Trends in Parasitology

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Review

Vector control and entomological capacity for onchocerciasis elimination

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Mass drug administration (MDA) of ivermectin is currently the main strategy to achieve elimination of transmission (EoT) of onchocerciasis. Modelling suggests that EoT may not be reached in all endemic foci using annual MDA alone. Onchocerciasis and loiasis are coendemic in forest areas of Central Africa where ivermectin treatment can lead to severe adverse events in individuals with heavy loiasis load, rendering MDA inappropriate. Vector control has been proposed as a complementary intervention strategy. Here, we discuss (i) achievements and pitfalls of previous interventions; (ii) epidemiological impact, feasibility, and combination with MDA to accelerate and/or protect EoT; (iii) role of modelling; (iv) opportunities for innovative methods of vector monitoring and control; and (v) strengthening entomological capacity in endemic countries.

Highlights

Modelling studies have suggested that elimination of transmission (EoT) of onchocerciasis may not be achieved by relying solely on mass drug administration (MDA) of ivermectin, particularly in hyperendemic areas and in those areas where onchocerciasis and loiasis are coendemic.

In onchocerciasis-loiasis coendemic areas, vector control methods could provide complementary strategies to accelerate elimination.

Study of host-seeking behaviour could inform the development of new control/monitoring tools against vectors. These new tools could be used against vectors of onchocerciasis, vectors of loiasis, or both.

Control and monitoring tools, exploiting the natural attraction of hosts, could be implemented by communities and enhance country ownership.

To ensure vector control capacity, well-trained, motivated, and appropriately funded local entomologists are essential to lead vector research and entomological operations.

Onchocerciasis

Onchocerciasis is among the 20 neglected tropical diseases (NTDs) prioritised by the World Health Organization (WHO) and targeted for **EoT** (see Glossary) in 12 countries by 2030 [1]. It is caused by *Onchocerca volvulus* (Nematoda: Filarioidea) and transmitted among humans by *Simulium* (Diptera: Simuliidae) blackflies [2].

The burden of onchocerciasis has been assessed by the Global Burden of Disease Study (GBD) for its contribution to years lived with disability (YLD) through visual impairment, blindness, and skin disease [3,4], with the 2019 estimate at 1.23 (95% uncertainty interval 0.765–1.82) million disability-adjusted life years (DALYs) [5]. However, onchocerciasis can cause excess mortality and, therefore, the values of DALYs ascribed to onchocerciasis are likely to be underestimates. For example, onchocerciasis-associated blindness may cause premature mortality [6,7]. Furthermore, even after adjusting for the impact of blindness on survival, heavy infection load with *O. volvulus* microfilariae is positively and statistically significantly associated with human mortality [8], with the relative mortality risk being statistically significantly higher for children than for adults [9]. Recently, a statistically significant dose–response relationship has been reported between microfilarial load in childhood and the probability of developing epilepsy (a cause of premature mortality) later in life [10].

Onchocerciasis is an anthroponotic infection for which preventive chemotherapy and transmission control (PCT) tools exist in the form of MDA with ivermectin. MDA is implemented in Africa through **community-directed treatment with ivermectin (CDTi)**, a strategy pioneered by the **African Programme for Onchocerciasis Control (APOC)** to increase the engagement of endemic communities, establish sustainable systems for ivermectin distribution, and reach coverage levels of at least 65% (of total population), to control onchocerciasis-associated morbidity [11]. Because the microfilariae are the parasite stage mainly associated with clinical manifestations and are also transmitted from humans to vectors, ivermectin MDA decreases morbidity and infection incidence. Based on evidence from some foci in Mali (Bakoye and Falémé)

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and Senegal (River Gambia), which had received 15–17 years of, respectively, annual or biannual (6-monthly) ivermectin MDA without vector control, APOC launched in 2010 a conceptual and operational framework for onchocerciasis elimination by ivermectin MDA alone [12].

However, modelling suggests that EoT may not be achieved in all endemic areas within the proposed timeframes using MDA alone, particularly when ivermectin is distributed annually in areas with high initial endemicity, high vector biting rates and, therefore, high values of the **basic reproduction ratio (R_0)** of the parasite. The problem is exacerbated in areas with high levels of systematic nonparticipation [13].

