

1 Preface

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

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

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

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Review

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

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23 Abstract

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

39 1. Introduction and history

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

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

61 Chromosomes of *Simulium* were first described in 1937 (Painter et al., 1937) and those of the vectors
62 in 1975 (Vajime and Dunbar, 1975), whereas for *Onchocerca* they were described later (Hirai et al., 1987;
63 Post et al., 1989). The complete genome of *O. volvulus* was first published in 2016 by Choi et al. (2016) and
64 Cotton et al. (2016). *Rickettsia*-like endobacteria, *Wolbachia*, were first reported in *Onchocerca* in 1977 by
65 Kozek and Figueroa-Marroquin (1977) and the genome of *Wolbachia* was described in 1999 by Bandi et al.
66 (1999) and Slatko et al. (1999).

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

74

75 Table 1. Milestones in onchocerciasis research

76

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

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78 2. Parasite *Onchocerca*

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80 2.1. *O. volvulus* life cycle

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82 2.1.1 Development of the filaria in the human host

83 The infective third stage larvae (L3) of the parasite with a length of 600-700 µm invade the skin when
84 an *O. volvulus*-infected blackfly bites the human host for blood (Fig. 1; Fig. 2). The L3 larvae moult in the
85 skin of the human host to fourth stage larvae which migrate in subcutaneous tissue and grow to the adult
86 female and male stages in 6-12 months. The adult females measure 30-60 cm, while the males are only
87 1.5-4.5 cm long (Fig. 2). The host reaction against the parasites leads to the formation of nodules known as
88 onchocercomata. Interestingly, the males of the cattle parasite *O. ochengi*, and probably those of *O.*
89 *volvulus* too, migrate between the nodules, thus from female to female.

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

98

99 2.1.2. Transmission by the vector *Simulium*

100 2.1.2.1. The genus *Simulium*

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

110 In addition to their importance as vectors, blackflies can be serious biting pests of man and animals
111 in both tropical and temperate climates, with examples including *S. erythrocephalum* in central Europe
112 and *S. posticum* in England. Particularly infamous was the Golubac fly *S. colombaschense* which in 1923
113 killed 22000 animals (sheep, goats, cattle) in the Danube valley in Yugoslavia, Hungary and Romania
114 (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

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

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

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

174

175 2.2. Endobacterium *Wolbachia*

176

177 2.2.1. *Wolbachia* in the parasite *Onchocerca*

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

183 *Wolbachia* are found in the hypodermal cells of the lateral cords of adult filariae and in embryonic
184 stages (Taylor and Hoerauf, 1999, Hoerauf et al., 2000) (Fig. 2.6). The absence of *Wolbachia* appears to be
185 an ancestral condition (Bandi et al., 2001). The *Wolbachia* were shown to be mutualistic in *Onchocerca*
186 (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

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

228

229 2.3. Phylogeny and biology of *Onchocerca*

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

238 On the basis of the genetic similarity of *O. volvulus* and *O. ochengi*, the bovine infection by *O. ochengi*
239 has become famous as a natural model or 'analogue' of human onchocerciasis (Trees et al., 2000;
240 Makepeace and Tanya, 2016). A multitude of experimental joint studies by the University of Ngaoundéré
241 and the University of Tübingen, Germany, demonstrated similarities in the stage-specific proteome
242 (Armstrong et al., 2016), in excretory-secretory (E/S) peptides (Eberle et al., 2015), in immune
243 recognition of ES proteins (Manchang et al., 2015), in cross-protection (Wahl et al., 1998), in cross-
244 vaccination (Achukui et al., 2007), and in the conserved nature of circulating miRNA (Quintana et al.,
245 2015). Further, similarities in the immune antigen recognition pattern was reported in *O. ochengi*-infected
246 cattle and in an *O. volvulus*-infected chimpanzee (Graham et al., 2000) confirming the use of the primate as
247 a surrogate host for *Onchocerca* infection. The comparability of both infections, nevertheless, appears to
248 be limited since in the evolutionarily primordial *O. ochengi* infections the parasite is highly adapted to its
249 bovine host eliciting minimal pathology, whereas in the evolutionarily younger parasitism by *O. volvulus*
250 severe damage often results (see section 3.3.).

251 ([https://pubmed.ncbi.nlm.nih.gov/27869790/?from_sort=pubdate&from_term=Cotton+JA&from_cauthor](https://pubmed.ncbi.nlm.nih.gov/27869790/?from_sort=pubdate&from_term=Cotton+JA&from_cauthor_id=27881553&from_pos=4)
252 [_id=27881553&from_pos=4](https://pubmed.ncbi.nlm.nih.gov/27869790/?from_sort=pubdate&from_term=Cotton+JA&from_cauthor_id=27881553&from_pos=4)).

253 Differences between the manifestation of onchocerciasis in forest and savannah regions, in particular
254 between blinding rates, gave rise to a two-strain hypothesis (Duke et al. 1966). Analyses of entomological
255 data (Cheke and Garms, 2013) and a reanalysis of pre-control blindness data (Cheke et al., 2020) have led
256 to this hypothesis being questioned. Although some molecular studies of different *O. volvulus* populations
257 revealed differences between savannah and forest strains, for instance by being distinguishable using the
258 0-150 repeat region sequence (Erttmann et al., 1987; Zimmermann et al., 1992), other studies did not

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

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

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

287

288 3. Disease

289

290 3.1. Prevalence

291

292 Estimates of prevalence vary substantially. Thus, the WHO stated for 1983 that globally 85.5 million
293 people were at risk and about 37 million people were infected with *O. volvulus* (Amazigo et al., 2008), with
294 0.34 million of the infected blinded by onchocerciasis (WHO, 1987). For 1995, the WHO noted 123 million
295 at risk, 17.7 million infected people and 0.27 million blinded people (WHO fact sheets, 2019, 2020; Fig. 4).

