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Onchodermatitis: where are we now?

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Abstract (172 words)

Onchocerciasis causes debilitating pruritus and rashes as well as visual impairment and blindness . Prior to control measures, eye disease was particularly prominent in savanna areas of sub-Saharan Africa whilst skin disease was more common across rainforest regions of tropical Africa. Mass drug distribution with ivermectin is changing the global scene of onchocerciasis. There has been successful progressive elimination in Central and Southern American countries and the World Health Organization has set a target for elimination in Africa of 2025. This literature review was conducted to examine progress regarding onchocercal skin disease. PubMed searches were performed using keywords "onchocerciasis", "onchodermatitis" and "onchocercal skin disease" over the past eight years. Articles in English, or with an English abstract, were assessed for relevance, including any pertinent references within the articles. Recent progress in awareness of, understanding and treatment of onchocercal skin disease is reviewed with particular emphasis on publications within the past 5 years. The global burden of onchodermatitis is progressively reducing and is no longer seen in children in many formerly endemic foci.

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1. Introduction

Onchocerciasis, caused by infection with the filarial worm *Onchocerca volvulus,* is one of the eleven neglected tropical diseases (NTDs) recently targeted for elimination by the World Health Organization (WHO) [1]. More than 99% of all cases are concentrated in 28 countries in sub-Saharan Africa. Small foci also occurred in the Americas, but there has been successful progressive elimination in this region and infection is currently found in a single large transmission zone (the "Yanomani area") which straddles the border of Venezuela and Brazil [2]. Small foci of infection also persist in Yemen [3].

Historically onchocerciasis was better known for its clinical effects of visual impairment and blindness, prompting its alternative name of “river blindness”. Over recent years, however, there has been significantly increased awareness of the skin manifestations associated with this disease and indeed the main clinical manifestations of onchocerciasis in the twenty countries formerly covered by the African Programme for Onchocerciasis Control (APOC) were related to skin disease [4].

Currently the WHO estimates that 198 million people are at risk of infection, though this number may increase as the mapping of areas of low transmission is finalised [5]. The Global Burden of Disease (GBD) Study 2013 estimated a global prevalence of 17 million infected cases [6]. Democratic Republic of Congo (DRC) had the highest number of onchocerciasis cases at 8.3 million [7]. In its 2015 iteration, the GBD collaborators estimated an overall prevalence of 15.53 million, comprising 12.22 million with skin disease and 1.03 million cases with vision loss due to

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onchocerciasis [8]. The most recent available data in GBD Study 2016 estimates a global prevalence of 14.65 million [9].

When ivermectin was first licensed for human use in 1987 Merck, Sharp and Dome (MSD), now known as Merck & Co. Inc., made the unprecedented decision to donate the drug (Mectizan®) to the world to treat onchocerciasis for as long as needed and it has remained the mainstay of treatment to date. In 2015 Dr. William Campbell, MSD and Prof. Satosh Ōmura of the Kitasato Institute shared the Nobel Prize in Physiology or Medicine for their development and use of ivermectin for onchocerciasis [10].

APOC was launched in 1995 with the objective of removing onchocerciasis as a public health and socio-economic problem in Africa [11]. The countries included in the programme were: Angola, Burundi, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo (DRC), Equatorial Guinea, Ethiopia, Gabon, Kenya, Liberia, Malawi, Mozambique, Nigeria, Rwanda, South Sudan, Sudan, Uganda and Tanzania. In 1997, APOC adopted community-directed treatment with ivermectin (CDTi) as its core strategy and the coverage and compliance with ivermectin steadily increased. In 2009 APOC changed its strategy to a target of elimination of the disease in Africa [12]. APOC closed at the end of 2015 and WHO established a new structure, the Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN), to co-ordinate technical support for activities focused on five neglected tropical diseases in Africa, including onchocerciasis elimination [13].

Onchocerciasis control and elimination efforts are among the most sustained, successful and cost-effective public health campaigns ever launched. By improving

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the general health of individuals they contribute to improvements in worker productivity, gender equality and education and hence they actively contribute towards achieving several of the Millenium Development Goals [14].

2. Cutaneous features

In 1989 Hay *et al.* reported an association between infection and skin changes associated with onchocerciasis in Ecuador [15]. The development of a formal clinical classification and grading system describing the cutaneous changes in onchocerciasis [16] facilitated more formal and extensive mapping of the true global burden of onchocercal skin disease (OSD). The categories of onchocercal skin disease delineated were *i)* acute papular onchodermatitis (APOD) *ii)* chronic papular onchodermatitis (CPOD) *iii*) lichenified onchodermatitis (LOD) *iv)* atrophy *v*) depigmentation and *vi)* hanging groin. The system was designed for easy use in the field by nurses or primary healthcare attendants, had good inter-observer variation *kappa* results and could be adapted for computer coding for large scale surveys.

A pre-control population survey of 6,790 residents in savanna mesoendemic villages in Kaduna State, northern Nigeria [17] where onchocercal blindness was common, revealed that 38.6% of the residents aged five and above complained of itching with normal skin or had one or more forms of onchocercal skin disease including nodules. The presence of nodules was the most common finding (21.2%), followed by atrophy(6.1% of those <50 years), APOD (3.4%), depigmentation(3.2%) and CPOD (2.3%). A further 9.5% of residents complained of itching but had clinically normal skin. Atrophy, hanging groin and nodules were more common in females, whereas APOD was more common in males. After controlling for age and sex, microfilarial

positivity was a risk factor for CPOD, depigmentation, hanging groin and nodules (OR 1.54, p = 0.046; OR 2.29, p = 0.002; OR 2.18, p = 0.002 and OR 3.80, p = <0.001 respectively). Similar though weaker odds ratios were found with microfilarial load *per se*.

The first multi-country study to explore OSD across Africa comprised seven rainforest or savanna-forest mosaic areas where onchocercal blindness was not common [18]. Following a census, individuals were randomly selected for examination in five of the study sites, though protocol deviation in the other two sites meant that individuals were asked to come to a central point for examination. Overall, onchocercal skin lesions (excluding nodules) affected 28% of the population aged five years and above. The commonest type of OSD was CPOD (13%), followed by depigmentation (10%) and APOD (7%). The prevalence of itching increased with age until 20 years and then plateaued, affecting 42% of the population aged 20 years and above. The prevalence of any onchocercal skin lesion and/or itching combined showed a very high correlation with the level of endemicity (as determined by the prevalence of nodules) of r = 0.8, p<0.001).

In Yemen an atypical and severe form of onchodermatitis known as *sowda* (or lichenified onchodermatitis) is prominent and use of ivermectin has concentrated on treating skin disease in this country. *Sowda* is common in older children, teenagers and young adults but current expertise now suggests that all ages, including the elderly can be affected [19]. Typically *sowda* presents as an extremely itchy hyperpigmented plaque or plaques on one leg; less commonly both legs or an arm or shouder can be involved. There is also often marked rubbery enlargement of the draining lymph nodes. Eye disease and palpable subcutaneous nodules are uncommon in Yemen. A general concept is that onchocerciasis has a spectrum of

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131 skin changes, with *sowda* representing one end of a clinico-parasitological spectrum
132 with low parasite loads and high levels of immune response.

133 A pre-control study in Edo State, Nigeria examined 2,020 individuals who had
134 visited primary health centres in each community and were recruited using simple
135 random sampling. The area was hyperendemic for onchocerciasis with a skin snip
136 positivity rate of 83%. The prevalence of depigmentation was very high at 87.5%,
137 itching was 84.16% and nodules 75.42% [20]. Another pre-control study in Anfilo
138 District of West Wellega, Ethiopia used a multistage sampling technique and a total
139 of 1114 individuals ≥ 15years were examined [21]. The prevalence of positive skin
140 snips was 74.8% and nodules 12.1%. The prevalence of pruritus was 64.3%, leopard
141 skin (19.1%), "skin lesions" 11.3%, lymphadenopathy 16.4%, and hanging groin the
142 least prevalent at 5.2%. The overall prevalence of pruritus and/or these clinical signs
143 was 26.4%, being more prevalent in males (32.4%) than in females (20.8%, $p<0.05$).
144 A study in Enugu State, Nigeria revealed lichenified onchodermatitis was the most
145 common clinical manifestation of onchocerciasis, occurring in 42/119 (35.29%) of
146 infected persons (as denoted by the presence of palpable onchocercal nodules) [22].

147 There is a paucity of literature exploring concurrence of skin and eye morbidities. In
148 a hyperendemic area of Cameroon, with a 63% nodule prevalence among males
149 aged ≥ 20, individuals aged 5 years and older were invited to present themselves at
150 a central point and 765 people were examined [23]. Onchocercal visual impairment
151 (which included low vision and blindness) and depigmentation were found to concur
152 significantly (OR 9.0, 95% CI 3.9-20.8) which was partly explained by age and
153 exposure to infection (OR 3.0, 95% CI 1.2 - 7.7). Host immune characteristics such
154 as the HLA-DQ alleles associated with depigmentation [24] might play a role in the
155 pathogenesis of both depigmentation and visual impairment.

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3. Imported onchodermatitis

Growth in international travel and immigration means patients with onchocerciasis may be diagnosed in countries in the western world but it is probably under-reported because of its relatively non-specific presentations and limited awareness among physicians practising outside endemic countries.

A retrospective study of 6,168 patients diagnosed with one or more NTDs at a Tropical Medicine Referral Unit in Madrid, Spain between 1989 -2007 found that onchocerciasis was the most common NTD in immigrants [25]. A diagnosis of definite onchocerciasis was based on positive skin snips *or* pruritus +/- skin lesions suggestive of onchocerciasis and a positive Mazzotti test (performed in patients with negative skin snips and no evidence of ocular onchocerciasis). Probable onchocerciasis was diagnosed in immigrants in the presence of pruritus +/- suggestive skin lesions and response to treatment with ivermectin. Onchocerciasis was present in 240 (9.1%) of immigrants (169 definite and 71 probable cases). All but two cases in immigrants occurred in African patients, with the majority coming from Equatorial Guinea (213/240, 88.8%), a reflection of the historical links between that country and Spain. The other countries of origin were Cameroon, Nigeria, Angola and Zaire and one each from Republic of Guinea, Mali, Togo, D.R. Congo, Ghana, Sierra Leone, Sao Tome, Ivory Coast, Colombia and Ecuador. The number of new cases of onchocerciasis per new African immigrants significantly decreased each year of the over the period of the study. In a further group of immigrants who had travelled back to endemic countries to visit family and friends, there were 14 more cases of onchocerciasis.

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With respect to the group of travellers in this study, definite onchocerciasis was diagnosed in those with positive skin snips *or* positive serology in the presence of pruritus +/- suggestive skin lesions. In contrast to immigrants, who presumably had had long periods of exposure to infection prior to immigration, the number of travellers with onchocericaisis was much smaller at only 17. Of these, 16 had had a trip duration > 3months, range 3-336 months, and 1 patient had travelled for 1 month). All had travelled to sub-Saharan Africa and some patients had visited more than one country during their trip.

A literature search for English and French articles between 1994 and 2014 identified 29 cases of onchocerciasis in migrants from endemic countries and in expatriates and travellers from non-endemic areas [26]. The most frequent clinical manifestations in these cases plus the authors' index case were pruritus (76.7%), unilateral leg or forearm swelling (43.3%) and rash (40%), whereas only two (6.9%) complained of eye symptoms. Eosinophilia was very common (92%). Eye symptoms, lymphadenopathy and chronic dermatitis were seen more frequently in migrants whereas rash and arm swelling were more frequent in returned travellers and expatriates.

A review of 31 filarial cases in a French University Centre between 2002 and 2011 revealed 4 cases due to onchocerciasis comprising 3 immigrants from Cameroon, Sierra Leone and Senegal with onchodermatitis and one traveller from Central Africa with arm swelling [27]. Another review of 289 NTD cases from 2000 and 2015 at the Infectious and Tropical Diseases Unit, Florence, Italy revealed just 2 cases of onchocerciasis from sub-Sarahan Africa with typical cutaneous manifestations and they both presented within the first five years of the review [28].

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In a group of 27 migrants who came to Israel from an onchocerciasis-endemic area in Ethiopia and who were referred for an atopic eczema-like rash, 14 had positive skin snips or positive IgG_4 antifilarial serology [29]. The migrants who did not have laboratory proof of infection had similar clinical findings. Considering the group as a whole, patients' main complaint was relentless pruritus, which began with an average of 2.2 years after immigration, which a range of 1 year prior to immigration to 11 years after immigration. The most common finding was LOD in combination with atrophy and depigmentation 8/27 (30%), followed by CPOD 7/27 (26%).