Achievements and pitfalls of previous vector control interventions

The most successful attempt to date was based on large-scale, prolonged aerial larviciding of *Simulium* breeding sites by the **Onchocerciasis Control Programme in West Africa (OCP)** [14]. After 14 years of weekly spraying (necessary because of the long lifespan of adult *O. volvulus* [15,16]), substantial declines in rates of transmission, infection, and blindness were achieved [17]. This programme was aimed at savannah areas of the seven initially participating countries where onchocerciasis-associated blindness was highly prevalent (hindering economic development), and aerial larviciding of breeding sites was possible, therefore targeting the savannah members of the *Simulium damnosum sensu lato* complex. (The prevailing notion was that the savannah 'strain' of *O. volvulus* was mostly responsible for blinding onchocerciasis [14], but see Cheke *et al*. [18].) Smaller-scale successes (in isolated foci) included the elimination of *Simulium neavei* from Kenya through DDT application during 1946–1955 [15,19]; the elimination by APOC of the Bioko form of *Simulium yahense* from the island of Bioko in Equatorial Guinea, by a combination of ground-based and aerial larviciding in 2005 [20]; and the elimination of *S. neavei* in several Ugandan foci between 1993 and 2014 [21].

The (wind-aided) ability for long-range seasonal migration of the savannah members of *S. damnosum s.l.* into mainland West Africa resulted in the reinvasion of controlled rivers by parous, infective flies, leading to the western and south-eastern extensions of the OCP, covering 11 countries [14,19]. Despite OCP's considerable achievements, large-scale larviciding is no longer considered feasible, economically viable, or environmentally desirable (L. Yaméogo, PhD thesis, Universite Claude Bernard- Lyon, 1994) [22].

The application of organophosphate larvicides, such as Temephos® and chlorphoxim, against *Simulium* led to resistance in the OCP area, requiring rotation using other compounds with different modes of action (L. Yaméogo, PhD thesis, Universite Claude Bernard- Lyon, 1994) [19,23]. Although Temephos® has a minimal negative impact on aquatic fauna [24], other insecticides vary in toxicity, with *Bacillus thuringiensis* H-14 (Bt-14) being the most selective and least environmentally damaging, and permethrin and carbosulfan among the most toxic (L. Yaméogo, PhD thesis, Universite Claude Bernard- Lyon, 1994) [23]. These are important considerations when pondering the use of chemical larviciding for vector control as prolonged campaigns would be required to achieve the sustained reductions in vector biting rates that would be necessary to accelerate EoT. Temephos® has been successfully used against *S. neavei* [25], but as this species has a phoretic association with freshwater (*Potamonautes* spp.) crabs in heavily shaded smaller rivers, its ecology may be more easily disrupted.

Epidemiological impact and feasibility of vector control in combination with ivermectin MDA

The principle of reducing vector biting rates to control onchocerciasis is well accepted and the only strategy used by the OCP, from 1975 through 1989, before the advent of ivermectin in the

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early 1990s [26]. At endemic equilibrium (i.e., before the implementation of control interventions) a positive (nonlinear) relationship exists between the annual biting rate and the prevalence and intensity of microfilarial infection, particularly well documented in savannah areas [27]. Ivermectin treatment reduces microfilarial load, but microfilariae repopulate the skin between 2 and 3 months following treatment [28]. Therefore, the potential for their transmission to vectors in the intertreatment period may be reinstated, particularly if ivermectin MDA is implemented annually and blackfly vectors bite throughout the year in large numbers. Biannual ivermectin MDA helps to curtail transmission of microfilariae to vectors, but depending on vector competence (intake of microfilariae and their establishment/development to infective, L3, larvae), survival, degree of anthropophagy and density, transmission may occur at low microfilarial loads [29,30]. Reducing vector density reduces the overall contact rate between vectors and humans, and therefore, the opportunity for microfilariae to be transmitted to vectors, and for L3 larvae to be transmitted to humans, decreasing incidence and reinfection. Other methods that would reduce vector–human contact by individuals living in areas of high biting densities include the use of repellents and the wearing of long-sleeve shirts, trousers, and skirts [31].