296 Onchocerciasis is almost exclusively (>99%) prevalent in 31 countries of sub-Saharan Africa, but about
297 20,000 infected persons live in Yemen (Büttner et al., 1982; Connor et al., 1983; WHO 2019). In terms of
298 populations living in areas where more than 50% live in areas where the predicted nodule prevalence is
299 greater than 20%, the main countries are the Democratic Republic of Congo with 23.3 million people,
300 Nigeria (14.3 million), Ethiopia (5.9 million) and Cameroon (5.2 million)(Zouré et al., 2014). In central
301 Africa – the Central African Republic, Gabon, Democratic Republic of Congo, Angola, Sudan, Ethiopia,
302 Uganda, Nigeria, Cameroon – onchocerciasis is co-endemic with loiasis. Loiasis, caused by the filaria *Loa*
303 *loa* and transmitted by horseflies (*Chrysops dimidiatus* and *C. silaceus*) affect the eyes (African eye worm)
304 (Vinkeles Melchers et al., 2020). Loiasis coinfection is a major concern for onchocerciasis elimination in
305 Africa (see 4.1.).

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

312

313 3.2. Diagnostics

314

315 Tests for diagnosing onchocerciasis are summarised in Table 2. Onchocerciasis is primarily diagnosed
316 clinically by detecting onchodermatitis, by subcutaneous nodules (onchocercomata), often located at the
317 hips, and by detection of microfilariae in skin snips (microfilaridermia) requiring a microscopic
318 examination (Picq et al., 1971; Albiez et al., 1988a; Alhassan et al., 2016). Skin patch testing (Mazzotti
319 reaction) with diethylcarbamazine (DEC) can indicate microfilaridermia (Mazzotti, 1951). Awadzi et al.
320 (2015) reported a clinical evaluation of a transdermal delivery technology-based patch for the diagnosis
321 of *O. volvulus* infection via skin exposure to diethylcarbamazine. Ocular status can also help diagnosis, if
322 pathological findings such as punctate keratitis or even microfilariae in the anterior chamber are noted
323 (O'Day and Mackenzie, 1985).

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

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

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

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

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

349

350

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

352

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)	<i>Onchocerca</i> antigens, hybrid: Ov16, Ov20 (Ov-FAR-1), Ov33, Ov10, Ov7, Ov103, OvSOD1, Oc9.3, Ov-MSA-1	Recognition of surface or secreted antigens of <i>Onchocerca</i> 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

353 ¹ quantitative polymerase chain reaction, ²Loop-mediated isothermal amplification, ³microRNA,

354 ⁴NATOG, N-acetyltyramine-O-glucuronide

355

356 3.3. Pathology

357
358 The primary manifestation of an *O. volvulus* infection is itching of the skin. The skin affliction results
359 from the migration of a myriad of microfilariae from the subcutaneous nodules (onchocercomata),
360 harbouring fertilised adult female and male filariae, into the adjacent skin. In the course of the infection an
361 acute papular rash develops into a chronic papular dermatitis which may be associated with
362 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

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

403 In the course of the infection the host elicits a sequence of defence mechanisms reviewed by Ottesen
404 (1995), Brattig (2004a) and Maizels et al. (2018). In response to the filarial antigens the B-lymphocytes of
405 the host produce antibodies, predominantly immunoglobulin G4 (IgG4) and IgE antibody isotypes (Brattig
406 et al., 1994; Garraud et al., 1996; Adjobimey and Hoerauf, 2010). The blocking IgG4 type antibodies
407 enhance the parasite's potential for host response evasion by inhibiting detrimental reactions since (i)
408 IgG4 represent non-complement-fixing immunoglobulins and (ii) IgG4 cannot induce antibody-dependent
409 cell-mediated cytotoxicity (ADCC) (Adjobimey and Hoerauf, 2010). Hence, high IgG4 concentrations are
410 found in immunosuppressed patients with high microfilarial loads (Adjobimey and Hoerauf, 2010;
411 Ottesen, 1995).

412 The defence mechanisms also include cellular responses of the adaptive and innate immune system:
413 lymphocyte and granulocyte populations are activated to secrete cytokines and toxic compounds which
414 affect the parasite (Ottesen 1995; Maizels et al. 2018). In *Onchocerca*-infected individuals the T helper
415 lymphocyte populations Th1, Th2, Th17 and regulatory T cells (Treg) are stimulated - predominantly
416 occurring as a Th2-response (Brattig et al., 1987; Plier et al., 1995; Timmann et al., 2003; Allen and
417 Sutherland, 2014). The helminth initiated lymphocyte subsets produce the cytokines IL-4, IL-13, IL-5, IL-
418 10, and TGF-beta which subsequently initiate multiple reactions from the innate immune system (Turaga
419 et al., 2000; Brattig et al., 1997; 2002; Soboslay et al., 1999; Dötze et al., 2000; Hoerauf and Brattig, 2002).

420 Characteristic of the innate immune response are eosinophilic and neutrophilic granulocytes, mast
421 cells and alternatively activated macrophages (Brattig, 2004a; Maizels et al., 2018). Predominant
422 eosinophilic granulocytes are activated by IL-5, released from Th2 cells, and their infiltration in the tissue
423 is regulated by IL-4 and IL-13. Such activated eosinophils adhere and degranulate at the surface of
424 microfilariae (Fig. 7.1-2) and infective larvae (Fig. 7.3-4) (Medina-De la Garza et al., 1990; Stroete et al.,
425 1990; Brattig et al., 1991; Abraham et al., 2004). Eosinophilic effector cells produce reactive oxygen
426 species and secrete, via extracellular granules, multiple toxic molecules including oxygen radicals,
427 eosinophil peroxidase, major basic proteins, eosinophil cationic proteins, eosinophil-derived neurotoxin
428 and cytokines such as IL-10 and even IL-13 (Tischendorf et al., 1992; Pearlman 1997; Weller and Spencer,
429 2017). In addition to the eosinophils, mast cells are also operative in the host responses against helminths
430 (Ottesen, 1995; Korten et al. 1998). The Th1-associated response of neutrophilic granulocytes reflect the
431 presence of the endobacteria (see section 3.5.) (Brattig et al., 2001; Tamarozzi et al., 2016). In addition to
432 anti-parasitic reactions, the innate immune system is involved in wound repair mechanisms (Weller and
433 Spencer, 2017).

