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Factors affecting onchocerciasis transmission: lessons for infection control

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ABSTRACT

Introduction: *Onchocerca volvulus* infects in excess of 15 million people. The vectors are *Simulium* blackflies, varieties of which differ in their ecologies, behaviour and vectorial abilities. Control of the vectors and mass administrations of ivermectin have succeeded in reducing prevalences with elimination achieved in some foci, particularly in Central and southern America. In Africa, progress towards elimination has been less successful.

Areas covered: Even with community directed treatment with ivermectin (CDTI), control has been difficult in African areas with initial prevalences in excess of 55%, especially if only annual treatments are dispensed. This is partly attributable to insufficient coverage, but the appearance of incipiently resistant non-responding parasites and lack of attention to vector biology in modelling and planning outcomes of intervention programmes have also played their parts, with recrudescence now appearing in some treated areas.

Expert commentary: The biology of onchocerciasis is complex involving different vectors with differing abilities to transmit parasites, diverse pathologies related to geographical and parasite variations and endosymbionts in both parasite and vector. Modelling to predict epidemiological and control outcomes is addressing this complexity but more attention needs to be given to the vectors' roles to further understanding of where and when control measures will succeed.

KEYWORDS: *Onchocerca volvulus* • *Simulium damnosum* complex • vector biology • ivermectin • doxycycline • moxidectin •

1. Introduction

The parasitic disease onchocerciasis or "river blindness" is caused by the filarial worm *Onchocerca volvulus* and is transmitted by blackflies of the genus *Simulium*. The disease is found in sub-Saharan Africa, the Yemen and in Central and South America. In sub-Saharan Africa about 15 and a half million people may still be infected [1]. A further half a million were at risk in Latin America [2] but recent control programmes have reduced this number considerably, with only about 27,000 needing preventive chemotherapy in Brazil and Venezuela [3]. Severe symptoms include punctate and sclerosing keratitis in the anterior segment and optic nerve atrophy in the posterior segment and, at worst, the infection leads to bilateral blindness. In addition, onchocerciasis causes serious skin conditions such as severe itching, erythematous rashes, de-pigmentation including "lizard skin", secondary infections after itchy areas are scratched, palpable nodules containing the adult worms, "hanging groin" and the condition known as "sowda". There are also associations between onchocerciasis and epilepsy and dwarfism and, in addition, there is circumstantial evidence that the affliction known as "nodding disease" is associated with onchocercal infections [4]. Excess mortality attributable to onchocerciasis has been reported [5,6,7]. Diagnosis is by finding microfilariae in skin snips, usually from the iliac crest, by immunological and molecular techniques and, in severe cases, by observing microfilariae within the eye or from biopsies of excised nodules.

There is a variety of factors that affect or could affect the transmission of the disease. These include (1) rates of vector-man contact and lengths of time that exposure to infected vectors persists; (2) the parasite reservoir within human hosts; (3) the identity of the vector; (4) the ecology of the vector, especially regarding whether it is perennial or seasonal at a transmission site; (5) the vectorial efficiency of the vector and factors affecting it; (6) the presence or absence of endosymbiotic *Wolbachia* bacteria in either or both of the vector and the parasite; (7) variation between the parasite populations being transmitted and (8) variation in the immunity of the human hosts to parasite challenge, which may be affected by zooprophylaxis in the presence of the bovine parasite *Onchocerca ochengi* [8,9]. Means to interrupt transmission to achieve infection control include (a) vector control using larvicides sprayed upstream of the insects' breeding sites in rivers or streams or by other means such as placing of briquettes impregnated with larvicide in breeding sites or vegetation control to remove larval supports; (b) nodulectomy, involving the excision from patients of sub-cutaneous nodules harbouring adult parasites; (c) mass drug administration (MDA) of microfilaricidal drugs such as ivermectin, now by community-directed treatment with

ivermectin (CDTI); (d) treatment with macrofilaricides and (e) various combinations of two or more of procedures (a) to (d). In this review, the salient features of the above topics are summarised and explanations are given of some of the constraints that can limit the effectiveness of actual or potential interventions be they against the vectors or the parasite. First, where onchocerciasis has been wholly or partially interrupted is briefly reviewed, to permit concentration on the geographical zones where the disease remains a major problem and where the lessons to be learnt for infection control from knowledge of the factors affecting transmission are most in need of implementation. The focus will thus be on African problems where CDTI has yet to prove its full potential in contrast to situations in the Americas where it has been successful. Possible reasons for this difference will be addressed.