Combining treatment of humans with vector control should therefore accelerate elimination. Both epidemiological [32] and modelling studies [33] support this notion. Combined elimination of *S. neavei* and biannual CDTi have led to EoT in some Ugandan foci [21], with modelling studies supporting the critical importance of this two-pronged strategy [34]. Recently, trials implementing community-directed vector control through the removal [**slash-and-clear (S&C)**] of trailing vegetation that acts as substrate for simuliid immature stages (eggs to pupae) [35], or optimising the **Esperanza window trap (EWT)** in different locations for capturing host-seeking female flies [36], have proven to be successful in reducing biting rates of *S. damnosum sensu stricto* (*s. str.*) in northern Uganda. The implementation of S&C reduced biting rates by 89–99% in intervention communities of the Madi-mid North focus along small and medium-sized (Ayago and Aswa) rivers [35]. The performance of optimised EWTs was more variable (90% reduction in biting rates in a school setting compared to 50% reduction or none at all in a field setting [36]). Accompanying modelling studies indicated that supplementing annual MDA with S&C could significantly accelerate EoT in this focus [37].

Onchocerciasis is coendemic with **loiasis**, another filarial infection, caused by *Loa loa* and transmitted by *Chrysops* spp. (Diptera: Tabanidae), in large areas of Central Africa [38]. In these coendemic areas, routine implementation of CDTi is hindered by the fact that ivermectin treatment of individuals with high *L. loa* microfilaraemia loads can lead to the development of **severe adverse events (SAEs)**, including fatal encephalopathy [39]. In areas of coendemicity, vector control could help decrease transmission and enhance the success of alternative strategies to MDA based on screening individuals for their *L. loa* or *O. volvulus* status to guide treatment decisions [40]. Moreover, the control of *Chrysops* could decrease the endemicity of loiasis [41], ultimately allowing the implementation of CDTi [42].

Modelling the role of vector control in accelerating and/or protecting EoT

The role of vector control in reducing onchocerciasis transmission in the OCP was first modelled by Plaisier *et al*. [43] using ONCHOSIM [44]. According to ONCHOSIM's assumed adult worm life expectancy (informed by fitting the model to data on microfilarial trends following interruption of transmission in four OCP villages [16]), and in the absence of immigration of infected humans and infective flies, 14 years of full-scale vector control would reduce by >99% the risk of onchocerciasis resurgence. Vector control was modelled by reducing the vector biting rate by 100% for the duration of the intervention, allowing it to bounce back to its precontrol level shortly after cessation of control operations. Addition of ivermectin MDA (at 65% coverage of total population),

Glossary

African Programme for Onchocerciasis Control (APOC): 1995–2015, covered 20 endemic countries not under the OCP. Included international development partners, non-governmental development organisations (NGDOs), foundations, and private sectors. It aimed to eliminate onchocerciasis-associated morbidity in Africa, mainly through CDTi. In 2010, its goals shifted from disease control to EoT.

Alternative (or complementary) treatment strategies (ATS): recommended when CDTi alone is unlikely to achieve EoT. Include vector control, increased treatment coverage and/or (biannual or pluriannual) frequency, improved CDTi timing, and use of better microfilaricidal and/or new macrofilaricidal (including anti-*Wolbachia*) therapies.

Basic reproduction number (R_0): in onchocerciasis, the average number of female worms generated by a (mated) female worm during its reproductive lifespan in a fully susceptible population. Linearly related to the annual biting rate (the number of bites/person/year). When R_0 >1, the parasite population will increase and eventually reach endemic equilibrium.

Community-directed treatment with ivermectin (CDTi): mass ivermectin distribution through community involvement to improve treatment coverage and sustainability. Preceded by rapid epidemiological mapping of onchocerciasis to assess endemicity.

Elimination (interruption) of transmission (EoT): defined as verifiable zero incidence in a defined geographical area, with minimal risk of infection resurgence/reintroduction, as a result of intervention efforts.

Esperanza window trap (EWT): designed to collect adult *Simulium* spp. and consisting of a sticky target of different sizes and combinations of blue and black fabrics.

Human African trypanosomiasis (HAT): sleeping sickness, caused by infection with *Trypanosoma brucei* and transmitted by tsetse (*Glossina*) flies.

Human landing catches (HLCs): a standard method for collecting human-seeking blackflies. Volunteers count, collect, and store (for vector identification and parasite detection) the blackflies that alight on their legs during defined collection periods. Ethical

commenced simultaneously or soon after initiation of vector control, would reduce the duration of antivectorial operations by approximately 2 years and prevent resurgence of infection and blindness [33].