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

440 Patients with a hyperreactive form of onchocerciasis, Sowda(h) (see section 3.3.) exhibit a particular
441 host-parasite interaction (Bartlett et al., 1978; Connor et al., 1983; Ottesen, 1995; Brattig, 2004a). The
442 high inflammatory potential visibly manifests in the skin showing hyper-pigmentation, lesions, pruritus
443 and lichenification (Fig. 5). This activated state corresponds with strong cellular immune responses.
444 Characteristic are Th2 and Th17-Th2 lymphocytes and their secreted products such as IL-13, IL-4 and IL-
445 17; they are associated with low Treg cells (CD4⁺CD25^{hi}Foxp3⁺) reactivity (Brattig et al., 1987; Hoerauf et
446 al., 2002; Katawa et al., 2015). Furthermore, high numbers of eosinophilic granulocytes, together with their
447 released toxic cell products, and mast cells occur in hyperreactive onchocerciasis (Medina-De la Garza et
448 al., 1990; Rubio-de Krömer et al., 1995; Tischendorf et al., 1992; Hoerauf et al., 2002). Although only a
449 small number of microfilariae occur in the skin, the lack of Treg cells results in uncontrolled inflammatory
450 responses (Brattig 2004a; Hoerauf and Brattig, 2002; Katawa et al., 2015). Serologically, strongly
451 increased antibody including autoantibody responses are characteristic of sowda patients (Brattig et al.,
452 1994; Gallin et al., 1995) (see section 3.3.). In consequence, these strong immune responses are associated
453 with the reported low level of microfilarial density (Omar et al., 1979; Büttner and Racz., 1982, 1983;
454 Siddiqui and Khawajah, 1991).

455 One major option for an effective host immune response is a prophylactic vaccine against the parasite,
456 notably that spurred on and advanced by Sarah Lustigman (Lustigman et al., 2002, 2018; Hotez et al.,
457 2015; George et al., 2019). Vaccines are aimed at preventing infection by infective larvae (anti-L3), and/or
458 reducing microfilariae thereby complementing the control or elimination of onchocerciasis. Numerous
459 proteins released by the filariae have been investigated for their vaccine potential; these comprise Ov-103,
460 Ov-RAL-2, Ov-CHI-1, Ov_ALT-1, Ov-B20, Ov28CRP, Ov-GAPDH (Steisslinger et al., 2015; Lagatie et al.,
461 2018; Lustigman et al., 2018). The alum-adjuvanted vaccine consisting of Ov-103, expressed at the surface
462 of microfilariae, and Ov-RAL-2, found in the hypodermis of infective larvae, have the potential of reducing
463 the infection by inhibition of moulting and survival of larvae. The development of cytophilic antibodies
464 against the antigens and of interleukins effect antibody-dependent cellular cytotoxicity (George et al.,
465 2019). Further, an immunomics approach with serum samples from putatively immune individuals has
466 been applied (Bennuru et al., 2016). Recently a multi-epitope subunit vaccine coding for selected B-cell
467 and T-cell epitopes, was constructed representing a novel approach for generating a specific immune
468 response thereby avoiding responses against other unfavourable epitopes in the complete antigen (Shey
469 et al., 2019). Another optional vaccine consists of nanoparticles or the use of non-protein molecules such

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

472

473 3.5. Role of *Wolbachia* in onchocerciasis

474

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

479 Immunologically, the *Wolbachia* stimulate innate and adaptive immune responses. The bacteria-
480 derived surface-associated and released molecules play immunological and pathological roles in
481 onchocerciasis. In particular, endotoxin-like molecules induce Th1-type inflammatory reactions as known
482 in all gram-negative lipopolysaccharide-exposing bacteria (Brattig et al., 2000; 2004b). In contrast to the
483 helminth-characteristic type 2 (Th2) and Th3 immune responses, the *Wolbachia* provoke bacteria-typical
484 predominant type 1 (Th1) reactions. Neutrophils - characteristically activated against bacteria -
485 accumulate within an onchocercoma at the surface of a female comprising a multitude of *Wolbachia* in the
486 lateral cord (see section 3.3., Fig. 7.5) (Brattig et al., 2001; Tamarozzi et al., 2016) - but neutrophils are
487 absent in the onchocercoma on the surface of a female when the onchocerciasis patient has been treated
488 with antibacterial doxycycline eliminating the *Wolbachia* (Fig. 9) (Brattig et al., 2001; 2004; Pearlman,
489 2003; Saint André et al., 2002). Subsequently, high peripheral levels of TNF-alpha, IL-1 beta, IL-6, IL-8 and
490 antibacterial acute phase reactants arise on site and in the circulation. The *Wolbachia* surface protein
491 (WSP) and heat-shock protein induce Th1-associated cytokines, TLR2/4 and IgG1 antibody responses
492 (Pearlman, 2003; Brattig, 2004b; Kamalakannan et al., 2012; Tamarozzi et al., 2016).

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

497

498 4. Onchocerciasis control and elimination programmes

499

500 4.1. Elimination of onchocerciasis by chemotherapy of infected patients

501

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

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

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

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

520 Ivermectin (Mectizan[®], Merck) a macrocyclic lactone, derived from *Streptomyces*, is an endectocide. In
521 2015, the Nobel Prize in physiology or medicine was jointly awarded to W. Campbell (University of
522 Wisconsin) and S. Omura (Kitasato University) at the Karolinska Institute (Sweden) for their discovery
523 and exploration of ivermectin and its mode of action, resulting in a novel therapy against onchocerciasis
524 and other nematode infections (Aziz et al., 1982; Campbell et al., 1983, 2016; Ömura, 2016; van Voorhis et
525 al., 2015) (Fig. 8). This molecule binds to the inhibitory neurotransmitter GABA on neurons and muscles
526 resulting in an irreversible activation of a chloride influx, in a hyperpolarization of the membrane, and in
527 paralysis and death of microfilariae. Ivermectin expresses micro- but not macrofilaricidal activity,
528 although it causes long-term sterility of the adult female worms. Ivermectin was introduced for anti-
529 filarial treatment in 1981. Albiez et al. (1988b) showed that ivermectin was a more effective
530 microfilaricidal agent than DEC that caused more frequent and severe side effects. Initially, ivermectin was
531 administered once a year (150 µg/kg) , but lately it is increasingly administered bi-annually (Frempong et
532 al., 2016). A 3-monthly treatment with ivermectin even may be most effective to prevent the appearance
533 of onchocercomata (Campillo et al., 2020). The 3-monthly treatments not only target microfilariae, but
534 probably in addition the moulting of third to fourth stage larvae and possibly can affect immature adults
535 suggesting a prophylactic effect. Further, Navarro et al. (2020) reviewed data on the safety of high doses
536 of ivermectin (>400 up to 800 µg/kg) but did not exclude ocular adverse events.