2. The Vectors

2.1. Sub-Saharan Africa and the Yemen

In most of sub-Saharan Africa and the Yemen, the vectors are members of the *Simulium damnosum* complex. Exceptions include *S. woodi* and other members of the *S. neavei* group, including *S. neavei* itself, which transmit the disease in parts of East Africa such as Uganda and have their immature stages phoretic on freshwater crabs (family Potamonautidae), and *S. albovirgulatum* which is a vector in the central basin region of the Democratic Republic of Congo [10]. The *S. damnosum* complex comprises at least 63 cytoforms, many of which have been given formal scientific names; 32 of the forms are known to be anthropophilic, a further three are presumed to be, and 22 are proven vectors [11]. At least two of these confirmed vectors (the Bioko form of *S. yahense* [12] and the Djodji form of *S. sanctipauli* [13]) have been rendered extinct by vector control measures and it is suspected that the "Chutes Milo" form of *S. soubrense* has suffered the same fate [14].

2.2. Central and South America

In Mexico, the main vectors in the only known foci in Chiapas and Oaxaca States are members of the *S. ochraceum* and *S. metallicum* complex but the disease has now been eliminated from the country [15]. In Guatemala, where transmission has been interrupted, there were four main foci where the vectors are members of the *S. ochraceum* complex. In northern Venezuela, the main vectors in both the north-eastern and north-central foci are members of the *S. metallicum* complex, whereas in southern Venezuela the main vectors in the Amazonas/Bolivar focus are members of the *S. guianense* complex. That focus is

contiguous with the Amazonas-Roraima or Amazônia focus in northern Brazil which has the same vectors (*S. guianense* complex and *S. incrustatum*) in highland areas, but in lowland parts of the Amazônia focus the main vectors are members of the *S. oyapockense* complex [16]. In the Minaçu focus in central Brazil, NNW of Brasilia, *S. nigrimanum* is suspected to be the main vector but there are other candidates [17]. In the Lópes de Micay focus of western Colombia, the main vectors are members of the *S. exiguum* complex, while in Ecuador the main vectors in the Esmeraldas / Pichincha focus are members of the *S. exiguum* complex and *S. quadrivittatum*.

3. Interruptions of Transmission in Latin America: probably permanent cases

The Onchocerciasis Elimination Program for the Americas (OEPA) has coordinated control efforts against the disease in 13 foci located in Brazil, Colombia, Ecuador, Guatemala, Mexico and Venezuela. OEPA is a consortium of those countries with the Pan American Health Organization, the ivermectin donor Merck & Co., Inc., the USA's Centers for Disease Control and Prevention (CDC) and The Carter Center, Lions Clubs International Foundation and the Christian Blind Mission, all international Nongovernmental Development Organizations. Reliant only on MDA, the aim is to treat all affected populations two to four times a year [18,19]. The programme has been successful, claiming 85% coverage, and the extent of the successes is briefly described below, with elimination or interruption of transmission reported from 11 foci. A map of the 13 OEPA foci with progress up to 2011 was given by Gustavsen et al. [19], but they omitted the Minaçu focus in Brazil which was not part of OEPA, as did Rodriguez-Perez et al. [20] who updated progress to 2013. Onchocerciasis elimination successes in the Americas according to country are as follows. ***Colombia:*** the disease has been declared as eliminated [21]; ***Ecuador:*** transmission has been eliminated [22]; ***Guatemala:*** the disease has been declared as eliminated [18]; ***Mexico***: transmission has been eliminated [15] and ***northern Venezuela***: transmission has been interrupted in the north-eastern focus and has been eliminated from the north-central focus [20, 23].