Currently, as the control strategy focusses on MDA, the relevant question is: how does the addition of vector control help to accelerate and protect EoT? Duerr *et al*. [45] showed that MDA would lead to a nonlinear increase in the threshold biting rate (the minimum biting rate necessary for endemic onchocerciasis persistence) and concluded that incorporation of vector control could help to achieve EoT. However, only reductions in microfilarial load ≥80% due to MDA would lead to substantial increases in the threshold biting rate. Verver *et al*. [46], using both ONCHOSIM and (deterministic) EPIONCHO, concluded that long-term and simultaneous implementation of MDA and vector control might be useful to accelerate EoT in areas of high baseline endemicity. Verver *et al*. assumed that vector control would attain a reduction of annual biting rates of 70% rather than 100% for the duration of vector control operations. All of these models were parameterised for savannah species of the *S. damnosum* complex in West Africa.

Michael *et al*. [34] used Bayesian-based data-model assimilation techniques to investigate onchocerciasis transmission in some East African foci where the vector is *S. neavei* (e.g., Uganda). These authors concluded that, although the magnitude of infection breakpoints and required durations of MDA for achieving elimination showed high spatial variability, the inclusion of vector control largely overcame this variability [34].

Most transmission models have been parameterised for the savannah *O. volvulus*–*S. damnosum s. str.*/ *Simulium sirbanum* combination [27]. Yet, there are many other onchocerciasis vector species within the *S. damnosum* complex for which paired transmission and epidemiological data have not been systematically collected or collated, and vector–parasite interactions are poorly elucidated [29].

Most of the onchocerciasis vector control modelling to date pertains to insecticidal operations against blackfly larvae in breeding sites. The impact of such operations has been modelled by reducing the biting rate for the duration of vector control [33,43,46]. The impact of interventions such as the (non-chemical) method of S&C, trialled by Jacob *et al*. [35] in the Madi-mid North focus of northern Uganda, was modelled by Smith *et al*. [37] for *S. damnosum s. str*., by describing the effect of the intervention on seasonal blackfly biting rates and coupling this with a population dynamics transmission model. Their results suggested that supplementing annual ivermectin MDA with S&C could accelerate onchocerciasis elimination even if vegetation were cleared only once yearly.

None of these models attempted to capture blackfly population dynamics (from eggs to imagoes), or understand the dynamics of recolonization of vector breeding sites following the interventions. This was first done by Cheke *et al*. [47], and subsequently by Routledge *et al*. [48], who adapted the Cheke *et al*. model to simulate larvicidal interventions in both savannah and forest settings. Routledge *et al*.'s SIMPOP (SIMuliid POPulation dynamics) model was fitted to data from large-scale aerial larviciding trials in savannah sites during the OCP (Ghana), and small-scale ground larviciding trials in forest areas (Cameroon). The model was validated against independent (savannah) data from Burkina Faso/Côte d'Ivoire (OCP) and (forest) data from the island of Bioko (APOC) in Equatorial Guinea. The efficacy of large-scale aerial larviciding in the savannah was estimated to be greater than that of ground-based larviciding in the forest. Larvicidal treatments with 93% or 70% efficacy, applied for 10 consecutive weeks, would reduce daily biting rates by 96% or 67%, respectively, by the end of the intervention. Junker (R. Junker, MRes dissertation, Ecole

concerns (exposure to potentially infective blackflies) have spurred interest in developing alternative/complementary methods for entomological monitoring.
Loiasis: infection caused by *Loa loa* (Nematoda: Filarioidea) and transmitted by *Chrysops* (Diptera: Tabanidae) in forested areas of West Africa (African eyeworm). In onchocerciasis–loiasis coendemic areas it can be an impediment to CDTi (see 'Severe adverse events').
Onchocerciasis Control Programme in West Africa (OCP): 1975–2002, WHO-supported programme aimed to eliminate blinding onchocerciasis in initially seven and finally 11 endemic West African countries. Before the use of ivermectin in the early 1990s, OCP relied on the use of larvicidal insecticides against onchocerciasis vectors.
Severe adverse events (SAEs): medical occurrences (following administration of a drug) that can be life-threatening, require hospitalization, and/or result in persistent disability/incapacity. In onchocerciasis–loiasis coendemic areas, SAEs are associated with the development of potentially fatal encephalopathies in individuals with high *Loa loa* parasitaemia who receive ivermectin.
Slash-and-clear (S&C): antivectorial strategy consisting of the removal of the riverine vegetation that acts as a substrate for the immature stages of blackflies. It has been suggested as a community-directed vector control method.