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

580 2003b, 2008; Abegunde et al., 2016).

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

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

606

607

608 Table 3. Therapeutic agents for treatment of onchocerciasis

609

Target	Therapeutic agents	Originator / Operator	Start of treatment
<i>Onchocerca</i>	Suramin	Wilson and Wormall	1949
	Diethylcarbamazine, DEC (Hetrazan)	Ruiz Reyes	1951
	Ivermectin	Aziz	1982
		Campbell Ömura Nobel prize, Karolinska Institute, Sweden	1983, 2016 2016 2015
Moxidectin, Milbemycin	van Voorhis	2015	
<i>Wolbachia</i>	Doxycycline Doxycycline versus Ivermectin Tolosin A analog: ABBV-4083, TylAMac AWZ1066S, CRB490/417	Monahan	1995
		Opoku	2018
		Hoerauf	2002
		Abegunde	2016
		von Geldern	2019
Taylor	2019		
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 km²) Riana focus in Kenya
622 and, in 1946, the vector *S. neavei* was eliminated from a focus in the Koderia 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 km² 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

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

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

678 The great success of the OCP by 2002 was to have freed for agriculture 250,000 km² of fertile land
679 from the threat of onchocerciasis, 40 million people had been protected from the disease and 600,000
680 cases of blindness prevented in seven countries (WHO, 2002). After the cessation of OCP, responsibility
681 for continuing onchocerciasis control was devolved to the eleven member countries' governments.

682

683 4.2.3. The African Programme for Onchocerciasis Control (APOC)

684 In 1995 WHO had instigated the African Programme for Onchocerciasis Control (APOC) aiming to
685 promote control (and from 2009 elimination) by establishing self-sustaining community-directed
686 treatment with ivermectin (CDTI), and, where appropriate, vector control with environmentally safe
687 methods. The participating 19 countries were the remaining non-OCP endemic countries: Angola, Burundi,
688 Cameroon, Central African Republic, Chad, Democratic Republic of Congo, Equatorial Guinea, Ethiopia,
689 Gabon, Kenya, Liberia, Malawi, Mozambique, Nigeria, Rwanda, Sudan, Tanzania and Uganda. APOC's vector
690 control activities were restricted to a few isolated foci, notably in Bioko (Equatorial Guinea) (Traoré et al.,
691 2009), Tanzania and Uganda (Garms et al., 2009; <https://www.who.int/apoc/vector/en/>). APOC
692 terminated in December 2015 and WHO's action on onchocerciasis control was subsumed in May 2016
693 within the Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN) that deals not
694 only with onchocerciasis but also with lymphatic filariasis, loiasis, schistosomiasis, soil-transmitted
695 helminthiasis and trachoma (<http://espen.afro.who.int/>; Hopkins, 2016).

696

697 4.3. Current status of onchocerciasis in selected countries

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

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

706

707 4.3.1. Africa

708 4.3.1.1. Guinea

709 The first research on onchocerciasis was conducted by staff of the Bernhard Nocht Institute in the
710 1960s. Knüttgen (1964) and Knüttgen and Büttner (1968) examined 18,634 people in northeastern
711 Guinea and reported that 45.8% carried microfilariae and 24% had nodules, with blindness rates varying
712 from 1.07 to 4.56%. Subsequently, Knüttgen (1971) and De Sole et al. (1991) summarized the
713 epidemiological situation. Garms and Post (1966) were the first to report the presence of *S. damnosum* s.l.
714 and later Garms and Vajime (1975) found that, of the then known cytospecies, *S. yahense*, *S. sanctipauli*, *S.*
715 *soubrense*, *S. damnosum* s.str. and *S. sirbanum* were present. This information was updated by Boakye et al.
716 (1998). Guinea was part of the western extension of the OCP and was identified as a source of flies
717 reinvading northern Cote d'Ivoire and Burkina Faso, involving distances of up to 500 km (Baker et al.,
718 1990; see section 4.2.2.). According to WHO 2018a,b in 2017 almost 7 million people in 24 districts still
719 required MDA with a reported coverage of 72.3%.

720

721 4.3.1.2. Liberia

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

733 Furthermore, those populations are genetically distinct from the Farmington form present in the
734 Farmington river (Kashan and Garms, 1987; Güzelhan and Garms, 1991). In addition *S. sanctipauli* s.str.
735 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 Katarwa 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).

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

774

775 4.3.1.4. Uganda

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

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

807 When annual distribution of ivermectin began in 1991 no vector control was planned, but treatments
808 were accompanied by studies on the transmission by the vector *S. neavei*. After 4 years, there was no clear
809 effect on the transmission and 1000 parous flies still had 151 infective larvae in their heads. In view of
810 these results and at the request of the local government it was decided to enhance the effect by vector
811 control. Before starting this, it had been confirmed that temephos, which had been used for 25 years in the
812 OCP (see section 4.2.2.), could be used safely, in particular, without harming the phoretic host crabs *P.*
813 *Aloysiisabaudiae* (Garms et al., 2017). After only a few monthly applications from mid-1995 to the end of
814 1996, *S. neavei* had disappeared from the main Itwara focus and never came back. Sub-foci on the Siisa
815 and Aswa rivers took a bit longer, but no positive crabs or biting flies were seen any more throughout the
816 focus after February 2003 (Garms et al., 2009; Michael et al., 2020).

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

830 Control of *S. damnosum* s.l. by removing the trailing vegetation upon which immature stages develop
831 was attempted in Mexico from 1932 to 1940 without success, in D.R. Congo in the early 1940s with only
832 partial success, and in Malawi in the early 1990s by destruction of the aquatic plant *Hydrostachys* sp. (M. J.
833 Roberts, unpubl., Burnham 1992, Davis, 1994). Also, Baker and Abdelnur (1986a,b) showed that in a rocky
834 breeding site of the Bussere River in south-western Sudan a small team armed with axes, saws and sickles
835 could do much to reduce larval and pupal supports in the breeding sites caused by vegetation trailing in
836 fast water flow. A similar strategy has also recently been applied in Uganda (Jacob et al., 2018; Smith et al.
837 2019) but it is unlikely to provide a long-term solution as it requires regular "slash and clear" and, besides,
838 the vectors will adapt and breed on other substrates such as rocks, which they often use when no trailing
839 vegetation is present. In addition, large torrential rivers and rapids, particularly those in the middles of
840 wide rivers cannot be completely cleared.