4. Incomplete interruptions of Transmission in Latin America

Brazil: transmission is continuing in the Amazonas [24] and possibly in the Minaçu foci. ***Venezuela***: transmission is continuing in the south focus where onchocerciasis remains in the

indigenous Yanomami population inhabiting the Amazon rainforest on both sides of the Venezuela and Brazil border [24].

5. Interruptions of Transmission in Africa: probably permanent cases

5.1. Equatorial Guinea

In 2005 the unique endemic Bioko form of *S. yahense* [25] was eradicated from the island of Bioko (formerly known as Fernando Po), Equatorial Guinea, in the Gulf of Guinea [12]. Although MDA with ivermectin was underway and was making progress, the cessation of transmission there can be attributed to the vector elimination programme. This was achieved by a combination of applications by helicopter and ground-based spraying of the organophosphate insecticide temephos that was managed by the WHO African Programme for Onchocerciasis Control (APOC). A follow-up study in early 2014 has shown that no children less than 10 years old have been infected showing that disease elimination is in progress [26].

5.2. Ethiopia

In the Tigray Region onchocerciasis has disappeared without any deliberate interventions against it, but probably as a result of human migrations and the introduction of commercial farming practices [27].

5.3. Kenya

Davies [28] reviewed control attempts against *Simulium* spp. when he could report that a combination of vegetation removal and DDT had successfully stopped transmission in Kenya, where the vector *S. neavei* was eradicated from six foci between 1946 and 1955 [29,3029].

5.4. Sudan

The first evidence in East Africa that long-term CDTI alone can interrupt transmission of onchocerciasis was provided by the case of the Abu Hamed focus on the River Nile in Sudan, where ivermectin was first distributed annually in 1998. From 2006 onwards, treatments were increased to twice per annum and by 2011 no infections were found [31].

5.5. Uganda

Successes in Uganda included use of DDT against *S. damnosum* in the Ruwenzori focus from 1963 to 1977 and at Jinja, where the River Nile drains from Lake Victoria, in 1973. *S. neavei* was eliminated from the Itwara focus, also in Uganda and where annual distributions of ivermectin were not succeeding, using ground-based applications of temephos in the late 1990s [32], followed by the disappearance of the disease by 2010 [33]. Onchocerciasis transmission by *S. neavei* was also interrupted in the Mpamba-Nkusi focus of Uganda by MDA that began in 1993 but the impact of vector control in 2002 was decisive as it led to the elimination of the vector by 2008 [34]. Similarly, vector control eliminated *S. neavei* in the Mt Elgon focus, perhaps assisted by environmental effects such as deforestation, and drug treatments were stopped there in 2012 after annual MDA since 1994 was increased to twice per annum in 2007 [35]. After MDA in the Wadelai focus, it was confirmed that onchocerciasis had been eliminated in 2010 but this was probably partly attributable to the earlier disappearance of the vectors for environmental reasons [36]. Elimination of *S. neavei* combined with MDA has stopped transmission in the Kashoya-Kitomi focus [37]. Transmission continues in the Kasese focus where the vector is *S. kilibanum*, a member of the *S. damnosum* complex [38].

6. Interruptions of Transmission in Africa: probably temporary

6.1. Eleven countries in West Africa

The rationale for the WHO Onchocerciasis Control Programme (OCP) was based on the prevailing notion that there was a difference between forest and savanna strains of the disease based on research by Duke and his colleagues [39], who developed the concept of *Simulium-Onchocerca* complexes after finding incompatibilities between savanna vectors and forest-derived parasites and *vice versa*. As there was also evidence that there was more blindness in savanna areas than in forest zones, where blindness was rarer, it was assumed that only the savanna form of the parasite was important in blinding onchocerciasis. Thus, with the objective of eliminating onchocerciasis as a disease of public health and socio-economic importance and prevent recrudescence, the initial plan was to use aircraft to treat only rivers where savanna vectors were present with the organophosphate larvicide temephos (Abate®) [40]. It was the biggest vector control programme ever mounted and its massive scale was partly based on experience gained from smaller operations after which vectors continued to re-appear from surrounding areas. The WHO Onchocerciasis Control Programme (OCP) began its campaign in seven different West African countries (Benin, Burkina Faso, Côte