The largest case series of imported onchocerciasis to date reviewed 400 cases attending a reference clinical unit in Madrid, Spain [30]**.** All the migrants came from sub-Saharan countries and the most frequently occurring dermatological symptom was pruritus.

4. Burden of Disease

Onchocerciasis is mainly a non-fatal disease and its public health impact is therefore best understood in terms of DALYs (DALYs = Years of Lives Lost (YLL) + Years Lived with Disability (YLD)). Both skin and eye disease caused by onchocerciasis result in a decrease in productivity [31]. Initially only the burden from onchocercal eye disease was considered in global estimates, but the burden from "itch" was first included in the GBD Study 1990, based on data from the multicountry prevalence study in Africa [18]. Physical onchocercal skin disease manifestations have also been included since the GDB Study 2010.

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The GBD study 2013 estimated that onchocerciasis was the sixth highest cause of NTD-related YLDs globally and it was ranked highly in the top 10 leading causes of YLDs in Liberia, Cameroon and South Sudan. In all these countries, the burden from onchocerciasis is predominantly due to onchocercal skin disease [7]. In its 2015 iteration the GBD Study provided an overall global estimate of 1,135,700 (YLDs) due to onchocercal infection [8]. In the GBD Study 2016, onchocerciasis was ranked as the first leading cause of YLDs for Liberia, as the second leading cause for DRC and South Sudan, the fifth for Cameroon and the sixth cause for both Central African Republic and Sierra Leone [9].

5. Immunopathogenesis

Filarial parasites are known to induce a large range of immunoregulatory mechanisms to evade and down-modulate the host's immune system in order to ensure the parasite's survival [32]. Such mechanisms include induction of regulatory T cells, which promote high levels of non-complement binding IgG_4 [33]. Survival of *O. volvulus* within the human host is thus the result of a complex interplay with the host's immune system, which itself may be dependent on genetic factors, and pathology ensues when pro-inflammatory processes override any immunomodulatory effects.

Wolbachia are endosymbiotic bacteria found in most human filariae,(except *Loa loa),* and appear to be essential for the filarial worm's fertility and survival. In an experimental murine model *Wolbachia* were found to be an essential component in the development of anterior segment onchocercal eye disease and mediated corneal

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pathology by activating Toll-like receptors on mammalian cells, which in turn stimulated recruitment and activation of neutrophils and macrophages [34].

Recruitment of neutrophils by *Wolbachia* around adult female worms in *O. ochengi* infection in cattle has been shown to confound eosinophil degranulation and may act to protect the adult worms from the host immune system [35]**.** Furthermore the major inflammatory motif of *Wolbachia* lipoproteins are able to directly activate human neutrophils *in vitro* [36].

The formation of Neutrophil Extracellular Traps (NETS), a process referred to as NETosis, is now regarded as a novel effector mechanism consisting of extrusion of nuclear contents with neutrophil-derived granular and cytoplasmic proteins which may limit microbial spread by entrapment and limit collateral inflammatory tissue damage by entrapping and degrading soluble cytokines and chemokines. Tamarozzi *et al.* visualised extracellular NETS and neutrophils around adult *O.volvulus* in nodules excised from untreated patients but not in nodules from patients treated with doxycycline which kills *Wolbachia.* [37]. In addition whole *Wolbachia* or latex microspheres coated with a synthetic *Wolbachia* lioprotein of the major nematode *Wolbachia* TLR2/6 ligand, peptidoglycan associated lipoprotein, induced NETosis in human neutrophils *in vitro* and TLR6 deficient mice were used to demonstrate that TLR6 was essential for this process. It is possible that NETosis triggered by *Wolbachia* is an anti-parasite response to limit the density of tens of thousands of uterine-released microfilariae (mf) produced daily by each adult female worm and that *Wolbachia*-induced NETs may directly modify inflammatory processes in the skin.

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TGF-β was preferentially observed in the skin of infected individuals with "generalized" or hyporeactive onchocerciasis and was reduced in patients with the hyperreactive form of onchocercal skin disease (LOD or *sowda*) [38]. In a similar vein, "hyperreactive onchocerciasis" has been found to be characterized by a combination of accentuated Th17 and Th2 immune responses and reduced regulatory T cells [39].

Secretory extracellular superoxide dismutase (*Ov*ES-SOD) from *O. volvulus,* which is found in the excretory/secretory products of adult worms, was able to trigger responses in sera from onchocerciasis patients, with IgG titres significantly higher in sera from individuals with the "hyperreactive" form compared with sera from those with the generalised form of onchocerciasis [40]. The authors proposed that, in addition to its role in superoxide anion reduction in the extracellular space, the *Ov*EC-SOD may help regulate inflammatory responses.

In patients who became mf-negative after repeated ivermectin treatments, parasite-specific cellular immune responsiveness and Th1 and Th2-type cytokine production becomes reactivated. Similarly, mf-negative patients after repeated ivermectin treatments have enhanced pro-inflammatory chemokines and reduced regulatory chemokines and cytokines [41].

Immunocytochemical examination of nodules using immuno-markers for blood and lymphatic vessels has suggested an intimate relationship between adult *O. volvulus* worms and lymphatic vessels, including the likely proliferation of lymphatic endothelial cells [42]. This has raised the possibility that the lymphatic system may be more involved in the migration of adult *O. volvulus* worms than was previously believed and may explain the lymphoedema which is sometimes seen in

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296 onchocerciasis [16]. Microfilariae, which have been documented in the blood in
297 heavily infected onchocerciasis patients and after treatment, might also migrate via
298 the lymphatic system. Angiogenesis and lymphangiogenesis within nodules is
299 characterised by the expression of CXCL 12, CXCR4, VEGF-C, Angiopoietin-1 and
300 Angiopoietin-2. A proportion of macrophages in the inflammatory infiltrate in nodules
301 were positive for the lymphatic endothelial cell marker Lyve-1 and some were
302 integrated into the endothelium of the lymphatic vessels [43] and angiogenesis and
303 lymphangiogenesis within nodules may provide new targets for drug treatment.

304 **Imported skin disease pathogenesis**

305 Baum et al. [29] noted a long interval for some Ethiopian immigrants in Israel before
306 they developed any sysmptoms and hypothesized that environmental factors
307 resulting from immigration from a developing to an industrialised country triggered an
308 immunological shift to strong T-helper (Th) 2 responses, in a similar manner that an
309 increased prevalence in asthma had been noted in Ethiopian migrants several years
310 after migrating to Israel.

311

312 **6. Immunogenetics**

313 HLA class II variants may influence susceptibility to infection by *O.volvulus* and
314 subsequent host immune responses causing pathology. Correlation between allelic
315 variants of HLA-DQA1 and HLA-DQB1 and various forms of onchocercal skin
316 disease have previously been documented in a Nigerian population [24] and recently
317 a protective role of DQA1*0401 against *O.volvulus* infection has been demonstrated
318 in both Cayapas Amerindians and Afro-Ecuadorians. Furthermore HLA-DQA1*0102

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and *0103 seemed to represent risk factors for infection in Afro-Ecuadorians and HLA-DQA1*0301 was a possible susceptibility allele in the Cayapas population [44].

7. New diagnostics

The quest for elimination of onchocerciasis requires newer, more sensitive diagnostic tests to verify that transmission of infection has been suppressed or interrupted. Such tests differ from previously used tests to diagnose infection in individuals.

Detection of parasite in humans

The sensitivity of the skin snip assay has been increased by replacing microscopic examination of the snip with detection of amplified parasite DNA. Most assays target the tandemly repeated sequence in the *O.volvulus* genome called the 0-150 repeat. Real-time PCR and isothermal loop amplification (LAMP) assays have also been developed [45], [46]. On comparsion of three PCR methods for evaluating onchocerciasis elimination efforts in areas co-endemic with other filarial nemaodes, the qPCR-O150 assay was deemed to be more appropriate for evaluating skin snips of OV-16 positive children when deciding when to stop MDA [47]. A novel O-5S qPCR assay targeting the *O.volvulus* O-5S rRNA gene, had 100% specificity and proved more sensitive than O-150 qPCR assay (66.5% vs 39% positivity rate) [48].

Serological tests to detect exposure to *O.volvulus*

The Ov16 ELISA is now recommended by WHO guidelines for demonstrating the interruption of transmission of *O.volvulus* [49]. According to these guidelines, the serological threshold for stopping MDA is an Ov16 antibody prevalence of < 0.1%

among children under 10 years of age who act as sentinels for recent infection, but the current tools are not reliably specific enough and an Ov16 threshold of < 2% may ultimately prove to be the most reliable serological threshold for stopping MDA [50]. Current assays have focussed on IgG_4 detection but the IgG_4 response takes time to develop and thus will not immediately reflect recent exposure. Two commercially available rapid diagnostic tests (RDTs) are a single Ov16 test and a combination test using Ov16 and the *W. bancrofti* antigen Wb123 [51]. The SD BIOLONE Ov16 rapid test was successfully field-tested in Senegal [52].

Detection of parasite in vector black flies

The O-150 PCR DNA amplification assay is the most widely used assay to screen pools of flies to verify elimination of transmission. Instead of using human bait to catch the vector black flies, as has been done in the past, the Esperanza Window Trap has been used in Mexico with success [53],[54] and such traps are being evaluated for use in Africa [55].

Detection of biomarkers

Recent research has also produced assays to detect potentially viable adult worms such as specific metabolites produced by female worms [56], [57] and detection of parasite microRNA in the blood [58], [59] though the latter may not be present in sufficient concentration to act as a biomarker for infection [60].

8. Treatment

Effect of ivermectin on cutaneous disease

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Ivermectin, a macrocyclic lactone, interacts with post-synaptic glutamate-gated chloride channels resulting in paralysis of mf, which are therefore transported to regional lymph nodes and killed by effector cells. Release of uterine mf is also temporarily inhibited.

The first multi-country study on the short-term effect of ivermectin on onchocercal skin disease in Africa was performed by Brieger and colleagues in 4 study sites in Nigeria, Ghana and Uganda [61]. They followed up rural villagers for 18 months and found that from 6 months onwards, the prevalence of severe itching was reduced by 40-50% among those receiving ivermectin compared to the trend in the placebo group. The prevalence of APOD, CPOD and LOD combined was significantly reduced in the ivermectin group at 9 months and the severity at 3 months. Furthermore there was no difference between ivermectin given at 3, 6 or 12 monthly intervals.

The first assessment of the effect of mass treatment with ivermectin in the Onchocerciasis Elimination Program for the Americas was Banic *et al*.'s report [62] in the hyperendemic Yanomani communities of Roraima State, Brazil. Pre-treatment, 18/103 individuals (17.5%) had atrophy +/or "scaling" of the skin. After 3 years of twice yearly ivermectin therapy, there was a very significant reduction in the prevalence and intensity of infection by skin snips but there was no reduction in the prevalence of nodules or onchodermatitis.

The first multi-country study on the longer term impact of ivermectin on onchocercal skin disease involved 7 study sites in Cameroon, Sudan, Nigeria and Uganda [63]. Two cross-sectional surveys were performed at baseline and after 5 or 6 years of CDTi. In phase I, 5,193 individuals were examined and 5,180 people participated in

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388 phase II. Within each study site, 10 villages underwent a census to cover
389 approximately 1,500 persons. Individuals aged 5 years and above were asked to
390 present themselves for examination at a central point until a sample size of
391 approximately 750 was obtained. The effect of 5 or 6 rounds of annual CDTi was
392 profound with significant ($p < 0.001$) reductions in the odds of itching (OR 0.32),
393 APOD (OR 0.28), CPOD (OR 0.34), depigmentation (OR 0.31) and nodules (OR
394 0.37). Reduction in the odds of LOD was also significant (OR 0.54, $p < 0.03$).

395 In Anfilo district, Western Ethiopia, 971 participants aged 15 years and above were
396 examined after 6 years of annual CDTi and the prevalences of microfilaridermia,
397 pruritus, leopard skin, nodules and hanging groin were reduced by 45.6%, 54.4%,
398 61.3%, 77.7% and 88.5% respectively [64].

399 In a previously hyperendemic rainforest area with a nodular rate of ≥ 40% in
400 Anambra State, Nigeria, a cross-sectional survey of 894 subjects after a decade of
401 CDTi identified nodules in 86 (9.62%) persons and 186 (20.81%) had one or more
402 forms of onchocercal skin disease. There was a total absence of OSD in children <
403 10 years old and only 5 (5.43%) with OSD in the second decade of life, indicative of
404 some encouraging success of the CDTi programme. The rate of APOD however
405 increased with age up to the third decade and decreased thereafter suggesting on-
406 going transmission either due to poor compliance or low coverage of treatment. All
407 the individuals with APOD had missed the annual ivermectin treatment more than
408 once during the programme. CPOD, LOD, ATR and DPM all increased with age for
409 both sexes [65].