841
842 4.3.1.5. Ghana

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

852 The initial euphoria about possible elimination of onchocerciasis from Africa using ivermectin
853 distributions was dealt a blow when incipient resistance to the drug was detected in Ghanaian patients
854 (Awadzi et al., 2004). Later, cohorts of patients were found in the Brong-Ahafo and Northern Regions to be
855 being re-populated with microfilariae sooner than was to be expected and these “non-responders” (Osei-
856 Atweneboana et al., 2007) were also possibly harbouring resistant worms (Osei-Atweneboana et al.,
857 2011).

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

861 The ivermectin distributions were originally annual but it is now the policy in Ghana to distribute bi-
862 annually. This has succeeded in reducing transmission and infection rates in some areas but not
863 everywhere that has been studied (Frempong et al., 2016, F.B.D. Vereigh, pers. comm.). Another
864 consideration relevant to continuing transmission is the lack of complete compliance with the drug
865 distribution programmes. Agyemang et al. (2018) investigated compliance in the Upper Denkyira East
866 Municipal area and reported that it was lower than given in official reports, with results ranging from 7 to
867 51% with an overall compliance of only 21%, even less than the 24.4% reported earlier by Kutin et al.
868 (2004).

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

877

878 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 (Katarwa 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 (Katarwa 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 $1 \text{ m}^3 \cdot \text{sec}^{-1}$ (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).

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

956

957 5. Future perspective

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

965 The priority is given to treatment with ivermectin. Recently, attention, however, is drawn to the
966 problems of poor coverage and inadequate compliance to MDA (Agyemang et al., 2018; Dissak-Delon et al.,
967 2019). Correspondingly, Verver et al. (2018) discussed why a wide-reaching elimination of onchocerciasis
968 cannot be guaranteed by 2025 and proposed a long-term biannual or quarterly MDA combined with
969 vector control activities as complementary approaches (Routledge et al., 2018) for high-endemicity areas
970 to accelerate progress toward elimination. The proof-of-principle in distinct foci in Mali, Senegal and
971 Sudan indicate a possibility to eliminate onchocerciasis with annual or 6-monthly ivermectin treatment in
972 some endemic foci in Africa. Correspondingly, the published *WHO 2030 goals* for onchocerciasis were
973 influenced by the cited models (EPIONCHO and ONCHOSIM) on the impact of biannual or quarterly
974 ivermectin treatment frequency and in addition complementary vector control (NTD Modelling
975 Consortium Onchocerciasis Group, 2019; Gates Open Research 2019; Hassan and Shaban, 2020).

976 Anthelmintic drug alternatives to ivermectin, include the aforementioned Moxidectin (Awadzi et al.
977 2014, Opoku et al., 2018) and novel anti-*Wolbachia* agents like the thienopyrimidine/quinazoline scaffold
978 AWZ1066 (Hong et al., 2019).

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

986 One major problem is that an elimination of onchocerciasis with ivermectin treatment alone has not
987 so far appeared to be feasible in many African countries where onchocerciasis was endemic over millions
988 of square kilometres spanning more than 30 countries. In addition, the vectors are highly efficient and
989 with much higher endemicity levels migrating over hundreds of kilometres (Dadzie et al., 2003)
990 threatening re-emergence of infected vectors and of onchocerciasis in their wake. Thus, exemplarily, on
991 Bioko where the unique endemic vector (the Bioko form of *S. yahense*) was rendered extinct (Traore et al
992 2009) some vectors may have returned. These are *S. squamosum* rather than *S. yahense* (D. Boakye, pers,
993 comm 2019) and it is unknown if they brought any *O. volvulus* with them.

994 Nevertheless, given that after nearly 15 years without any transmission on the island very few
995 onchocercal cases remained (Hernández-González et al., 2016; Moya et al., 2016; Herrador et al., 2018; Ta
996 et al., 2018), prospects for confirming elimination are good. The interruption of transmission was
997 considered to have been permanent, but the Bioko case is salutary and illustrates that, however good
998 planning and forecasts can be, there is room for the unexpected to affect our perspectives. In contrast, in
999 the Americas, onchocerciasis elimination with ivermectin treatment has been considered feasible, since
1000 most onchocerciasis foci in the Americas were small and circumscribed, and most vector species are
1001 relatively inefficient. Thus, interruption of the transmission was feasible by 6-monthly or even 3-monthly
1002 ivermectin treatments (Sauerbrey et al., 2018).

1003 Planning MDA programmes is now often based on the outputs of mathematical models such as
1004 ONCHOSIM (Plaisier et al 1990) or EPIONCHO (Basáñez et al. 2016) but these models skimmed on details
1005 of blackfly biology. Only recently have models begun to model vector biology explicitly and started to take
1006 account of future uncertainties regarding climate change (Cheke et al., 2015) and the likelihood of needing
1007 to supplement MDA with vector control (Routledge et al., 2018). Such vector control in isolated foci could
1008 include ground larviciding, slash-and-clear vegetation destruction and killing host-seeking adult female
1009 flies in traps such as the Esperanza window trap (Rodríguez-Pérez, 2013; Toé et al., 2014; Hendy et al.,
1010 2017; NTD Modelling Consortium Onchocerciasis Group, 2019; NTD Modelling Consortium, Gates Open
1011 Research, 2019). These could be supplemented by deploying traps to catch ovipositing female flies such as
1012 “Bellec plates” placed beside breeding sites (Bellec, 1976; Cheke et al., 1982).

1013 Difficulties surrounding the elimination of the transmission of onchocerciasis were reviewed by
1014 Cheke (2017), who drew attention to cases of successful control where transmission had probably been
1015 eliminated in contrast to areas where such interruptions were likely to be only temporary. These included
1016 areas in Africa with >55% prevalence, where mass drug administration (MDA) alone was thought of as
1017 unlikely to succeed.

