Carter Center; 2019 kindly provided by Moses Katabarwa, 2020).