d'Ivoire, Ghana, Mali, Niger and Togo) in 1975 which, with later additions of more countries (Guinea, Guinea-Bissau, Senegal, Sierra Leone) and MDA of ivermectin, it continued until 2002. The ivermectin (150 µg/kg of body weight, orally) was donated as Mectizan® (ivermectin-MSD) by Merck & Co. Inc. (Kenilworth, NJ, USA) and was freely available to OCP from 1989. The widespread benefits of the operation included the elimination of the disease as a public health problem (except in Sierra Leone because of civil strife), 600,000 cases of blindness were prevented, 18 million children born in now-controlled areas spared from the risk of river blindness and 25 million hectares of land were made safe for cultivation and resettlement [18, 41]. Nevertheless, pockets of transmission remain where it was never successfully interrupted, as documented for Ghana [42] and where some patients do not respond to ivermectin [43,44]. Furthermore, there is a continuous threat of reinvasion of the OCP-controlled areas by infected vectors or by infected human migrants and recrudescence has now been reported in Burkina Faso, particularly in the Comoé valley where one site had a prevalence in excess of 71% in March 2010 [45].

6.2. Mali

After 17 years of annual distributions of ivermectin in the R. Bakoye focus, including being part of the western extension of the OCP where MDA without any vector control was initiated in 1988, followed by 4 years of no treatments, the prevalence of microfilariae and infectivity levels in the vectors, estimated by pool-screening methods [46], had both declined to zero [47]. In the R. Faleme focus that straddles the Mali / Senegal border, overall prevalence fell from 34% to 0.84% after 15 years of annual treatments and dropped to 0.07% a further 2.5 to 5 years later. There were still some infections present in vectors so complete elimination was not achieved, but this was claimed as there was no evidence of recrudescence of either infection or of transmission rates [47]. Time will tell if this achievement is maintained or if transmission resumes once infected vectors reinvade from neighbouring territories.

6.3. Nigeria

Tekle *et al*. [48] reported successful elimination after using ivermectin for 15 to 17 years in the Birnin Gwari Local Government Area (LGA) and in the Kauru and Lere LGAs of Kaduna State. The median initial prevalence was 52% and was reduced to zero in a sample of 3703 patients following the APOC-led CDTI programme. As with the Malian case, time will tell if

this achievement is maintained or if transmission resumes once infected vectors reinvade from neighbouring territories.

6.4. Senegal

In the R. Gambia focus, prevalences of onchocerciasis and vector infectivity rates were reduced to zero by six-monthly treatments for 14 to 16 years, from an initial level of 49.6% [47]. For details of the R. Faleme focus see under Mali (above). The same caveats about potential vector reinvasions into cleared areas of Mali and Nigeria also pertain for Senegal.

6.5. Uganda

Applications of DDT eliminated *S. neavei* in parts of the Kasowka-Bokwe subfocus within the Budongo forest of Uganda [49,50], but the vector has now returned [51].

7. Entomological factors important in transmission

7.1. Man-vector contact rates

Rates of microfilarial densities and blindness due to onchocerciasis in savanna regions tend to be higher in males than females [52] so, in addition to absolute rates of man-vector contact that will affect transmission rates, there are differences within human populations [53]. These have been attributed to gender- and age-related behavioural differences. Thus, in the Sudan savanna of North Cameroon, boys are subject to more than twice the exposure to vector bites as are girls and this gender-based difference is usually maintained later in life [54].

7.2. Vector competence and zoophily

Vector competence differs between species and cytoforms. Amongst the South American forms, some of the differences can be ascribed to the presence or absence of cibarial teeth in the female insects' mouthparts [55]. For those species such as *S. ochraceum* s.l., *S. oyapockense* s.l. and *S. incrustatum* that have these structures, the likelihood of microfilariae escaping into a fly's abdomen undamaged is greater the more that are taken up by the fly, a relationship that is density dependent and species specific [56]. The armature protects flies from death if they take up an excessive number of microfilariae, which happens rapidly in these circumstances for species without the structure such as *S. metallicum* [57]. There are also many other interactions such as the effects of parasite loads on fly fecundity [58], fly survival, the availability to the flies of microfilariae from humans, the frequency distributions

of *Onchocerca* within the flies, the survival of the worms within the flies (and thus the proportions of microfilariae that become established to develop into third stage infective larvae (L3s)) and the extent of the flies' zoophily, all of which influence transmission dynamics [56,59].