410

411 In 2015 after more than 15 years of CDTi in the West Region of Cameroon, a cross-
412 sectional survey of 2,058 individuals aged 5 years and above was performed to

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assess progress towards elimination. The weighted prevalence of positive skin snip results was 5.5% and that of nodules 2.1%. The weighted prevalence of skin disease excluding nodules was 1.7% and varied from 1.1% in men to 2.2% in women. Of note, treatment compliance was again found to be poor with only 39.3% of participants declaring they had taken five treatments during the last five years [66].

Prior to control measures on the island of Bioko, Equatorial Guinea, a survey in the mid 1980s reported that 28.8% of the study population suffered from dermatitis, pigmentation changes and cutaneous atrophy. After vector elimination in 2005 and more than 16 years of CDTi on Bioko Island, a community-based cross-sectional survey was performed in 2014, including a full cutaneous examination [67]. Although these workers found that 50.4% individuals reported never having taken ivermectin and only 28% had taken it more than twice within the past 5 years, there was a reduction in pruritus and skin lesions (14.9% complained of pruritus, 3% had nodules, 1.3% had "onchodermatitis" and a further 1.8% had leopard skin. Nodules were more common in subjects older than 10 years and pruritus was more frequently found in adults (17.6%) than children (5.9%, p=0.002).

With standard annual dosing, ivermectin was initially thought to have minimal macrofilarical activity, but recent mathematical modelling suggests that multiple doses of ivermectin, even at standard (150µg/kg) doses and annual frequency, can have a modest permanent sterilizing effect after 4 or more consecutive treatments. The life expectancy of adult *O.volvulus* was reduced by 50% and 70% respectively after 3 years of annual or 3-monthly treatment with ivermectin [68]. There have been reports of suboptimal responses in some patients in Ghana after repeated treatment. In a Ghanian study of 42 patients treated with ivermectin and 204 randomly selected

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individuals, a significantly higher *MDR1* variant allele frequency was noted in suboptimal responders (21%) than in patients who responded to treatment (12%) or the random population sample (11%). *CYP3A5*1/CYP3A5*1 and CYP3A5*1/CYP3A5*3* genotypes were also significantly different for responders and suboptimal responders, suggesting a possible role of these haplotypes in an individual's response to ivermectin [69].

In Yemen, ivermectin was initially distributed only to *sowda,* (or lichenified onchodermatitis), cases four times a year, but a mass drug distribution program to treat the entire community has now begun. In the northern endemic valleys, there has been a marked reduction in the number of *sowda* cases from more than 50% pre-drug treatment to approximately 6% and in most areas it is uncommon to find new cases of *sowda* [19].

Effect on imported skin disease

In Baum *et al.'s* study of Ethiopian immigrants to Israel [29], both patients with confirmed, and those with suspected, onchocerciasis, responded equally to ivermectin with reduction in itching and lichenification. Overall 9/17 (52%) had remission of more than12 months , 5/17 (30%) had temporary relief lasting 3 -12 months and required repeat treatment and 3/17 (18%) did not respond to treatment.

Puente's case series [30] reported that ivermectin was used as first-line therapy and adverse events were described in 11 (3.2%) cases.

Effect of ivermectin on psychosocial and socio-economic aspects of onchodermatits

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In the past sufferers with OSD were considered unclean and were stigmatised because of fear of transmission of OSD, resulting in social ostracism. OSD has also been associated with reduced productivity [31], difficulties breastfeeding, poor school attendance and reduced marriage prospects for affected teenage girls. Vlassof *et al.'s* pre-control multicountry study in Africa had identified that one third of residents with OSD reported low self-esteem, about half of those affected perceived onchocercal skin disease as a very serious health issue and 1-2% had even considered suicide [70]. Higher levels of stigma were noted in individuals with APOD, CPOD or LOD than persons with depigmentation.

After a decade of CDTi, a cross-sectional survey of 894 subjects in Anambra State, Nigeria, identified that itching (40%) and onchocercal skin manifestations (34.3%) remained the most troublesome symptom and sign for this population and social seclusion (or stigmatisation) (34.3%) the most worrisome consequence. A preponderance of onchodermatitis on the limbs (visible area of the body to others), plus involvement of the buttocks (an area considered 'private') were deemed contributory factors for the psychological impact of the skin disease [71]. In a random sample exit interview of 594 /40,914 persons treated with ivermectin in Ezinihitte, Nigeria, (an area with predominantly onchocercal skin disease) the most common reason cited for seeking treatment was "to gain treatment and prevention of skin problems" [72]. The fifth and sixth rank-order reasons were "to prevent hanging groin" and "to prevent/relieve enlargement of the scrotum or clitoris". Genital lymphoedema is caused by filarial blockage of lymphatics in the pelvic region. Although both hanging groin and genital lymphoedema have low prevalences they have important implications for married life and sexuality.

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A multicountry study in Africa in Cameroon, DRC, Nigeria and Uganda after at least 4 years of CDTi used random sampling of household treatment records to capture factors that reflected individuals' perception of benefits of CDTi. In this study, 84.7% of respondents indicated that ivermectin treatment had many benefits: social benefits included improved ability to work, peer acceptance and improved school attendance; individual benefits included self-respect/esteem, election to political office and improved domestic relationships and health benefits included improved skin texture and less ill health [73].

A subsequent multicountry study using multi-stage sampling after 7 -10 years of CDTi revealed that although people with OSD were still stigmatised and people still feared sexual intimacy with affected persons, avoidance of people with OSD had decreased from 32.7% before CDTi activities to 4.3% [74]. People who had lived in the community for less than 5 years tended to stigmatise those with OSD more than those who had lived in the community for longer and the youth stigmatised the most. Reasons given for avoiding people with OSD included "considered infectious", "looked ugly", "were irritating", "were dirty", "were scary" and "were embarrassing". An example of the changes in perception towards OSD is this quote from a young Nigerian man in a focus group discussion *"Although we know better now, there is still the fear that something like hanging groin is hereditary. Really, people no longer avoid sufferers so much but I know that here we think that if it gets to the stage where one's groin is hanging, then it will be hereditary. Before no-one would go into marriage with a girl whose mother had leopard skin because it was believed that she would develop it and no female would ordinarily marry a man whose father had hanging groin. But these things are changing now because we know better".*

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An interesting study asked schoolchildren aged 6-16 years to draw their perceptions of onchocerciasis and CDTi in their communities. Out of a total of 50 drawings generated, 30 pictures were categorised as showing symptoms of the disease which included rashes and swellings (nodules) and a further 5 represented multiple perceptions on symptoms, benefits and effects of treatment [75]. The results highlighted that children were cognisant of the external signs of onchocerciasis and the authors recommended that children be included in health promotion activities to maintain successful compliance with CDTi.

9. Update on Onchocerciasis Control Programmes and Elimination

Onchocerciasis Elimination Program for the Americas (OEPA)

Right from its outset in 1993, this programme used six monthly mass ivermectin distribution with a target coverage of 85% with the goal of elimination of onchocerciasis from the region. Ivermectin distribution four times / year was also used in some areas. WHO has recently produced guidelines to help countries know when they can safely stop MDA and transition to a period of post-treatment surveillance (PTS) based on entomological evaluation to detect infection in the black fly vector and serological evaluation in humans to detect the presence of antibodies to *O. volvulus* Ov16 antigen [49]. When all foci in a country have satisfactorily completed the PTS, the country may request a visit by a WHO verification team to assess elimination of transmission. By the end of 2012, transmission had been eliminated in 11 of the 13 foci in the Americas [6]. Elimination was first demonstrated by Colombia in 2103 [76], followed by Ecuador in 2014, Mexcio in 2015 and Guatemala in 2016 [77]**.** Elimination of transmission in Ecuador was particularly

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gratifying as the main vector here, *Simulium exiguum*, was a very effective transmitter of infection and the skin and eye disease in this focus was probably the most severe in the Americas [78].

The remaining two onchocerciasis foci in the Americas form a single epidermiological transmission unit (the Yanomani Area) along the border between Brazil and Venezuela. There are challenges to treating the Yanomani Area which is a remote area and difficult to reach. Furthermore the Yanomani people can freely move across the country borders whereas program officials cannot, so increased political co-operation between the countries is needed.

African Programme for Onchocerciasis Control (APOC)

The African Programme for Onchocerciasis Control (APOC) initially focussed on control of the disease as a public health problem. It was uncertain whether ivermectin could actually interrupt transmission and eliminate the parasite in Africa as here the vectors are very efficient and the epidemiology very different with large endemic areas which were often not well defined. The first evidence that elimination of onchocerciasis with ivermectin treatment was feasible in Africa came from studies in Senegal and Mali published in 2009 [79] and 2012 [80] which led to a paradigm shift from one of control of the disease to a target of elimination.

A further encouragement came from Tekle's *et al's* report of a skin snip survey in 3,703 individuals above the age of one year performed after 15 -17 years of CDTi in Kaduna State, Nigeria. (These were the same villages where the onchocerciasis skin classification had originally been field-tested). These workers found that all examined individuals were skin snip negative, which was the first evidence from an APOC

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557 country that elimination of onchocerciasis infection with ivermectin might be feasible
558 in Africa [81]. Unfortunately Boko Haram activities interrupted fieldwork and
559 entomological evaluations are still awaited.
560
561 From its outset APOC included a small number of projects where it was judged that
562 local eradication of the vector would be possible and cost-effective and could be
563 combined with CDTi. The island of Bioko, Equatorial Guinea [82] and the Itwara
564 focus in Uganda [83] both achieved vector elimination. Bioko Island had no
565 subsequent reported cases of infection and a recent study on 5-9 year old school
566 children revealed no evidence of infection by skin snipping and blood spot for Ov16
567 and Wb123 IgG_4 [84]. Current WHO serological criteria for stopping MDA were
568 therefore met and 3 years of post-treatment surveillance are currently underway to
569 identify any new cases of infection.
570 The Abu Hamed focus in Sudan, which had predominantly the severe form of skin
571 disease *"sowda"* or lichenified onchodermatitis, was the first focus in Africa to have
572 successfully completed the entire WHO-recommended process to confirm
573 elimination [85].
574 In 2007 Uganda launched a national elimination policy based on twice yearly
575 ivermectin treatment and vector control/elimination. By 2017, 1,157,303 people in six
576 foci were living free of onchocerciasis which is the largest population to date
577 declared free under WHO elimination guidelines, providing further evidence that
578 elimination of onchocerciasis in Africa is possible [86]. Ethiopia, Mali, Niger and
579 Senegal also have eliminated onchocerciasis in subnational areas. Although APOC
580 faced certain challenges it achieved overall major success as a control programme
581 [11]. All areas where *O. volvulus* might be transmitted and where ivermectin has not

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been distributed in the past, now require careful 'elimination mapping' to determine whether they are onchocerciasis endemic or not so that appropriate treatment plans can be made [87].

Yemen

Although Yemen initially used a strategy of treating only symptomatic individuals with *"sowda"* or lichenified onchodermatitis, since February 2016 it has been using MDA with ivermectin in *sowda*-endemic areas with the goal of eliminating onchocerciasis in that country [88].

Challenges faced by APOC

APOC faced several challenges, especially in conflict and post-conflict situations and in areas co-endemic with *Loa loa.* In DRC for example, the country had been devasted by political unrest and two civil wars and even after the signing of peace in 2003, fighting continued in the eastern provinces. Although the annual therapeutic and geographical coverage of CDTi projects slowly increased from 2001 - 2012, targets could not be met [89]. In Sierra Leone, civil conflict also resulted in limited onchocerciasis control activities from 1991 -2002, but after the war, good CDTi was achieved between 2005 and 2009. In 2010, after 5 rounds of ivermectin, 10 out of 12 endemic districts had a >50% reduction in mf prevalence and 11 of 12 districts had ≥ 50% reduction in mean mf density among the positives, suggesting that Sierra Leone will now be on course to achieve elimination by the year 2025 [90].