1018 In summary, anthelmintic MDA complemented by appropriate vector control measures may
1019 increasingly lead to control and hopefully eradication of onchocerciasis which may be fulfilled in mid-
1020 century.

1021

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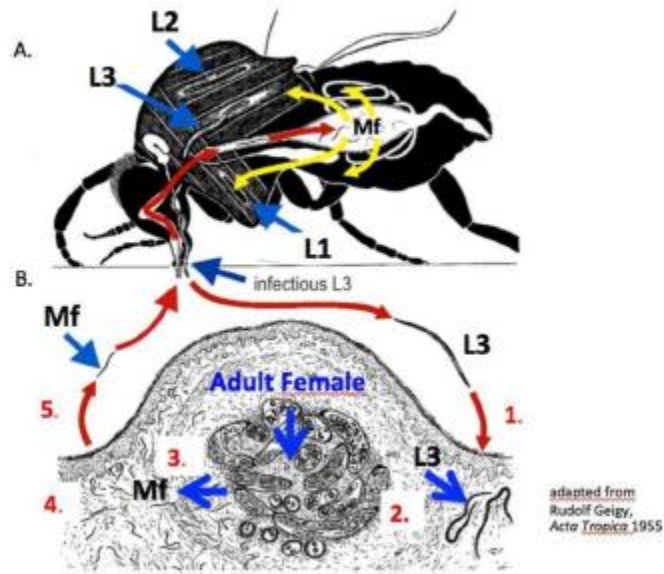
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1887 endemicity levels and estimated number infected. Parasit. Vectors 7, 326.

Legends

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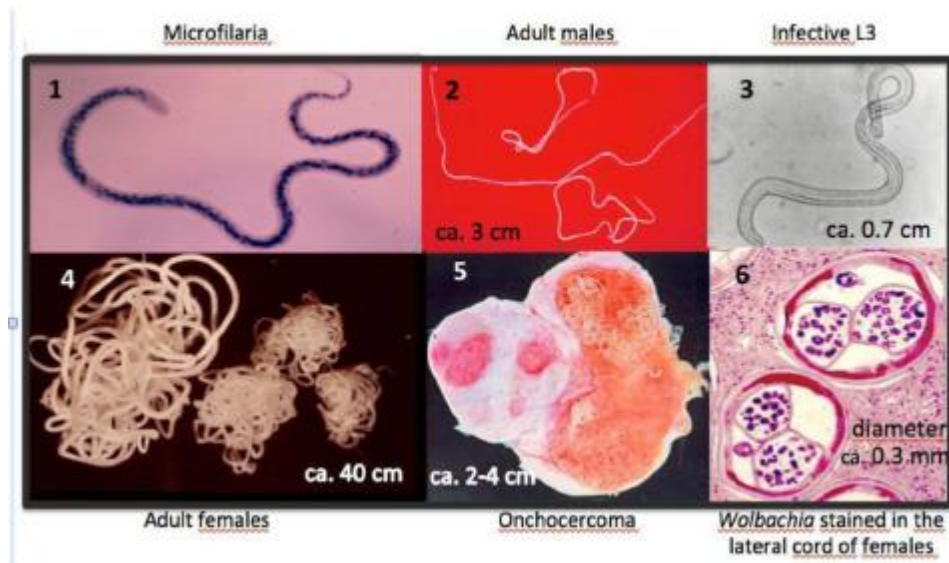
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1895 Figure 1. *Onchocerca volvulus* life cycle: B. Infection: (1.) infective third-stage larva (L3) of *O. volvulus* is
1896 transmitted by the vector *Simulium* (A.);(2.) a histological section through an onchocercoma in the human
1897 host comprising a coiled adult female developed from a fourth-stage larva; (3.) microfilariae produced by
1898 the adult female worm which (4.) migrate from the onchocercoma into the skin (5.) to be taken up by the
1899 pool-feeding *Simulium*. (A.) In the vector a microfilaria develops into a first stage "sausage" form larva
1900 (L1), moults into the second-stage larva (L2) and then moults again to become a third-stage infective larva
1901 (L3) which is transmitted into the skin of the human host when the vector pool feeds (1.) (figure modified
1902 from Rudolf Geigy, *Acta Tropica* Supplement 6, Geigy and Herbig, *Erreger und Überträger tropischer*
1903 *Krankheiten*, 1955).

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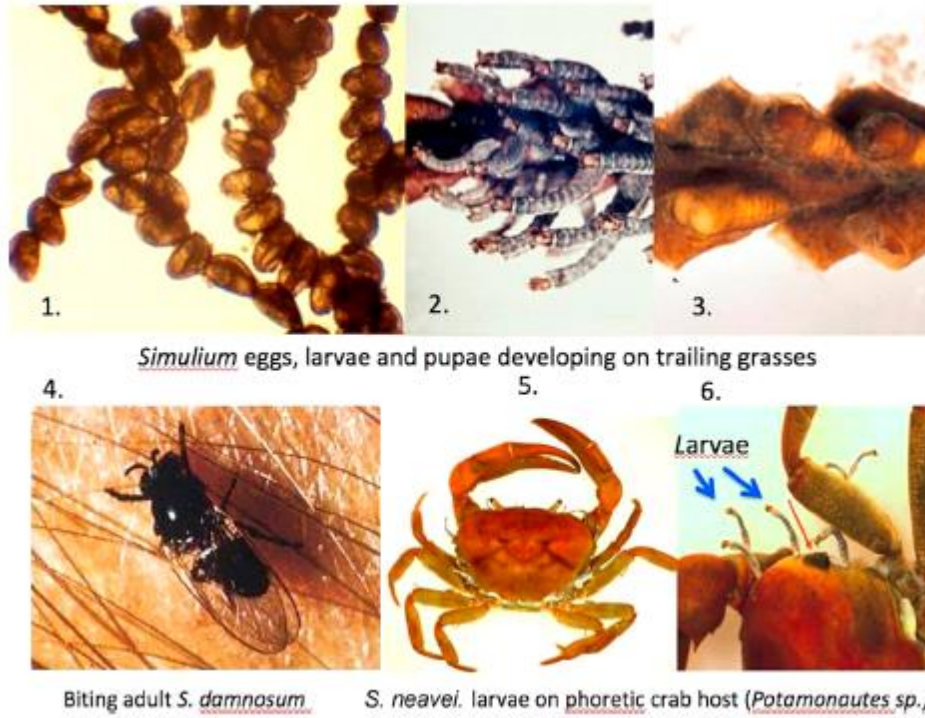
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Figure 2. Stages of the *Onchocerca volvulus*: (1.) microfilaria (about 0.2-0.3 mm long), (2.) adult males (1.5-4.5 cm), (3.) infective third-stage larva (0.7-0.8 mm); (4.) adult females (30-60 cm), (5.) an onchocercoma with cut adult females, (6.) 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).