Normale Supérieure Paris-Saclay, and Imperial College London, 2020) extended SIMPOP to consider the effects of S&C upon all simuliid immature stages (eggs, larvae, and pupae), and fitted it to the short- and long-term trials conducted in [35], concluding that one S&C cycle per year (applied at the beginning of the rainy season) would reduce annual biting rates by 34%, whereas two cycles (the second one at the end of the rainy season) or three cycles (the third one at the end of the dry season) would reduce it by 61% and 80%, respectively.

Know thy vectors: opportunities for innovative methods of entomological surveillance and control

Lessons learned from other vector-borne diseases (VBDs) have demonstrated that studies on vector behaviour to locate, approach, and land on a host can provide means for vector control. Studies on host-seeking behaviour of tsetse flies led to the development of effective visual and olfactory attractants (Box 1). *Simulium* and *Chrysops* vectors share several features: (i) their breeding sites are generally close (*Simulium* breed in fast-flowing rivers, and *Chrysops* breed in the muddy areas of riverine forests); (ii) both are diurnal; and (iii) females of both groups obtain a proportion of their blood meals from human hosts. These commonalities suggest that both, *Simulium* and *Chrysops*, might respond to similar cues to locate and feed on their hosts.

Host-seeking behaviour of *Simulium* and its use for improving adult female traps

Simulium breed in fast-flowing, highly oxygenated, rivers and streams, where the immature stages live and imagoes emerge [49,50]. The adult female flies rely on visual and olfactory stimuli to locate their hosts [49]. Like tsetse flies (Box 1), simuliids show a preference for dark colours, especially blue [51–53]. Early studies showed that blackflies' landing responses on fabric panels depended on the colour and the intensity of the light reflected from the cloth, with dark colours, especially dark blue, eliciting the highest alighting rates [53].

Until recently, vector control against onchocerciasis has lacked an artificial bait to control or monitor adult blackfly populations, or the tools to quantify their responses to host stimuli. Lately, a new trap for *Simulium* has been developed, named EWT [54]. The original model was a 1 m^2 sticky black panel. Subsequently, the design was improved by replacing a solid black panel with a black and blue striped pattern [36,55,56]. EWT has shown promise as a monitoring tool, but a quantitative analysis of responses to colour, shape, and size could lead to substantial improvements in the design (as seen with targets against tsetse). Interestingly, the trap is reminiscent of the devices used to monitor and control tsetse (Figure 1).

Box 1. The tsetse experience

Lessons learned with other vectors have implications for the development of new methods to trap, control, and monitor *Simulium* spp. populations. Analysis of the host-seeking behaviour of tsetse flies [95–97] led to the development of bait technologies to control sleeping sickness vectors [95–98]. *Simulium* spp. share several of the behavioural traits displayed by tsetse, as they are diurnally active and responsive to odour and visual cues [49].

From 1950 to the 1980s, tsetse control relied on the release of large amounts of insecticide. Increasing environmental and economic concerns motivated scientists to find more affordable and environmentally friendly approaches [99]. Studies on the responses of tsetse to host odours were possible after the development of new tools to analyse tsetse behaviour, such as electric grids [100] and video tracking [101]. These tools allowed researchers to quantify responses of tsetse to visual and olfactory stimuli. It was established that host odours attract savannah tsetse from a distance of ~100 m. However, at close range, tsetse flies are unable to locate the exact source of odour, and the final approach to, and alighting on, the host are driven by visual stimuli (colour, shape, size) [102]. Understanding these responses led to the development of odour-baited targets that attract and kill tsetse [103]. Similar analyses of the responses of riverine tsetse showed that this group was highly responsive to visual cues [96,97] leading to the development of Tiny Targets [95]. Differences in the responses of riverine and savannah-dwelling tsetse are likely related to the local ecology, vegetation, and seasonal changes of each habitat [97,99] (see Table 1 in the main text).