Co-endemicity with *L. loa* has been another significant challenge for APOC. In areas co-endemic with loaisis, ivermectin treatment in people with high loads of *L. loa* mf can cause severe and occasionally fatal encephalopathy reactions. Little was known about the geographical distribution of loiasis in DRC at the start of CDTi projects and in 2004 adverse events in CDTi areas co-infected with loiasis resulted in 14 deaths

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607 [89]. Mass treatment was temporally halted whilst the situation was re-evaluated. A
608 rapid assessment procedure for *L. loa* which assesses an individual's history of eye
609 worm (RAPLOA) was subsequently introduced in co-endemic areas. If ≥ 40% of the
610 population report eye worm, this is deemed to pose an unacceptable risk of
611 encephalopathy and MDA is withheld from that area. Recently the LoaScope, a
612 mobile phone-based imaging device which can rapidly determine the mf density of *L.*
613 *loa* infections has proven useful in determining more accurately whether or not MDA
614 can safely proceed. In the Okola health district of Cameroon, persons with very high
615 *L.loa* microfilarial counts (>20,000 mf / ml) were thus able to be excluded form
616 ivermectin therapy and no serious adverse events occurred [91]. Individuals at risk of
617 ivermectin-related side-effects in loiasis- co-endemic areas may safely be treated
618 with doxycycline but a course of treatment (4-6 weeks) is required.

619 Additional challenges to APOC included cross-border transmission of infection.
620 Although Uganda has some areas clear of disease, conflict in the north of the
621 country meant that maximum control activities have only been carried out over the
622 past 3-4 years and cross borders areas continue to cause difficulties because of
623 delay in programmes in the DRC and South Sudan. A strategy meeting between
624 Uganda and DRC, initially triggered by the Ebola outbreak, led to improved cross-
625 border co-operation for onchocerciasis control and elimination [92] and lessons
626 learnt from the Sierra Leone/ Liberia and Guinea (Conakry) Mano River Union
627 collaboration on onchocerciasis should help with other neglected tropical disease
628 programmes in the future [93]. Although international borders that intersect endemic
629 regions present the biggest challenge, intra-country borders (e.g. administrative
630 districts, or loiasis-endemic and non-endemic areas) can also pose problems [94].
631 Migrant populations are also part of cross-border challenges. Non-compliance with

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632 treatment has been another issue is some areas [95] but can be improved using
633 traditional kinship structures [96]. Hostility towards health workers occurred during
634 the Ebola outbreak as some people feared they were responsible for spreading
635 Ebola [97].

636 **Health and economic impacts of MDA with ivermectin**

637 Using updated disability weights for visual impairment , blindness and troublesome
638 itching (0.033, 0.195 and 0.108 respectively), Coffeng *et al.* estimated that APOC
639 had cumulatively averted an impressive 19 million DALYs from 1995 up until 2015
640 [98]. This represented some 80% reduction in loss of DALYs for APOC countries,
641 though in reality the true burden averted by APOC is even larger still as these
642 updated estimates did not include disfiguring skin disease or other sequelae
643 potentially associated with onchocerciais, such as epilepsy and head-nodding
644 syndrome.

645 Redekop *et al.*considered mild and moderate skin disease and moderate and severe
646 vision loss and blindness and estimated that the global economic benefit
647 (productivity loss prevented) for the period 2011 - 2030 for onchocerciasis was 7.1
648 billion I$ (International dollars) if a target of elimination by 2020 was achieved [99].

649 GBD 2010 data has been used to estimate the global health impact of meeting the
650 London Declaration 2012 targets on NTDs [100]. Regarding onchocerciasis, for the
651 period 2011 - 2020, 7 million DALYs were averted and for 2021 - 2030, 12.6 DALYS,
652 giving a total of 19.6 DALYS averted over the entire period, compared to a
653 counterfactural scenario of no control/elimination programme. The projected health
654 benefits were thus deemed to justify the enormous effort involved. With respect to
655 Ethiopia, the GBD study 2015 data, estimated that the age-standardized DALY rates

for onchocerciasis have encouragingly decreased by a dramatic 66.2% between 1990 and 2015 [101] .

Using a mathematical dynamical transmission model called ONCHOSIM, Kim *et al.* simulated trends for the prevalence of severe itching, low vision and blindness in two scenarios of elimination of onchocerciasis in Africa versus a control scenario of continuing measures simply aimed at keeping the disease at a locally acceptable level [102]. Using the same vision disability weights as above but a disability weight for severe itching of 0.187 [103], [104] Kim and colleagues estimated that elimination of the disease in Africa would avert 4.3 million – 5.6 million (DALYs) over 2013 - 2045 compared with staying in the control mode. The decrease in the prevalence of severe itching was faster than those of low vision and blindness and the majority of DALYs averted were associated with the reduction in severe itching cases.

As ivermectin is a broad-spectrum anti-parasitic agent, it also has an effect on so-called off-target diseases, including soil-transmitted helminthiasis, lymphatic filariasis and scabies. Krotneva *et al.* [105] have estimated that between 1995 and 2010 annual MDA with ivermectin cumulatively averted about an extra 500 thousand DALYs from these co-endemic infections. This represents approximately an additional 5.5% relative to the total burden of 8.9 million DALYs averted from onchocerciasis, thus indicating that the overall cost-effectiveness of APOC is even higher than previously thought.

Effect on HIV

As HIV and helminth co-infection may be associated with a higher viral load and lower CD4+ cell counts, treatment with ivermectin could potentially benefit people living with HIV beyond simply treating the worm infection. Specific evidence for this

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680 to date is limited but there is no suggestion that anti-helminthic drugs are harmful for
681 HIV-positive individuals [106]. NTDs may also lead to a worse prognosis in TB and
682 malaria sufferers and further research on these interactions is needed [107].

683 **Changeover to ESPEN**

684 Successful integrated chemotherapy for both onchocerciasis (with ivermectin) and
685 lymphatic filariasis (ivermectin + albendazole) has been underway in some co-
686 endemic areas [108]. APOC has now been superseded by a new programme, the
687 Expanded Special Project for the Elimination of Neglected Tropical Diseases
688 (ESPEN) which aims to co-implement control activities of onchocerciasis alongside
689 other neglected tropical diseases. WHO currently recommends the use of preventive
690 chemotherapy (PC) for lymphatic filariasis, onchocerciasis, schistosomiasis, soil
691 transmitted helminthiasis (hookworm, ascariasis and trichuriasis) and trachoma.

692

693 **10. Newer treatments**

694 Alternative (or complementary) strategies (ATSs) are needed in some African
695 settings in order to achieve elimination of onchocerciasis by 2025. Examples of
696 ATSs include additional vector control [109],[110] biannual or pluriannual CDTi,
697 community-directed treatment with combinations of antihelminthics or new drugs and
698 'test and treat' strategies.

699 **Anti-Wolbachia treatments**

700 Antibiotics which are already registered for human use are undergoing evaluation
701 for anti-*Wolbachia* activity to try to identify drugs which could have shorter treatment
702 regimes than the current six week course of doxycycline. High-dose rifampicin has

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had promising results in animal studies [111]. A Cochrane review performed in 2015 [112] identified three randomized controlled trials which compared the effectiveness of doxycyline plus ivermectin versus ivermectin alone. The authors concluded that there was only limited evidence of very low quality from two of the studies that a six-week course of doxycyline followed by ivermectin may result in more frequent macrofilaricidal and microfilaricidal acitivity and sterilization of female adult worms compared with ivermectin alone. Only one study measured clinical outcomes, which were visual outcomes at six months but the results were graded as very low quality and hence the vision-related outcomes were uncertain. Similar RCTs assessing skin-related outcomes have not been reported to date.

In loiasis co-endemic areas community-directed delivery of a six week course of doxycycline proved feasible and doxycycline was a safe and effective macrofilaricidal agent [113]. A meta-analytical model using field trial data estimated that the efficacy of doxycycline (the maximum proportional reduction of adult female *O. volvulus* worms positive for *Wolbachia*) was 91% - 94%, irrespective of a variety of treatment regimes of four, five or six weeks. The life span of adult worms was reduced by 70-80%, from approximately 10 years to 2-3 years [114]. A pilot trial in Ghana confirmed that a four week course of doxycycline was sufficient for *Wolbachia* depletion and that minocycline 200mg /day for 3 weeks was more potent than a three week course doxycycline [115]. An Anti-*Wolbachia* Consortium (A-WOL) has been established to look for new drugs with macrofilaricidal activity by targeting *Wolbachia* and the capacity of this screening programme has been significantly enhanced via the development of a high-throughput assay [116].

Moxidectin

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Moxidectin is a more effective microfilaridial agent than ivermectin and 12 months after moxidectin treatment, dermal mf were still lower or comparable to the nadir seen one month after ivermectin treatment [117]. A double-blind, parallel group superiority trial in four study sites in Ghana, Liberia and DRC confirmed that at 12 months post dosing the skin microfilarial density was lower in the moxidectin group than the ivermectin group (adjusted geometric mean difference 3.9 [3.2-4.9], p<0.0001) [118]. EpiOncho modelling suggests that the number of years to reach thresholds for onchoerciasis elimination with annual moxidectin is similar to that with biannual CDTi [119]. A not-for-profit organization, Medicines Development for Global Health is planning for affordable access to moxidectin for countries to incorporate moxidectin into their control and elimination programmes.

Ivermectin-diethylcarbamazine-albendazole

Triple therapy is being considered for onchocerciasis. A strategy is needed to ensure that *O.volvulus*-infected patients with high microfilarial loads are excluded from treatment as diethylcarbamazine can cause general and irreversible ocular side effects [120].

Emodepside

Emodepside, which has known efficacy in animal models, paralyses adult filarial worms by facilitating a nematode Ca^{2+}-activated K^{+} channel called SLO-1in a sustained way, but does not affect human channels [121]. It is therefore hoped it may prove to be a useful macrofilaricidal agent for human use and is undergoing a phase 1 study to determine its safety, tolerability and pharmacokinetics in healthy volunteers by the Drugs for Neglected Diseases Initiative (DND*i*) (NCT02661178).

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Genome assemblies

Recently genome assemblies for *O. volvulus* and *Wolbachia* have been generated, allowing identification of enzymes that are likely to be essential for *O.volvulus* survival. This will hopefully provide a rich resource of potential new targets for drug development [122].

Vaccine

In 2015 an international consortium launched a new global initiative, known as TOVA "The Onchocerciasis Vaccine for Africa", with the goal of evaluating and pursuing vaccine development as a complementary control tool to eliminate onchocerciasis. Two recombinant proteins, *Ov*-103 and *Ov*-RAL-2, have been identified that individually or in combination induced significant protection against infection in animal models [123] and it is hoped that initial vaccine candidates could be in human safety trials by 2022 [124].

11. Concept of Skin NTDs and Integrated Control and Management of Neglected Tropical Skin Diseases

In addition to onchocerciasis, several other neglected tropical diseases (NTDs) have cutaneous manifestations and a new proposal is for an integrated strategy for the management of Skin NTDs using preventive chemotherapy, or intensified disease management, or both, depending on the overall health needs of an area [125]**.** Such an approach will require *i)* assessment of which diseases are present within an area *ii)* roll-out of training packages to help workers screen for several conditions and *iii)* care pathways for diagnosis and treatment in the local community and onward

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773 referral to health centres and district hospitals as needed, with appropriate
774 strengthening of health infrastructure. Targeting skin NTDs should also help treat
775 other common skin conditions and hopefully lead to wider public health benefits.
776 WHO has recently produced a training guide to help front-line health workers
777 recognise NTDs through examination of the skin [126] and the key pointers identified
778 for onchodermatitis were *i)* itchy skin, *ii)* subcutanous lumps (large lumps suggest
779 onchocercal nodules; small itchy lumps suggest acute or chronic onchodermatitis)
780 and iii) patches (raised dark scaly patches on one leg suggests lichenified
781 onchodermatitis and non-itchy speckled loss of pigment on shins suggests
782 onchocercal depigmentation).

783 Hofstraat and Brakel reviewed social stigma towards NTDs in general and proposed
784 that further research was needed to study the efficacy of joint approaches to reduce
785 stigmatisation in society and that lessons learnt from leprosy should be incorporated
786 [127].

787

788 12. Mathematical modelling of onchodermatitis

789 The mathematical model ONCHOSIM has been extended to include predicted
790 trends for various forms of onchocercal skin disease up to 2025 [128]. The
791 prevalence of reversible skin disease (e.g. troublesome itching, acute and chronic
792 papular and lichenified onchodermatitis) was shown to decline rapidly with waning
793 infection prevalence, with the rate of the decline depending on achieved therapeutic
794 coverage. In contrast, irreversible manifestations such as cutaneous atrophy,
795 depigmentation and hanging groin declined much more slowly.