Amongst the *S. damnosum* complex in Africa, there are many species that do not transmit onchocerciasis at all or do so very inefficiently. For example *S. pandanophilum, S. kulfoense* and *S. soderense* seem to be entirely zoophilic [11], whereas type 4 cytotypes of *S. sirbanum* can transmit but are also highly zoophilic [60,61]. The extent of zoophily in vectors studied in Ghana ranged from a human biting index (HBI, measured as proportion of meals taken on man) of 0.44 in *S. squamosum* cytoform E to 0.92 in the Beffa form of *S. soubrense* [62]. That study also revealed the extent of intraspecific variation in vectorial abilities as the human biting index of *S. squamosum* cytoform C was 0.86 (i.e. nearly twice that of cytoform E), thereby further emphasising the importance of correct vector identifications in studies of onchocerciasis transmission. This is also important for understanding transmission rates in different areas where the vectors may differ, which were summarised by Cheke & Garms [63]. For instance, in East Africa, *S. kilibanum* transmits at a rate of 19 L3s per 1000 biting flies, whereas the maximum value reported was for the Pra form of *S. sanctipauli* in Ghana with 191 [63]. The latter species is adapted to forest habitats, so the result is paradoxical since manifestations of the disease, particularly in terms of percentages of bilateral blindness, are more severe in savanna areas [64] where the transmission rates of the main vectors, *S. damnosum* s.str. and *S. sirbanum* were only 84 L3s per 1000 biting flies [63]. Furthermore, in Liberia, another forest vector, *S. yahense*, is associated with blindness rates of 2.1 to 8.9%, which together with other evidence led Cheke & Garms [63] to question the prevailing paradigm derived from Duke's work [39] of there being forest and savanna strains of *O. volvulus* with contrasting epidemiological effects and transmitted as part of differing systems of *Simulium-Onchocerca* complexes. Whilst there certainly are geographical differences between epidemiological patterns it does not now seem plausible that they can be explained by a simple forest-savanna dichotomy, especially since molecular data have demonstrated gene flow from savanna to forest "strains" and the existence of admixed populations [64] There are, however, major differences between vectors not only regarding their vectorial abilities but also with respect to their behaviour and ecologies with implications for disease management. Regarding the vectorial abilities, the crude indices of numbers per 1000 biting flies or numbers per 1000 parous flies mask a complication that is linked to the paradox raised above. Flies adapted to predominantly forest habitats often harbour far more parasites

per infected fly than do those adapted to mostly savanna zones. Thus, frequency distributions of numbers of parasites per fly in forest taxa, such as members of the *S. sanctipauli* sub-complex and *S. yahense*, have longer tails and higher maxima than other forms [66]. This is reflected in lower values of the parameter k of the negative binomial distribution (NBD) when NBDs are fitted to frequency distributions of numbers of larvae of each of the different stages, meaning that the forest forms have more overdispersed, or clumped, parasite distributions than do their savanna cousins. In terms of mean numbers of L3 parasites per fly with L3s, the savanna *S. damnosum* / *S. sirbanum* have only 1.9 whereas the St. Paul form of *S. soubrense* boasts 6.6 [63]. These results are difficult to reconcile with the *Onchocerca-Simulium* complex idea given that when forest-associated taxa such as the Beffa form of *S. soubrense* and the savanna-associated *S. damnosum* / *S. sirbanum* are biting the same human populations in sympatry the vectors retain their taxon-specific characteristic transmission patterns [66].