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1923 Figure 3. *Simulium damnosum* s.l. stages: (1.) Masses of eggs Niger, Guinea, photo R. Garms, 1963), (2.)

1924 larvae on trailing vegetation and (3.) pupae, St. Paul River Liberia (photo R. Garms, 1983). (4.) Adult

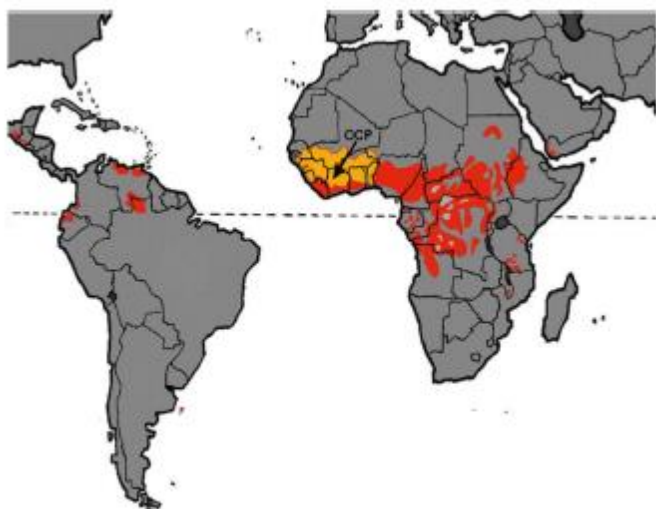
1925 *Simulium* s.l., photo R. Garms, Liberia, 1983), (5.) Drop of blood after pool-feeding by a *Simulium* (photo R.

1926 Gams, Guatemala, 1974).

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1932 Figure 4. Prevalence of onchocerciasis (marked red) in 30 sub-saharan African countries, in Yemen

1933 (Arabian Peninsula) and in 6 countries of central and south America. The area of the Onchocerciasis

1934 Control Programme (1974-2002) is marked yellow (modified, WHO, 1995).

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1940 Figure 5. Pathology of onchocerciasis. A. Skin pathology and microfilariae: (1.) depigmentation, (2.)
1941 dermatitis, (3.) lichenification and hyperpigmentation (sowda) (Brattig, 2004; photo D.W. Büttner, Liberia
1942 1995), (4.) microfilariae in a histological section of skin (photo D.W. Büttner, Liberia, 1999), (5.)
1943 microfilaria released *in vitro* from a skin snip (photo N.W. Brattig, 2000); B. Onchocercomata (6.) nodules
1944 in the torso of a man (photo D.W. Büttner, Liberia, 1985), (7.) nodule in the leg of a boy (photo R. Garms,
1945 Liberia, 1971), (8.) A bisected onchocercoma with adult females (Brattig, 2004).

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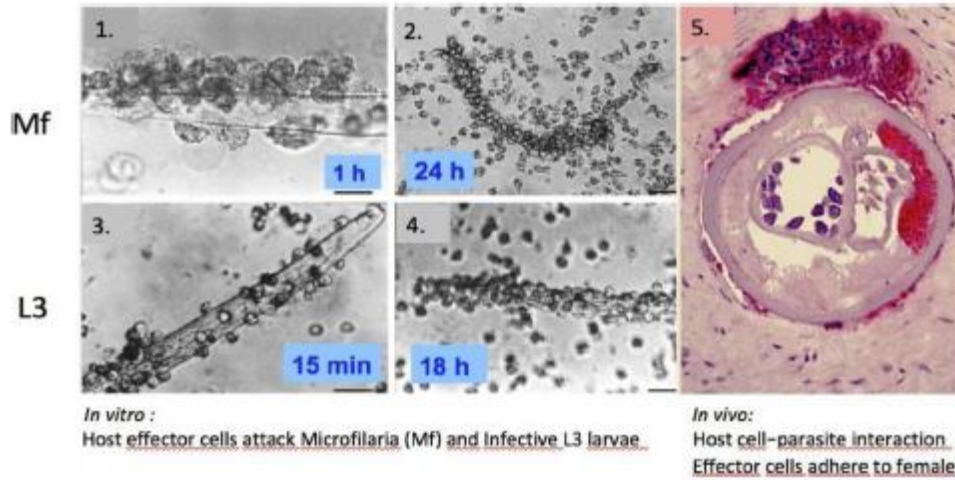
1951

1952 Figure 6. Eye pathology (River blindness). (1.) Two onchocercomata in the forehead of a young child
1953 which can release microfilariae in the close proximity of the eyes (DW Büttner, Liberia,1993), (2.) cornea
1954 opacification,sclerosing keratitis (R. Garms, Kouroussa, Guinea, 1963), (3.) man blinded by onchocerciasis
1955 guided by a child (photo R. Garms, Sérékoroiba Guinea, 1963). Microfilariae releasing the onchocercoma
1956 can infiltrate the eye and can lead to visual impairment and blindness.