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13. Conclusion

In 2016, more than 131 million people were treated with ivermectin for onchocerciasis and 85.9% of all districts globally had achieved effective coverage of ≥ 65% [129]. As a result of MDA with ivermectin, onchocerciasis has been significantly reduced in many countries, transmission has been eliminated in four Central and South American countries and in foci in several African countries, and onchodermatitis is no longer seen in children in many formerly endemic foci. Continued vigilance is needed to check for the development of resistance to ivermectin, a single-dose macrofilaricidal agent remains the "Holy Grail" for drug developers and alternative strategies need to be implemented in some areas. Much concerted effort needs to continue to hope to achieve WHO's target for elimination of onchocerciasis by 2025. Even after transmission has been interrupted, certain individuals will have irreversible deforming hanging groin and visible depigmentation but hopefully the incessant and debilitating pruritus due to onchocerciasis will become a thing of the past.

14. References

1. World Health Organization. Accelerating work to overcome the global impact of neglected tropical diseases: a roadmap for implementation. **2012**, 1–42., doi:WHO/HTM/NTD/2012.1.

2. World Health Organization. Elimination of onchocerciasis in the WHO region of the Americas: Ecuador's progress towards verification of elimination. *Wkly. Epid. Rec.* **2014**, *89*, 401–405.

3. Mahdy, M.A.K.; Abdul-Ghani, R.; Abdulrahman, T.A.A.; Al-Eryani, S.M.A.; Al-Mekhlafi, A.M.; Alhaidari, S.A.A.; Azazy, A. A. Onchocerca volvulus infection in Tihama region - west of Yemen: continuing transmission in ivermectin-targeted endemic foci and unveiled endemicity in districts with previously unknown status. *PLoS Negl.Trop.Dis.* **2018**, *12*, 1–16.

4. ME, M.; Murdoch, M. E. Onchodermatitis. *Curr. Opin. Infect. Dis.* **2010**, doi:10.1097/QCO.0b013e328336a256.

5. World Health Organization. Progress report on the elimination of human onchocerciasis, 2016–2017. *Wkly. Epidemiol. Rec.* **2017**, *92*, 681–694.

6. Vos, T.; Barber, R.M.; Bell, B.; Bertozzi-Villa, A.; Biryukov, S.; Bolliger, I.; Charlson, F.; Davis, A.; Degenhardt, L.; Dicker, D. et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systemic analysis for the Global Burden of Disease Study 2013. *Lancet* **2015**, *386*, 743–800., doi:10.1016/S0140-6736(15)60692-4.

7. Herricks, J. R.; Hotez, P. J.; Wanga, V.; Coffeng, L. E.; Haagsma, J. A.; Basáñez, M. G.; Buckle, G.; Budke, C. M.; Carabin, H.; Fèvre, E. M. et al. The

838 global burden of disease study 2013: What does it mean for the NTDs? *PLoS*
839 *Negl. Trop. Dis.* **2017**, *11*, e0005424., doi:10.1371/journal.pntd.0005424.

840 8. Vos, T.; Allen, C.; Arora, M.; Barber, R. M.; Bhutta, Z. A.; Brown, A.; Carter, A.;
841 Casey, D.C.; Charlson, F.J.; Chen, A. Z. et al. Global, regional, and national
842 incidence, prevalence, and years lived with disability for 310 diseases and
843 injuries, 1990-2015: a systematic analysis for the Global Burden of Disease
844 Study 2015. *Lancet* **2016**, *388*, 1545–1602, doi:10.1016/S0140-
845 6736(16)31678-6.

846 9. Vos, T.; Abajobir, A.A.; Abbafati, C.; Abbas, K.M.; Abate, K.H.; Abd-Allah, F.;
847 Abdulle, A.M.; Abebo, T.A.; Abera, S.F.; Aboyans, V. et al. Global,
848 regional,and national incidence, prevalence, and years lived with disability for
849 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis
850 for the Global Burden of Disease Study 2016. *Lancet* **2017**, *390*, 1211–1259.,
851 doi:10.1016/S0140-6736(17)32154-2.

852 10. Stokstad, E.; Vogel, G. Neglected tropical diseases get the limelight in
853 Stockholm. *Science (80-.).* **2015**, *350*, 144–145.,
854 doi:10.1126/science.350.6257.144.

855 11. Fobi, G.; Yameogo, L.; Noma, M.; Aholou, Y.; Koroma, J. B.; Zouré, H. M.;
856 Ukety, T.; Lusamba-Dikassa, P. S.; Mwikisa, C.; Boakye, D. A.; Roungou, J. B.
857 Managing the Fight against Onchocerciasis in Africa: APOC Experience. *PLoS*
858 *Negl. Trop. Dis.* **2015**, doi:10.1371/journal.pntd.0003542.

859 12. Hopkins, A. D. From “control to elimination”: A strategic change to win the end
860 game. *Int. Health* **2015**, *7*, 304–305., doi:10.1093/inthealth/ihv056.

13. Hopkins, A. D. Neglected tropical diseases in Africa: a new paradigm. *Int. Health* **2016**, doi:10.1093/inthealth/ihv077.

14. Dunn, C.; Callahan, K.; Katabarwa, M.; Richards, F.; Hopkins, D.; Withers, P. C.; Buyon, L. E.; McFarland, D. The Contributions of Onchocerciasis Control and Elimination Programs toward the Achievement of the Millennium Development Goals. *PLoS Negl. Trop. Dis.* **2015**, doi:10.1371/journal.pntd.0003703.

15. Hay, R, J.; Mackenzie, C.D.; Guderian, R.; Noble, W.C.; Proano, J.R.; Williams, J. F. Onchodermatitis - correlation between skin disease and parasitic load in an endemic focus in Ecuador. *Brit J Dermatol* **1989**, *121*, 187–198.

16. Murdoch, M. E.; Hay, R. J.; Mackenzie, C. D.; Williams, J. F.; Ghalib, H. W.; Cousens, S.; Abiose, A.; Jones, B. R. A clinical classification and grading system of the cutaneous changes in onchocerciasis. *Br. J. Dermatol.* **1993**, doi:10.1111/j.1365-2133.1993.tb11844.x.

17. Murdoch, M. E.; Murdoch, I. E.; Evans, J.; Yahaya, H.; Njepuome, N.; Cousens, S.; Jones, B. R.; Abiose, A. Pre-control relationship of onchocercal skin disease with onchocercal infection in Guinea Savanna, Northern Nigeria. *PLoS Negl. Trop. Dis.* **2017**, doi:10.1371/journal.pntd.0005489.

18. Murdoch, M. E.; Asuzu, M. C.; Hagan, M.; Makunde, W. H.; Ngoumou, P.; Ogbuagu, K. F.; Okello, D.; Ozoh, G.; Remme, J. Onchocerciasis: the clinical and epidemiological burden of skin disease in Africa. *Ann. Trop. Med. Parasitol.* **2002**, doi:10.1179/000349802125000826.

19. Al-Kubati, A. S.; Mackenzie, C. D.; Boakye, D.; Al-Qubati, Y.; Al-Samie, A. R.; Awad, I. E.; Thylefors, B.; Hopkins, A. Onchocerciasis in Yemen: Moving forward towards an elimination program. *Int. Health* **2018**, doi:10.1093/inthealth/ihx055.

20. Olusegun, A. F.; Ehis, O. C. Hyperendemicity of Onchocerciasis in Ovia Northeast Local Government Area, Edo State, Nigeria. *Malaysian J. Med. Sci.* **2010**, *17*, 20–24., doi:10.4314/eajph.v7i1.64702.

21. Dori, G. U.; Belay, T.; Belete, H.; Panicker, K. N.; Hailu, A. Parasitological and clinico-epidemiological features of onchocerciasis in West Wellega, Ethiopia. *J. Parasit. Dis.* **2012**, doi:10.1007/s12639-011-0063-2.

22. Eyo, J. E.; Onyishi, G. C.; Ugokwe, C. U. Rapid epidemiological assessment of onchocerciasis in a tropical semi-urban community, Enugu State, Nigeria. *Iran. J. Parasitol.* **2013**, *8*, 145–151.

23. Coffeng, L. E.; Fobi, G.; Ozoh, G.; Bissek, A. C.; Nlatté, B. O.; Enyong, P.; Olinga Olinga, J. M.; Zouré, H. G. M.; Habbema, J. D. F.; Stolk, W. A.; de Vlas, S. J.; Boussinesq, M.; Noma, M. Concurrence of dermatological and ophthalmological morbidity in onchocerciasis. *Trans. R. Soc. Trop. Med. Hyg.* **2012**, doi:10.1016/j.trstmh.2011.12.006.

24. Murdoch, M. E.; Payton, A.; Abiose, A.; Thomson, W.; Panicker, V. K.; Dyer, P. A.; Jones, B. R.; Maizels, R. M.; Oilier, W. E. R. HLA-DQ alleles associate with cutaneous features of onchocerciasis. *Hum. Immunol.* **1997**, doi:10.1016/S0198-8859(97)00089-X.

25. Norman, F. F.; de Ayala, A. P.; Pérez-Molina, J. A.; Monge-Maillo, B.;

907 Zamarrón, P.; López-Vélez, R. Neglected tropical diseases outside the tropics.
908 *PLoS Negl. Trop. Dis.* **2010**, doi:10.1371/journal.pntd.0000762.

909 26. Antinori, S.; Parravicini, C.; Galimberti, L.; Tosoni, A.; Giunta, P.; Galli, M.;
910 Corbellino, M.; Ridolfo, A. L. Is imported onchocerciasis a truly rare entity?
911 Case report and review of the literature. *Travel Med. Infect. Dis.* **2017**, *16*, 11–
912 17., doi:10.1016/j.tmaid.2017.02.006.

913 27. Develoux, M.; Hennequin, C.; Le Loup, G.; Paris, L.; Magne, D.; Belkadi, G.;
914 Pialoux, G. Imported filariasis in Europe: A series of 31 cases from
915 Metropolitan France. *Eur. J. Intern. Med.* **2017**, *37*, e37–e39,
916 doi:10.1016/j.ejim.2016.09.021.

917 28. Zammarchi, L.; Vellere, I.; Stella, L.; Bartalesi, F.; Strohmeyer, M.; Bartoloni, A.
918 Spectrum and burden of neglected tropical diseases observed in an infectious
919 and tropical diseases unit in Florence, Italy (2000–2015). *Intern. Emerg. Med.*
920 **2017**, doi:10.1007/s11739-016-1597-1.

921 29. Baum, S.; Greenberger, S.; Pavlotsky, F.; Solomon, M.; Enk, C. D.; Schwartz,
922 E.; Barzilai, A. Late-onset onchocercal skin disease among Ethiopian
923 immigrants. *Br. J. Dermatol.* **2014**, doi:10.1111/bjd.13005.

924 30. Puente, S.; Ramirez-Olivencia , G.; Lago, M,; Subirats, M.; Perez-Blazquez,
925 E.; Bru, F.; Garate, T.; Vicente, B.; Belhassen-Garcia, M.; Muro, A.
926 Dermatological manifestations in onchocerciasis: a retrospective study of 400
927 imported cases. *Enferm. Infecc. Microbiol . Clin.* **2017**,
928 doi:10.1016/j.eimc.2017.11.016.

929 31. Lenk, E. J.; Redekop, W. K.; Luyendijk, M.; Rijnsburger, A. J.; Severens, J. L.

930 Productivity Loss Related to Neglected Tropical Diseases Eligible for
931 Preventive Chemotherapy: A Systematic Literature Review. *PLoS Negl. Trop.*
932 *Dis.* **2016**, doi:10.1371/journal.pntd.0004397.

933 32. Tamarozzi, F.; Halliday, A.; Gentil, K.; Hoerauf, A.; Pearlman, E.; Taylor, M. J.
934 Onchocerciasis: The role of Wolbachia bacterial endosymbionts in parasite
935 biology, disease pathogenesis, and treatment. *Clin. Microbiol. Rev.* **2011**,
936 doi:10.1128/CMR.00057-10.

937 33. Adjobimey, T.; Hoerauf, A. Induction of immunoglobulin G4 in human filariasis:
938 an indicator of immunoregulation. *Ann. Trop. Med. Parasitol.* **2010**, *104*, 455–
939 464, doi:10.1179/136485910X12786389891407.

940 34. Kwarteng, A.; Ahuno, S. T.; Akoto, F. O. Killing filarial nematode parasites:
941 Role of treatment options and host immune response. *Infect. Dis. Poverty*
942 **2016**, doi:10.1186/s40249-016-0183-0.

943 35. Hansen, R. D. E.; Trees, A. J.; Bah, G. S.; Hetzel, U.; Martin, C.; Bain, O.;
944 Tanya, V. N.; Makepeace, B. L. A worm's best friend: Recruitment of
945 neutrophils by wolbachia confounds eosinophil degranulation against the
946 filarial nematode Onchocerca ochengi. *Proc. R. Soc. B Biol. Sci.* **2011**, *278*,
947 2293–2302, doi:10.1098/rspb.2010.2367.