Irrespective of variations in parasite loads, variation in the longevities of different species is also critical for transmission. Species with short life-spans have low parous rates and in some cases so few individuals live long enough for the parasites to develop to the infective stage that their vectorial efficiencies are low. For example, one of the reasons that the St.Paul form of *S. soubrense* is an inefficient vector is its low parous rate while, in contrast, some *S. sirbanum* may live for more than two months [67] and hence are capable of transmitting several times. This ability will also be affected by increased longevity in dry seasons and gonotrophic cycle lengths, for which evidence from both pteridine accumulation rates [68] and time series analysis [69] suggest may be longer in *S. squamosum* than in *S. damnosum* / *S. sirbanum*. A further complication is that parous rates are inversely density dependent [70].

In some cases, such as with *S. yahense* in Liberia (see above), only one vector species is responsible for all of the transmission in a zone but more often vectors occur sympatrically, as in the above example, so that there are a mixture of species in biting populations. For instance, in the Dayi river at Kudzra and Wegbe in the Volta region of Ghana at least five different members of the *S. damnosum* complex (*S. damnosum* s.str.*, S. sirbanum, S. squamosum, S. yahense* and *S. sanctipauli*) have been recorded simultaneously (supplementary data of [71]). This makes interpretation of transmission patterns and effects of control difficult without painstaking identifications of individual flies. For example, at Djodji (known as Pillar 83 in Ghana on the opposite side of the river) beside the Gban-Houa river (known as the Wawa river in Ghana) flies are still biting in the post-OCP era but monthly biting rates are less than they used to be (e.g. approx 7,000 versus approx 12,000 in

February and March [72]). This is because most of the biting is now attributable to *S. squamosum* following the elimination by OCP of a more efficient vector (the Djodji form of *S. sanctipauli*) [13].

The forest-dwelling vector taxa are generally more sedentary than the savanna species, which are renowned for very long distance movements of 300km or more [73], so vector control is easier to maintain in forests. In savannas controlled zones are liable to be reinfested by immigrants from afar, a phenomenon that afflicted the OCP [73,74,75,76] which was resolved by extending the treated zones. Another problem that affected OCP was the development in some cytoforms of resistance to the insecticides of choice that was circumvented partly by introducing alternative larvicides and partly by a policy of rotating the ones in use [77].

7.3. Vectors and Wolbachia

The endosymbiont *Wolbachia* is important in the pathology of cutaneous and ocular manifestations of onchocerciasis as the bacteria engender inflammatory reactions [78,79]. These *Wolbachia* are also crucial for the parasites' survival, which is exploited in antibiotic treatments with doxycycline (see below). However, the significance of *Wolbachia* within the vectors has received less attention. A phylogenetically unique form of *Wolbachia* has been identified from *S. squamosum* E in Ghana [80], together with an associated bacteriophage that could potentially act as a vehicle for genetic modification of insect *Wolbachia* [81]. In addition to the finding of *Wolbachia* in *S. squamosum* E, the endosymbionts have also been found in another forest vector (*S. yahense*) and, rarely, in a third forest form (*S. sanctipauli*) but so far only once in a savanna vector (*S. damnosum* s.str.) (J. L. Crainey, pers. comm., January 2017) so, although speculative, it is possible that *Wolbachia* may play a part in how onchocerciasis is differentially transmitted by vectors from different biomes, given that *Wolbachia* can affect how mosquitoes transmit some pathogens. Further research on *Wolbachia* in different members of the *S. damnosum* complex is urgently needed to elucidate its role or roles, if any, in the transmission of onchocerciasis and its potential as a control agent, given that *Wolbachia* is now used to control mosquito vectors of the dengue virus and other pathogens.