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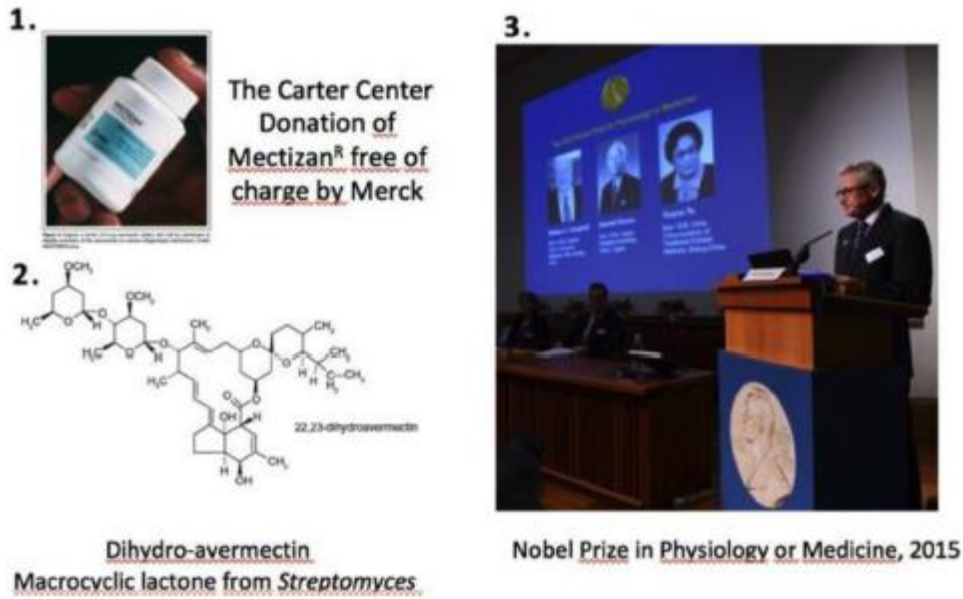
1961 Figure 7. Host-parasite interaction. (1., 2.) time-dependent *in vitro* attack of microfilariae (Mf) by human
1962 eosinophilic effector cells (3., 4.) and of infective 3rd stage larvae (L3) (modified figures from Brattig,
1963 2004), (5.) Host neutrophilic granulocytes assembled at the surface of a female in a section of an
1964 onchocercoma with *Wolbachia* in the lateral cords of the female; the *Wolbachia* were stained with
1965 antibodies against *Wolbachia* heat shock protein 60, the neutrophils with antibodies against defensin
1966 (Brattig et al., 2001).

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1972 Figure 8. Container with Ivermectin (dihydro-ivermectin), the principal drug against onchocerciasis (1.);

1973 (2) the chemical formula: a macrocyclic lactone, synthesized by *Streptomyces* sp., administered as

1974 *Mectizan*[®] (Merck Inc.) is donated free to millions of onchocerciasis patients organized by the Carter

1975 Center. (3.) In 2015, the Nobel Prize in Physiology or Medicine was awarded at the Karolinska Institute to

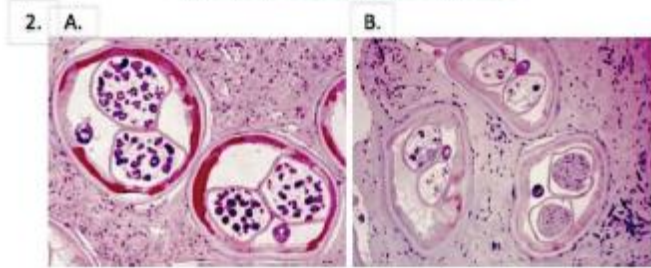
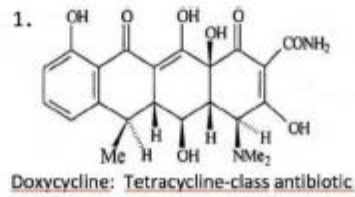
1976 *William C. Campbell* and *Satoshi Ōmura* for their discovery of the anti-filarial compound Ivermectin.

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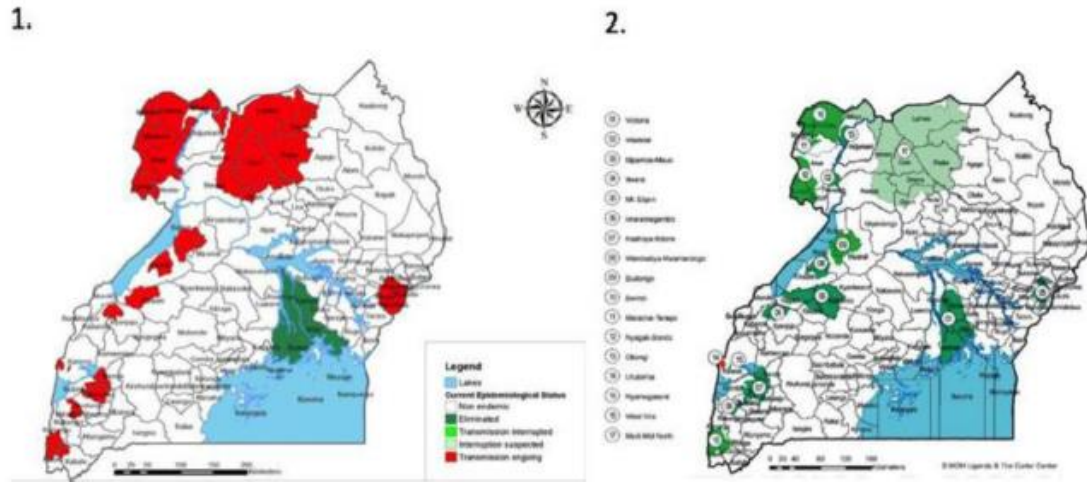
1982 Figure 9. Antibacterial doxycycline, (1.) a tetracycline-class polycyclic antibiotic agent kills *Wolbachia*
1983 endobacteriae in *Onchocerca* microfilariae and is introduced for treatment of onchocerciasis in 2003
1984 (Hoerauf et al., 2001; Walker et al., 2015). (2.) Sections through onchocercomata (A.) from an untreated
1985 patient which comprise *Wolbachia* stained red in the cords and (B.) females in an onchocercoma from
1986 doxycycline-treated patients with depleted *Wolbachia* (Brattig et al., 2001).

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1993 Figure 10. Progress of onchocerciasis elimination in Uganda by 2019. Comparison of transmission in 1992
 1994 (1.) and in 2019 (2.) In 1992 (1.), only the historical large Victoria Nile focus (green) had been eliminated
 1995 after intensive vector control activities. In 2019 (2.), onchocerciasis had been very successfully eliminated
 1996 from 15 (green) of the original 17 foci, transmission was possible still ongoing in the Madi Mid North focus
 1997 (focus 17; light green) and still active in the small Lhubiriha focus on the border with D.R. Congo (focus 14;
 1998 red) (copyright MOH Uganda and The Carter Center; 2019 kindly provided by Moses Katarbarwa, 2020).

1999

2000