948 36. Tamarozzi, F.; Wright, H. L.; Johnston, K. L.; Edwards, S. W.; Turner, J. D.;
949 Taylor, M. J. Human filarial Wolbachia lipopeptide directly activates human
950 neutrophils in vitro. *Parasite Immunol.* **2014**, doi:10.1111/pim.12122.

951 37. Tamarozzi, F.; Turner, J. D.; Pionnier, N.; Midgley, A.; Guimaraes, A. F.;
952 Johnston, K. L.; Edwards, S. W.; Taylor, M. J. Wolbachia endosymbionts

induce neutrophil extracellular trap formation in human onchocerciasis. *Sci. Rep.* **2016**, doi:10.1038/srep35559.

38. Korten, S.; Hoerauf, A.; Kaifi, J. T.; Büttner, D. W. Low levels of transforming growth factor-beta (TGF-beta) and reduced suppression of Th2-mediated inflammation in hyperreactive human onchocerciasis. *Parasitology* **2011**, doi:10.1017/S0031182010000922.

39. Katawa, G.; Layland, L. E.; Debrah, A. Y.; von Horn, C.; Batsa, L.; Kwarteng, A.; Arriens, S.; Taylor, D. W.; Specht, S.; Hoerauf, A. et al. Hyperreactive Onchocerciasis is Characterized by a Combination of Th17-Th2 Immune Responses and Reduced Regulatory T Cells. *PLoS Negl. Trop. Dis.* **2015**, doi:10.1371/journal.pntd.0003414.

40. Ajonina-Ekoti, I.; Ndjonka, D.; Tanyi, M. K.; Wilbertz, M.; Younis, A. E.; Boursou, D.; Kurosinski, M. A.; Eberle, R.; Lüersen, K.; Perbandt, M. et al. Functional characterization and immune recognition of the extracellular superoxide dismutase from the human pathogenic parasite Onchocerca volvulus (OvEC-SOD). *Acta Trop.* **2012**, doi:10.1016/j.actatropica.2012.05.013.

41. Lechner, C. J.; Gantin, R. G.; Seeger, T.; Sarnecka, A.; Portillo, J.; Schulz-Key, H.; Karabou, P. K.; Helling-Giese, G.; Heuschkel, C.; Banla, M. et al. Chemokines and cytokines in patients with an occult Onchocerca volvulus infection. *Microbes Infect.* **2012**, doi:10.1016/j.micinf.2011.12.002.

42. Mackenzie, C. D.; Huntington, M. K.; Wanji, S.; Lovato, R. V; Eversole, R. R.; Geary, T. G. The association of adult Onchocerca volvulus with lymphatic

vessels. *J Parasitol* **2010**, *96*, 219–221, doi:10.1645/GE-2236.1.

43. Attout, T.; Hoerauf, A.; Dénécé, G.; Debrah, A. Y.; Marfo-Debrekyei, Y.; Boussinesq, M.; Wanji, S.; Martinez, V.; Mand, S.; Adjei, O. et al. Lymphatic vascularisation and involvement of Lyve-1+ macrophages in the human Onchocerca nodule. *PLoS One* **2009**, *4*, doi:10.1371/journal.pone.0008234.

44. de Angelis, F.; Garzoli, A.; Battistini, A.; Iorio, A.; de Stefano, G. F. Genetic response to an environmental pathogenic agent: HLA-DQ and onchocerciasis in northwestern Ecuador. *Tissue Antigens* **2011**, doi:10.1111/j.1399-0039.2011.01811.x.

45. Unnasch, T. R.; Golden, A.; Cama, V.; Cantey, P. T. Diagnostics for onchocerciasis in the era of elimination. *Int. Health* **2018**, doi:10.1093/inthealth/ihx047.

46. Thiele, E. A.; Cama, V. A.; Lakwo, T.; Mekasha, S.; Abanyie, F.; Sleshi, M.; Kebede, A.; Cantey, P. T. Detection of onchocerca volvulus in skin snips by microscopy and real-time polymerase chain reaction: Implications for monitoring and evaluation activities. *Am. J. Trop. Med. Hyg.* **2016**, *94*, 906–911, doi:10.4269/ajtmh.15-0695.

47. Prince-Guerra, J. L.; Cama, V. A.; Wilson, N.; Thiele, E. A.; Likwela, J.; Ndakala, N.; wa Muzinga, J. M.; Ayebazibwe, N.; Ndjakani, Y. D.; Pitchouna N. A. et al. Comparison of PCR methods for onchocerca volvulus detection in skin snip biopsies from the Tshopo Province, Democratic Republic of the Congo. *Am. J. Trop. Med. Hyg.* **2018**, *98*, 1427–1434, doi:10.4269/ajtmh.17-0809.

48. Mekonnen, S. A.; Beissner, M.; Saar, M.; Ali, S.; Zeynudin, A.; Tesfaye, K.;

999 Adbaru, M. G.; Battke, F.; Poppert, S.; Hoelscher, M. et al. O-5S quantitative
1000 real-time PCR: A new diagnostic tool for laboratory confirmation of human
1001 onchocerciasis. *Parasites and Vectors* **2017**, doi:10.1186/s13071-017-2382-3.

1002 49. World Health Organization. *Guidelines for stopping mass drug administration*
1003 *and verifying elimination of human onchocerciasis: criteria and procedures.*
1004 *Document WHO/HTM/NTD/PCT/2016.1*; WHO Press, Geneva, 2016;

1005 50. Gass, K. M. Rethinking the serological threshold for onchocerciasis
1006 elimination. *PLoS Negl. Trop. Dis.* **2018**, doi:10.1371/journal.pntd.0006249.

1007 51. Steel, C.; Golden, A.; Stevens, E.; Yokobe, L.; Domingo, G. J.; De los Santos,
1008 T.; Nutman, T. B. Rapid point-of-contact tool for mapping and integrated
1009 surveillance of Wuchereria bancrofti and Onchocerca volvulus infection. *Clin.*
1010 *Vaccine Immunol.* **2015**, *22*, 896–901, doi:10.1128/CVI.00227-15.

1011 52. Dieye, Y.; Storey, H. L.; Barrett, K. L.; Gerth-Guyette, E.; Di Giorgio, L.;
1012 Golden, A.; Faulx, D.; Kalnoky, M.; Ndiaye, M. K. N.; Sy, N. et al. Feasibility of
1013 utilizing the SD BIOLINE Onchocerciasis IgG4 rapid test in onchocerciasis
1014 surveillance in Senegal. *PLoS Negl. Trop. Dis.* **2017**,
1015 doi:10.1371/journal.pntd.0005884.

1016 53. Rodríguez-Pérez, M. A.; Adeleke, M. A.; Burkett-Cadena, N. D.; Garza-
1017 Hernández, J. A.; Reyes-Villanueva, F.; Cupp, E. W.; Toé, L.; Salinas-
1018 Carmona, M. C.; Rodríguez-Ramírez, A. D.; Katholi, C. R. et al. Development
1019 of a Novel Trap for the Collection of Black Flies of the Simulium ochraceum
1020 Complex. *PLoS One* **2013**, *8*, e76814., doi:10.1371/journal.pone.0076814.

1021 54. Rodríguez-Pérez, M. A.; Adeleke, M. A.; Rodríguez-Luna, I. C.; Cupp, E. W.;

Unnasch, T. R. Evaluation of a Community-Based Trapping Program to Collect Simulium ochraceum sensu lato for Verification of Onchocerciasis Elimination. *PLoS Negl. Trop. Dis.* **2014**, *8*, e3249., doi:10.1371/journal.pntd.0003249.

55. Toé, L. D.; Koala, L.; Burkett-Cadena, N. D.; Traoré, B. M.; Sanfo, M.; Kambiré, S. R.; Cupp, E. W.; Traoré, S.; Yameogo, L.; Boakye, D. et al. Optimization of the Esperanza window trap for the collection of the African onchocerciasis vector Simulium damnosum sensu lato. *Acta Trop.* **2014**, *137*, 39–43, doi:10.1016/j.actatropica.2014.04.029.

56. Denery, J. R.; Nunes, A. A. K.; Hixon, M. S.; Dickerson, T. J.; Janda, K. D. Metabolomics-based discovery of diagnostic biomarkers for onchocerciasis. *PLoS Negl. Trop. Dis.* **2010**, *4*, e834., doi:10.1371/journal.pntd.0000834.

57. Globisch, D.; Moreno, A. Y.; Hixon, M. S.; Nunes, A. A. K.; Denery, J. R.; Specht, S.; Hoerauf, A.; Janda, K. D. Onchocerca volvulus-neurotransmitter tyramine is a biomarker for river blindness. *Proc. Natl. Acad. Sci.* **2013**, *110*, 4218–4223, doi:10.1073/pnas.1221969110.

58. Tritten, L.; Burkman, E.; Moorhead, A.; Satti, M.; Geary, J.; Mackenzie, C.; Geary, T. Detection of Circulating Parasite-Derived MicroRNAs in Filarial Infections. *PLoS Negl. Trop. Dis.* **2014**, *8*, e2971, doi:10.1371/journal.pntd.0002971.

59. Quintana, J. F.; Makepeace, B. L.; Babayan, S. A.; Ivens, A.; Pfarr, K. M.; Blaxter, M.; Debrah, A.; Wanji, S.; Ngangyung, H. F.; Bah, G. S. et al. Extracellular Onchocerca-derived small RNAs in host nodules and blood. *Parasites and Vectors* **2015**, *8*, 1–11, doi:10.1186/s13071-015-0656-1.

60. Lagatie, O.; Batsa Debrah, L.; Debrah, A.; Stuyver, L. J. Plasma-derived parasitic microRNAs have insufficient concentrations to be used as diagnostic biomarker for detection of Onchocerca volvulus infection or treatment monitoring using LNA-based RT-qPCR. *Parasitol. Res.* **2017**, *116*, 1013–1022, doi:10.1007/s00436-017-5382-5.

61. Brieger, W. R.; Awedoba, A. K.; Eneanya, C. I.; Hagan, M.; Ogbuagu, K. F.; Okello, D. O.; Ososanya, O. O.; Ovuga, E. B. L.; Noma, M.; Kale, O. O. et al. The effects of ivermectin on onchocercal skin disease and severe itching: Results of a multicentre trial. *Trop. Med. Int. Heal.* **1998**, *3*, 951–961, doi:10.1046/j.1365-3156.1998.00339.x.

62. Banic, D. M.; Calvão-Brito, R. H. S.; Marchon-Silva, V.; Schuertez, J. C.; de Lima Pinheiro, L. R.; da Costa Alves, M.; Têva, A.; Maia-Herzog, M. Impact of 3 years ivermectin treatment on onchocerciasis in Yanomami communities in the Brazilian Amazon. *Acta Trop.* **2009**, *112*, 125–130, doi:10.1016/j.actatropica.2009.07.009.

63. Ozoh, G. A.; Murdoch, M. E.; Bissek, A. C.; Hagan, M.; Ogbuagu, K.; Shamad, M.; Braide, E. I.; Boussinesq, M.; Noma, M. M.; Murdoch, I. E. et al. The African Programme for Onchocerciasis Control: Impact on onchocercal skin disease. *Trop. Med. Int. Heal.* **2011**, *16*, 875–883, doi:10.1111/j.1365-3156.2011.02783.x.

64. Samuel, A.; Belay, T.; Yehalaw, D.; Taha, M.; Zemene, E.; Zeynudin, A. Impact of six years community directed treatment with ivermectin in the Control of Onchocerciasis, Western Ethiopia. *PLoS One* **2016**, *11*, e0141029, doi:10.1371/journal.pone.0141029.

65. Mbanefo, E. C.; Eneanya, C. I.; Nwaorgu, O. C.; Otiji, M. O.; Oguoma, V. M.; Ogolo, B. A. Onchocerciasis in Anambra State, Southeast Nigeria: Endemicity and clinical manifestations. *Postgrad. Med. J.* **2010**, *86*, 578–583, doi:10.1136/pgmj.2009.094946.

66. Kamga, G. R.; Dissak-Delon, F. N.; Nana-Djeunga, H. C.; Biholong, B. D.; Ghogomu, S. M.; Souopgui, J.; Kamgno, J.; Robert, A. Important progress towards elimination of onchocerciasis in the West Region of Cameroon. *Parasites and Vectors* **2017**, *10*, 373, doi:10.1186/s13071-017-2301-7.