8. Treatments

8.1. Microfilaricides

Ivermectin, the mainstay of MDA and CDTI programmes, is contra-indicated in areas where the eye-worm *Loa loa* is also present [82], so alternative drugs are needed where *O.volvulus* and *L. loa* are sympatric and when a test and treat approach has demonstrated co-infection. Diethylcarbamazine is also contra-indicated because of the risk of a strong Mazzotti reaction and exacerbation of ocular pathology, but a combination of doxycycline and albendazole [83] or doxycycline alone [84] can be used under these circumstances. Apart from ivermectin, other microfilaricides include moxidectin, which has a longer-lasting effect than ivermectin and with little re-population [85] but it has yet to be licensed. Doxycycline, a macrofilaricide (see below) also has a deleterious effect on microfilariae as it inhibits their rate of development in vectors and so influences transmission rates [86]. There are also other reasons for seeking alternatives to ivermectin since Awadzi *et al*. [87,88] reported that some patients treated with the drug were not responding as expected since their microfilarial loads re-populated rapidly, a phenomenon confirmed by Osei-Atweneboana *et al*. [43,44]. There is also evidence of incipient resistance in Cameroon [89,909]. Clearly, if common or spreading, the presence of non-responding parasites will increase the probability that transmission will continue or be enhanced. Other entomological issues related to ivermectin delivery concern the need to time interventions at the times when transmission is at its height. This is because modelling has shown that the timing of drug distributions in relation to seasonal transmission peaks has an impact on the period needed for a MDA programme to achieve maximum reductions in skin microfilarial loads [91]. The frequency of ivermectin treatments is also a factor. Indeed some failures of annual distributions to interrupt transmission [90,93,94,95] have led to the adoption by many health authorities of biannual treatments which have been shown to improve the efficacy of ivermectin, except in the case of sub-optimally responding parasites [96].

8.2. Macrofilaricides

Doxycycline is the only usable macrofilaricide at present but the need for daily doses of 100 or 200 mg orally for 4-6 weeks precludes its use in MDA or CDTI, plus it cannot be prescribed for pregnant women and children less than 8 years old. Doxycycline, being an antibiotic, functions by killing endosymbiotic *Wolbachia* within the adult worms. This leads to sterility of the worms and hence reduced production of microfilariae and the adults' longevity declines from about 10 years to 2 to 3 years [97]. Doxycycline is also valuable as a potential drug for use where *L. loa* is sympatric with *O. volvulus*, since *L. loa* does not contain *Wolbachia* and so treatments do not lead to adverse reactions in co-infected patients.

8.3. Compliance with treatments

Despite some claims of very high rates of compliance in MDA or CDTI programmes, compliance is often less than adequate in many parts of Africa when it fails to reach the target of 65% [98]. There may also be discrepancies between officially released compliance estimates and results from questionnaires. For example, Kutin *et al*. [99] reported a compliance rate of only 24.4% in Ghana whereas other estimates from the same country based on official returns ranged from 50 to 90% [42] and 42–96% [96].

9. Vector and parasite criteria for declarations of onchocerciasis elimination

Larvicidal treatments were stopped in the OCP once transmission indices had reached a level of one infective larva per 1000 parous flies. Subsequently APOC, which has shifted its main aim from the control of onchocerciasis morbidity to elimination of the parasite reservoir, where feasible, with annual (or biannual) ivermectin MDA, proposed criteria for declarations of onchocerciasis elimination. These were that CDTI could be stopped once a microfilarial prevalence of <5% in all surveyed villages and <1% in 90% of such villages had been achieved, together with transmission indices of <0.5 infective larvae per 1000 dissected flies [100]. Computer models of onchocerciasis transmission have been used to estimate thresholds of parasite densities below which transmission would be so low as to lead to the collapse of the parasite population. Such transmission break points and similar thresholds were investigated with respect to MDA by Stolk *et al*. [101], who concluded that APOC's operational thresholds need adjustment in relation to pre-control endemicity levels. This conclusion was based on comparisons of outputs from the individual-based simulation model ONCHOSIM [102] and a deterministic population model EPIONCHO [103]. Results from the latter were more pessimistic than those from the former and suggested that local elimination using CDTI, even biannually, would take more than 25 years at baseline endemicity levels >55%. Further model comparisons have been presented by Basáñez *et al*. [59] who also emphasised the need to adjust criteria for elimination based largely on elaborations of EPIONCHO. Both ONCHOSIM and EPIONCHO are complex models seeking to tackle most aspects of the biology and control of onchocerciasis, which include scenarios involving vector control and aspects of parasite establishment within vectors. However, they make no attempts to include vector population dynamics, which are treated as

a fixed input (the annual biting rate, with an option for considering seasonal variations), nor what happens when different vector taxa, each with differing vectorial characteristics, are transmitting in sympatry. Thus, some of the most important factors in transmission are side-lined and the biggest threat to onchocerciasis control programmes, reinvasion of infected vectors from outside controlled zones, is ignored. It is expected that future modelling work will remedy some of these omissions by including vector dynamics, following initial work linking them to EPIONCHO [104].