67. Moya, L.; Herrador, Z.; Ta-Tang, T. H.; Rubio, J. M.; Perteguer, M. J.; Hernandez-González, A.; García, B.; Nguema, R.; Nguema, J.; Ncogo, P. et al. Evidence for Suppression of Onchocerciasis Transmission in Bioko Island, Equatorial Guinea. *PLoS Negl. Trop. Dis.* **2016**, doi:10.1371/journal.pntd.0004829.

68. Walker, M.; Pion, S. D. S.; Fang, H.; Gardon, J.; Kamgno, J.; Basáñez, M. G.; Boussinesq, M. Macrofilaricidal Efficacy of Repeated Doses of Ivermectin for the Treatment of River Blindness. *Clin. Infect. Dis.* **2017**, *65*, 2026–2034, doi:10.1093/cid/cix616.

69. Kudzi, W.; Dodoo, A. N. O.; Mills, J. J. Genetic polymorphisms in MDR1, CYP3A4 and CYP3A5 genes in a Ghanaian population: A plausible explanation for altered metabolism of ivermectin in humans? *BMC Med. Genet.* **2010**, *11*, doi:10.1186/1471-2350-11-111.

70. Vlassoff, C.; Weiss, M.; Ovuga, E. B. L.; Eneanya, C.; Nwel, P. T.; Babalola, S. S.; Awedoba, A. K.; Theophilus, B.; Cofie, P.; Shetabi, P. Gender and the

stigma of onchocercal skin disease in Africa. *Soc. Sci. Med.* **2000**, *50*, 1353–1368, doi:10.1016/S0277-9536(99)00389-5.

71. Mbanefo, E. C.; Eneanya, C. I.; Nwaorgu, O. C.; Oguoma, V. M.; Otiji, M. O.; Ogolo, B. A. Onchocerciasis in Anambra State, Southeast Nigeria: Clinical and psychological aspects and sustainability of community directed treatment with ivermectin (CDTI). *Postgrad. Med. J.* **2010**, *86*, 573–577, doi:10.1136/pgmj.2010.100248.

72. Abanobi, O.; Chukwuocha, U.; Onwuliri, C.; Opara, K. Primary motives for demand of ivermectin drug in mass distribution programmes to control onchocerciasis. *N. Am. J. Med. Sci.* **2011**, doi:10.4297/najms.2011.389.

73. Okeibunor, J. C.; Amuyunzu-Nyamongo, M.; Onyeneho, N. G.; Tchounkeu, Y. F. L.; Manianga, C.; Kabali, A. T.; Leak, S. Where would I be without ivermectin? Capturing the benefits of community-directed treatment with ivermectin in Africa. *Trop. Med. Int. Heal.* **2011**, *16*, 608–621, doi:10.1111/j.1365-3156.2011.02735.x.

74. Tchounkeu, Y. F. L.; Onyeneho, N. G.; Wanji, S.; Kabali, A. T.; Manianga, C.; Amazigo, U. V; Amuyunzu-Nyamongo, M. Changes in stigma and discrimination of onchocerciasis in Africa. *Trans. R. Soc. Trop. Med. Hyg.* **2012**, *106*, 340–347, doi:10.1016/j.trstmh.2012.02.009.

75. Amuyunzu-Nyamongo, M.; Tchounkeu, Y. F. L.; Oyugi, R. A.; Kabali, A. T.; Okeibunor, J. C.; Manianga, C.; Amazigo, U. V Drawing and interpreting data: Children's impressions of onchocerciasis and community-directed treatment with ivermectin (CDTI) in four onchocerciasis endemic countries in Africa. *Int.*

J. Qual. Stud. Health Well-being **2011**, *6*, doi:10.3402/qhw.v6i2.5918.

76. Nicholls, R. S.; Duque, S.; Olaya, L. A.; López, M. C.; Sánchez, S. B.; Morales, A. L.; Palma, G. I. Elimination of onchocerciasis from Colombia: First proof of concept of river blindness elimination in the world. *Parasites and Vectors* **2018**, *11*, 237, doi:10.1186/s13071-018-2821-9.

77. World Health Organization. Progress towards eliminating onchocerciasis in the WHO Region of the Americas: verification of elimination of transmission in Guatemala. *Wkly . Epid. Rec.* **2016**, *91*, 501–505.

78. Guevara, Á.; Lovato, R.; Proaño, R.; Rodriguez-Perez, M. A.; Unnasch, T.; Cooper, P. J.; Guderian, R. H. Elimination of onchocerciasis in Ecuador: Findings of post-treatment surveillance. *Parasites and Vectors* **2018**, *11*, 265, doi:10.1186/s13071-018-2851-3.

79. Diawara, L.; Traore, M.O.; Badji, A.; Bissan, Y.; Doumbia, K.; Goita, S.F.; Konate, L.; Mounkoro, K.; Sarr, M.D.; Seck, A. F. et al. Feasibility of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: first evidence from studies in Mali and Senegal. *PLoS Negl Trop Dis* **2009**, *3*, e497, doi:doi:10. 1371/journal.pntd.0000497.

80. Traore, M. O.; Sarr, M. D.; Badji, A.; Bissan, Y.; Diawara, L.; Doumbia, K.; Goita, S. F.; Konate, L.; Mounkoro, K.; Seck, A. F. et al. Proof-of-Principle of Onchocerciasis Elimination with Ivermectin Treatment in Endemic Foci in Africa: Final Results of a Study in Mali and Senegal. *PLoS Negl. Trop. Dis.* **2012**, *6*, e1825, doi:10.1371/journal.pntd.0001825.

81. Tekle, A. H.; Elhassan, E.; Isiyaku, S.; Amazigo, U. V; Bush, S.; Noma, M.;

Cousens, S.; Abiose, A.; Remme, J. H. Impact of long-term treatment of onchocerciasis with ivermectin in Kaduna State, Nigeria: First evidence of the potential for elimination in the operational area of the African Programme for Onchocerciasis Control. *Parasites and Vectors* **2012**, *5*, 28, doi:10.1186/1756-3305-5-2822313631.

82. Traoré, S.; Wilson, M. D.; Sima, A.; Barro, T.; Diallo, A.; Aké, A.; Coulibaly, S.; Cheke, R. A.; Meyer, R. R. F.; Mas, J. et al. The elimination of the onchocerciasis vector from the island of Bioko as a result of larviciding by the WHO African Programme for Onchocerciasis Control. *Acta Trop.* **2009**, *111*, 211–218, doi:10.1016/j.actatropica.2009.03.007.

83. Garms, R.; Lakwo, T. L.; Ndyomugyenyi, R.; Kipp, W.; Rubaale, T.; Tukesiga, E.; Katamanywa, J.; Post, R. J.; Amazigo, U. V. The elimination of the vector Simulium neavei from the Itwara onchocerciasis focus in Uganda by ground larviciding. *Acta Trop.* **2009**, *111*, 203–210, doi:10.1016/j.actatropica.2009.04.001.

84. Herrador, Z.; Garcia, B.; Ncogo, P.; Perteguer, M. J.; Rubio, J. M.; Rivas, E.; Cimas, M.; Ordoñez, G.; de Pablos, S.; Hernández-González, A. et al. Interruption of onchocerciasis transmission in Bioko Island: Accelerating the movement from control to elimination in Equatorial Guinea. *PLoS Negl. Trop. Dis.* **2018**, *12*, e0006471, doi:10.1371/journal.pntd.0006471.

85. Zarroug, I. M. A.; Hashim, K.; ElMubark, W. A.; Shumo, Z. A. I.; Salih, K. A. M.; ElNojomi, N. A. A.; Awad, H. A.; Aziz, N.; Katabarwa, M.; Hassan, H. K. et al. The first confirmed elimination of an onchocerciasis focus in Africa: Abu Hamed, Sudan. *Am. J. Trop. Med. Hyg.* **2016**, *95*, 1037–1040,

doi:10.4269/ajtmh.16-0274.

86. Katabarwa, M. N.; Lakwo, T.; Habomugisha, P.; Unnasch, T. R.; Garms, R.; Hudson-Davis, L.; Byamukama, E.; Khainza, A.; Ngorok, J.; Tukahebwa, E. et al. After 70 years of fighting an age-old scourge, onchocerciasis in Uganda, the end is in sight. *Int. Health* **2018**, *10*, i79–i88, doi:10.1093/inthealth/ihx044.

87. Rebollo, M. P.; Zoure, H.; Ogoussan, K.; Sodahlon, Y.; Ottesen, E. A.; Cantey, P. T. Onchocerciasis: Shifting the target from control to elimination requires a new first-step-elimination mapping. *Int. Health* **2018**, *10*, i14–i19, doi:10.1093/inthealth/ihx052.

88. World Health Organization. Progress report on the elimination of human onchocerciasis, 2015-2016. *Wkly Epid Rec* **2016**, *43*, 505–514.

89. Makenga Bof, J. C.; Maketa, V.; Bakajika, D. K.; Ntumba, F.; Mpunga, D.; Murdoch, M. E.; Hopkins, A.; Noma, M. M.; Zouré, H.; Tekle, A. H. et al. Onchocerciasis control in the Democratic Republic of Congo (DRC): Challenges in a post-war environment. *Trop. Med. Int. Heal.* **2015**, *20*, 48–62, doi:10.1111/tmi.12397.

90. Koroma, J. B.; Sesay, S.; Conteh, A.; Koudou, B.; Paye, J.; Bah, M.; Sonnie, M.; Hodges, M. H.; Zhang, Y.; Bockarie, M. J. Impact of five annual rounds of mass drug administration with ivermectin on onchocerciasis in Sierra Leone. *Infect. Dis. Poverty* **2018**, *7*, 30, doi:10.1186/s40249-018-0410-y.

91. Kamgno, J.; Pion, S. D.; Chesnais, C. B.; Bakalar, M. H.; D'Ambrosio, M. V.; Mackenzie, C. D.; Nana-Djeunga, H. C.; Gounoue-Kamkumo, R.; Njitchouang, G.-R.; Nwane, P. et al. A Test-and-Not-Treat Strategy for Onchocerciasis in

1185 Loa loa –Endemic Areas. *N. Engl. J. Med.* **2017**, *377*, 2044–2052,
1186 doi:10.1056/NEJMoa1705026.

1187 92. Lakwo, T.; Ukety, T.; Bakajika, D.; Tukahebwa, E.; Awaca, P.; Amazigo, U.
1188 "Cross-border collaboration in onchocerciasis elimination in Uganda: Progress,
1189 challenges and opportunities from 2008 to 2013." *Global. Health* **2018**, *14*, 16,
1190 doi:10.1186/s12992-018-0333-1.

1191 93. Gustavsen, K.; Sodahlon, Y.; Bush, S. Cross-border collaboration for
1192 neglected tropical disease efforts-Lessons learned from onchocerciasis control
1193 and elimination in the Mano River Union (West Africa). *Global. Health* **2016**,
1194 *12*, 44, doi:10.1186/s12992-016-0185-5.

1195 94. Bush, S.; Sodahlon, Y.; Downs, P.; Mackenzie, C. D. Cross-border issues: An
1196 important component of onchocerciasis elimination programmes. *Int. Health*
1197 **2018**, *10*, i54–i59, doi:10.1093/inthealth/ihx058.

1198 95. Senyonjo, L.; Oye, J.; Bakajika, D.; Biholong, B.; Tekle, A.; Boakye, D.;
1199 Schmidt, E.; Elhassan, E. Factors Associated with Ivermectin Non-Compliance
1200 and Its Potential Role in Sustaining Onchocerca volvulus Transmission in the
1201 West Region of Cameroon. *PLoS Negl. Trop. Dis.* **2016**, *10*, e0004905,
1202 doi:10.1371/journal.pntd.0004905.

1203 96. Katabarwa, M. N.; Habomugisha, P.; Agunyo, S.; McKelvey, A. C.; Ogweng,
1204 N.; Kwebiiha, S.; Byenume, F.; Male, B.; McFarland, D. Traditional kinship
1205 system enhanced classic community-directed treatment with ivermectin (CDTI)
1206 for onchocerciasis control in Uganda. *Trans. R. Soc. Trop. Med. Hyg.* **2010**,
1207 *104*, 265–272, doi:10.1016/j.trstmh.2009.10.012.

97. Bogus, J.; Gankpala, L.; Fischer, K.; Krentel, A.; Weil, G. J.; Fischer, P. U.; Kollie, K.; Bolay, F. K. Community attitudes toward mass drug administration for control and elimination of neglected tropical diseases after the 2014 outbreak of ebola virus disease in Lofa County, Liberia. *Am. J. Trop. Med. Hyg.* **2016**, *94*, 497–503, doi:10.4269/ajtmh.15-0591.

98. Coffeng, L. E.; Stolk, W. A.; Zouré, H. G. M.; Veerman, J. L.; Agblewonu, K. B.; Murdoch, M. E.; Noma, M.; Fobi, G.; Richardus, J. H.; Bundy, D. A. P. et al. African Programme for Onchocerciasis Control 1995-2015: Updated Health Impact Estimates Based on New Disability Weights. *PLoS Negl. Trop. Dis.* **2014**, *8*, e2759, doi:10.1371/journal.pntd.0002759.

99. Redekop, W. K.; Lenk, E. J.; Luyendijk, M.; Fitzpatrick, C.; Niessen, L.; Stolk, W. A.; Tediosi, F.; Rijnsburger, A. J.; Bakker, R.; Hontelez, J. A. C. et al. The Socioeconomic Benefit to Individuals of Achieving the 2020 Targets for Five Preventive Chemotherapy Neglected Tropical Diseases. *PLoS Negl. Trop. Dis.* **2017**, *11*, e0005289, doi:10.1371/journal.pntd.0005289.

100. de Vlas, S. J.; Stolk, W. A.; le Rutte, E. A.; Hontelez, J. A. C.; Bakker, R.; Blok, D. J.; Cai, R.; Houweling, T. A. J.; Kulik, M. C.; Lenk, E. J. et al. Concerted Efforts to Control or Eliminate Neglected Tropical Diseases: How Much Health Will Be Gained? *PLoS Negl. Trop. Dis.* **2016**, *10*, e0004386, doi:10.1371/journal.pntd.0004386.

101. Deribew, A.; Kebede, B.; Tessema, G. A.; Adama, Y. A.; Misganaw, A.; Gebre, T.; Hailu, A.; Biadgilign, S.; Amberbir, A.; Desalegn, B. et al. Mortality and Disability-Adjusted Life-Years (Dalys) for Common Neglected Tropical Diseases in Ethiopia, 1990-2015: Evidence from the Global Burden of Disease

Study 2015. *Ethiop. Med. J.* **2017**, *55*, 3–14.

102. Kim, Y. E.; Stolk, W. A.; Tanner, M.; Tediosi, F. Modelling the health and economic impacts of the elimination of river blindness (onchocerciasis) in Africa. *BMJ Glob. Heal.* **2017**, *2*, e000158, doi:10.1136/bmjgh-2016-000158.

103. Salomon, J. A.; Vos, T.; Hogan, D.R.; Gagnon, M.; Naghavi, M.; Mokdad, A.; Begum N.; Shah R.; Karyana, M.; Kosen, S. et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* **2012**, *380*, 2129–2143, doi:10.1016/S0140-6736(12)61680-8.

104. Salomon, J. A.; Vos, T.; Murra, C. J. L. Disability weights for vision disorders in Global Burden of Disease study- Authors' reply. *Lancet* **2013**, *381*, 23–24, doi:10.1016/S0140-6736(12)62131-X.

105. Krotneva, S. P.; Coffeng, L. E.; Noma, M.; Zouré, H. G. M.; Bakoné, L.; Amazigo, U. V.; de Vlas, S. J.; Stolk, W. A. African Program for Onchocerciasis Control 1995–2010: Impact of Annual Ivermectin Mass Treatment on Off-Target Infectious Diseases. *PLoS Negl. Trop. Dis.* **2015**, *9*, e0004051, doi:10.1371/journal.pntd.0004051.

106. Means AR; Burns, P.; Sinclair, D.; JL, W. Antihelminthics in helminth-endemic areas : effects on HIV disease progression (Review). *Cochrane Database Syst. Rev.* **2016**, doi:10.1002/14651858.CD006419.pub4.

107. Simon, G. G. Impacts of neglected tropical disease on incidence and progression of HIV/AIDS, tuberculosis, and malaria: scientific links. *Int. J. Infect. Dis.* **2016**, *42*, 54–57, doi:10.1016/j.ijid.2015.11.006.

1255 108. Luroni, L. T.; Gabriel, M.; Tukahebwa, E.; Onapa, A. W.; Tinkitina, B.;
1256 Tukesiga, E.; Nyaraga, M.; Auma, A. M.; Habomugisha, P.; Byamukama, E. et
1257 al. The interruption of Onchocerca volvulus and Wuchereria bancrofti
1258 transmission by integrated chemotherapy in the Obongi focus, North Western
1259 Uganda. *PLoS One* **2017**, *12*, e0189306, doi:10.1371/journal.pone.0189306.

1260 109. Lakwo, T.; Garms, R.; Wamani, J.; Tukahebwa, E. M.; Byamukama, E.;
1261 Onapa, A. W.; Tukesiga, E.; Katamanywa, J.; Begumisa, S.; Habomugisha, P.
1262 et al. Interruption of the transmission of Onchocerca volvulus in the Kashoya-
1263 Kitomi focus, western Uganda by long-term ivermectin treatment and
1264 elimination of the vector Simulium neavei by larviciding. *Acta Trop.* **2017**, *167*,
1265 128–136, doi:10.1016/j.actatropica.2016.12.029.

1266 110. Boakye, D.; Tallant, J.; Adjami, A.; Moussa, S.; Tekle, A.; Robalo, M.; Rebollo,
1267 M.; Mwinza, P.; Sitima, L.; Cantey, P. et al. Refocusing vector assessment
1268 towards the elimination of onchocerciasis from Africa: A review of the current
1269 status in selected countries. *Int. Health* **2018**, *10*, i27–i32,
1270 doi:10.1093/inthealth/ihx066.

1271 111. Aljayyoussi, G.; Tyrer, H. E.; Ford, L.; Sjoberg, H.; Pionnier, N.; Waterhouse,
1272 D.; Davies, J.; Gamble, J.; Metugene, H.; Cook, D. A. N. et al. Short-course,
1273 high-dose rifampicin achieves Wolbachia depletion predictive of curative
1274 outcomes in preclinical models of lymphatic filariasis and onchocerciasis. *Sci.*
1275 *Rep.* **2017**, doi:10.1038/s41598-017-00322-5.

1276 112. Abegunde, A. T.; Ahuja, R. M.; Okafor, N. J. Doxycycline plus ivermectin
1277 versus ivermectin alone for treatment of patients with onchocerciasis (Review).
1278 *Cochrane Database Syst. Rev.* 2016.

113. Tamarozzi, F.; Tendongfor, N.; Enyong, P. A.; Esum, M.; Faragher, B.; Wanji, S.; Taylor, M. J. Long term impact of large scale community-directed delivery of doxycycline for the treatment of onchocerciasis. *Parasit. Vectors* **2012**, *5*, 53, doi:10.1186/1756-3305-5-53.

114. Walker, M.; Specht, S.; Churcher, T. S.; Hoerauf, A.; Taylor, M. J.; Basáñez, M. G. Therapeutic efficacy and macrofilaricidal activity of doxycycline for the treatment of river blindness. *Clin. Infect. Dis.* **2015**, *60*, 1199–1207, doi:10.1093/cid/ciu1152.

115. Klarmann-Schulz, U.; Specht, S.; Debrah, A. Y.; Batsa, L.; Ayisi-Boateng, N. K.; Osei-Mensah, J.; Mubarik, Y.; Konadu, P.; Ricchiuto, A.; Fimmers, R. et al. Comparison of Doxycycline, Minocycline, Doxycycline plus Albendazole and Albendazole Alone in Their Efficacy against Onchocerciasis in a Randomized, Open-Label, Pilot Trial. *PLoS Negl. Trop. Dis.* **2017**, *11*, e0005156, doi:10.1371/journal.pntd.0005156.

116. Clare, R. H.; Cook, D. A. N.; Johnston, K. L.; Ford, L.; Ward, S. A.; Taylor, M. J. Development and validation of a high-throughput anti-Wolbachia whole-cell screen: A route to macrofilaricidal drugs against onchocerciasis and lymphatic filariasis. *J. Biomol. Screen.* **2015**, *20*, 64–69, doi:10.1177/1087057114551518.

117. Awadzi, K.; Opoku, N. O.; Attah, S. K.; Lazdins-Helds, J.; Kuesel, A. C. A Randomized, Single-Ascending-Dose, Ivermectin-Controlled, Double-Blind Study of Moxidectin in Onchocerca volvulus Infection. *PLoS Negl. Trop. Dis.* **2014**, *8*, e2953, doi:10.1371/journal.pntd.0002953.

118. Opoku, N. O.; Bakajika, D. K.; Kanza, E. M.; Howard, H.; Mambandu, G. L.; Nyathirombo, A.; Nigo, M. M.; Kasonia, K.; Masembe, S. L.; Mumbere, M. et al. Single dose moxidectin versus ivermectin for Onchocerca volvulus infection in Ghana, Liberia, and the Democratic Republic of the Congo: A randomised, controlled, double-blind phase 3 trial. *Lancet* **2018**, *6736*, doi:10.1016/S0140-6736(17)32844-1.

119. Turner, H. C.; Walker, M.; Attah, S. K.; Opoku, N. O.; Awadzi, K.; Kuesel, A. C.; Basáñez, M.-G. The potential impact of moxidectin on onchocerciasis elimination in Africa: an economic evaluation based on the Phase II clinical trial data. *Parasit. Vectors* **2015**, *8*, 167, doi:10.1186/s13071-015-0779-4.

120. Fischer, P. U.; King, C. L.; Jacobson, J. A.; Weil, G. J. Potential Value of Triple Drug Therapy with Ivermectin, Diethylcarbamazine, and Albendazole (IDA) to Accelerate Elimination of Lymphatic Filariasis and Onchocerciasis in Africa. *PLoS Negl. Trop. Dis.* **2017**, *11*, e0005163, doi:10.1371/journal.pntd.0005163.

121. Crisford, A.; Ebbinghaus-Kintscher, U.; Schoenhense, E.; Harder, A.; Raming, K.; O'Kelly, I.; Ndukwe, K.; O'Connor, V.; Walker, R. J.; Holden-Dye, L. The Cyclooctadepsipeptide Anthelmintic Emodepside Differentially Modulates Nematode, Insect and Human Calcium-Activated Potassium (SLO) Channel Alpha Subunits. *PLoS Negl. Trop. Dis.* **2015**, *9*, e0004062, doi:10.1371/journal.pntd.0004062.

122. Cotton, J. A.; Bennuru, S.; Grote, A.; Harsha, B.; Tracey, A.; Beech, R.; Doyle, S. R.; Dunn, M.; Hotopp, J. C. D.; Holroyd, N. et al. The genome of Onchocerca volvulus, agent of river blindness. *Nat. Microbiol.* **2016**, *2*, doi:10.1038/nmicrobiol.2016.216.

123. Lustigman, S.; Makepeace, B. L.; Klei, T. R.; Babayan, S. A.; Hotez, P.; Abraham, D.; Bottazzi, M. E. Onchocerca volvulus: The Road from Basic Biology to a Vaccine. *Trends Parasitol.* **2018**, *34*, 64–79, doi:10.1016/j.pt.2017.08.011.

124. Lustigman, S. Sara Lustigman: Developing a vaccine to accelerate onchocerciasis elimination. *Trends Parasitol.* **2018**, *34*, 1–3, doi:10.1016/j.pt.2017.11.001.

125. Mitjà, O.; Marks, M.; Bertran, L.; Kollie, K.; Argaw, D.; Fahal, A. H.; Fitzpatrick, C.; Fuller, L. C.; Garcia Izquierdo, B.; Hay, R. et al. Integrated Control and Management of Neglected Tropical Skin Diseases. *PLoS Negl. Trop. Dis.* **2017**, *11*, e0005136, doi:10.1371/journal.pntd.0005136.

126. World Health Organization. *Recognizing Neglected Tropical Diseases Through Changes on the Skin A Training Guide for Front-line Health Workers*; 2018; ISBN 978-92-4-151353-1.

127. Hofstraat, K.; van Brakel, A. H. Social stigma towards neglected tropical diseases: A systematic review. *Int. Health* **2016**, *8*, i53–i70, doi:10.1093/inthealth/ihv071.

128. Vinkeles Melchers, N.V.S.; Coffeng, L..E.; Murdoch, M.E.; Pedrique, B.; Bakker, R.; Ozoh, G.A.; de Vlas, S.J.; Stolk, W. A. Impact of ivermectin mass treatment on the burden of onchocercal skin and eye disease: detailed model predictions up to 2025. *Am J Trop Med Hyg* **2016**, *95*, 345, doi:10.4269/ajtmh.abstract2016.

129. World Health Organization. Summary of global update on preventive

chemotherapy implementation in 2016: crossing the billion. *Wkly. Epid. Rec. Epid Rec* **2017**, *92*, 589–593.