10. Vaccines for onchocerciasis

Based on successful results using animal models, some candidate vaccines against onchocerciasis have been found [105,106] and further trials are planned. The potential deployment of a vaccine has been modelled and it was concluded that after 15 years of a childhood vaccination programme it would have a protective effect and be valuable for preventing re-emergence of the disease in areas cleared of the infection [107].

11. Expert Commentary

Onchocerciasis remains an important cause of morbidity in parts of Brazil, Venezuela and Yemen and throughout much of sub-Saharan Africa despite more than 40 years of concerted control efforts. Mass drug administration programmes in Africa have not been as successful as they have been in central and southern America because the African foci are larger, coverage and compliance are less good, incipient resistance to ivermectin has appeared in parts of Ghana and Cameroon, ivermectin is contra-indicated for 14 million people where loiasis is co-endemic and recrudescence is appearing in areas previously subject to intense vector control. Apart from some areas with initial prevalences of 55% or less, where local eliminations using MDA/CDTI have been reported, successful eliminations in Africa, such as those in Equatorial Guinea and Uganda have been driven by vector control. Thus, in future, renewed consideration needs to be given to localised vector control coupled with CDTI, especially in hyperendemic areas, and to vector migrations.

12. Five-year View

As progress towards elimination of onchocerciasis proceeds, there is a need to seek alternatives to ivermectin that are amenable to mass distribution, as incipient resistance to ivermectin may spread. The publication of the genome of *O. volvulus* [108] should assist this

search. Means to improve coverage and compliance of CDTI and the discovery of a reliable macrofilaricide are also required, together with continuing research to find a vaccine. Although speculative at this stage, understanding of the roles of endosymbionts within vectors and of any taxon-specific differences between them could lead to breakthroughs in elucidating geographical variation in epidemiological patterns and pathologies and to new control techniques. Models describing dynamics of the human parasite need to be linked to sub-models of vector population dynamics and migrations. Future climate changes may lead to the disease spreading or contracting its geographical range according to rainfall and temperature shifts.

13. Conclusion

Before its closure APOC has altered its main aim from controlling onchocerciasis morbidity to eliminating the parasite reservoir, where feasible, with annual (or biannual) ivermectin distributions. The Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN) now has the responsibility for oversight of onchocerciasis control [109]. To be successful, especially where prevalences exceed 55%, CDTI programmes such as those under ESPEN's guidance need to ensure high levels of coverage and compliance combined with localised vector management and recognition of the reality of vector movements, particularly in savanna habitats. CDTI needs to be extended to all endemic areas, including hypoendemic zones. Elimination is unlikely to be achieved with reliance on a single drug but may be successful given new micro- and macrofilaricides and a vaccine. Modelling efforts to predict the outcomes of control programmes need to take more account of vector biology.

14. Key Issues

- In most onchocerciasis-endemic areas ivermectin is still efficacious against the microfilariae of *Onchocerca volvulus* and is being deployed successfully.
- The potential for resistance to ivermectin spreading needs to be monitored and alternatives such as moxidectin developed for widespread use.
- A macrofilaricide capable of being used in MDA programmes and / or a vaccine would substantially improve the chances of onchocerciasis elimination.
- In contrast to successes in central and southern America, mass drug administration (MDA) in Africa is unlikely to succeed in areas with >55% prevalences without supplementary vector control or enhanced coverage of and compliance with MDA.

- Treated areas are threatened by invasions of infected vectors from surrounding untreated areas
- Correct vector identification and vector incrimination is crucial for understanding the epidemiology of onchocerciasis and vector population dynamics should be included in future modelling work designed to assist long-term planning and decision-making

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