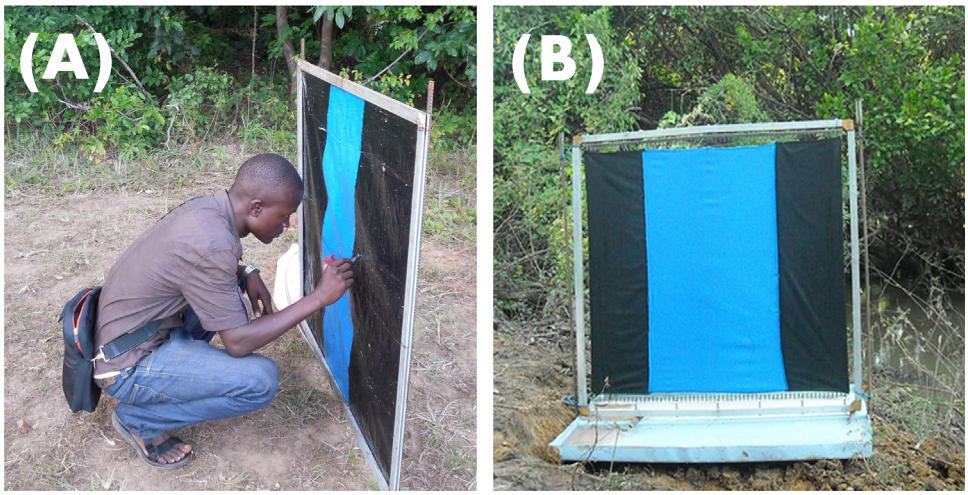

Figure 1. Esperanza window trap (EWT) versus tsetse target. Comparative view of (A) an EWT, designed to monitor and collect *Simulium* spp. in the Americas and Africa (photo courtesy of Dr Lassane Koala, Institut de Recherche en Sciences de la Santé, Burkina Faso), and (B) a tsetse target, designed originally as a tool to control populations of savannah species of tsetse in Southern Africa (from [108]). Although the two tools were intended to attract and trap/kill different vectors, the final versions of both devices converged into similar designs.

Potential benefits of using EWTs include the lack of ethical concerns surrounding the collection of host-seeking flies by **human landing catches (HLCs)**, which still constitute the standard method to capture and monitor *Simulium* biting and infection rates [57], their usefulness in providing blackfly samples for xenomonitoring of infection levels to evaluate MDA progress and support stop-MDA decisions in the context of reaching elimination goals [36], and their offering of a sampling device with which to test putative semiochemicals in field trials.

However, EWTs have some limitations as adult female flies of sympatric sibling species of *S. damnosum s.l.* are difficult to identify to morphospecies [58], and the ability of EWT to attract blackflies varies widely across locations and species of the *S. damnosum s.l.* complex [36,59] (which may be explained by their differential responses to visual and olfactory cues [49,60] and the importance of trap placement [36]). Besides, in the northernmost areas of the distributional range of onchocerciasis, close to the Sahel, sand may also be trapped, which worsens during sand storms, decreasing EWT's usefulness.

During a study in Cameroon, EWTs trapped substantially less host-seeking *Simulium squamosum* than a human decoy trap (HDT) [61], adapted from work with anophelines [62]. The HDT uses olfactory cues (body odours and exhaled CO_2, from a person resting in a tent), visual cues (covering the barrel-shaped trap with a plain black cloth), and thermal cues (filling the insulated trap with warm water to simulate human body temperature). Their usefulness to monitor adult blackfly populations is being tested in a variety of settings (Frances Hawkes, personal communication).

Although HLCs have been the standard method for entomological surveillance and biting-rate estimations [57] they also have important limitations. In addition to the ethical concerns they raise (exposing collectors to blackfly bites and *O. volvulus* infection), their use to quantify human exposure to vector bites can lead to biased estimates. Not only are the human attractants/collectors maximally exposed during the collection periods, but also there is a limited number of sites at

which flies can feasibly be collected. HLCs usually take place close to breeding sites, not yielding a balanced picture of human–vector contact across the temporal and spatial range of daily human activities. EWTs and HDTs have the potential to provide a more complete picture as they could be simultaneously positioned in a larger number of representative sites and at increasing distances from breeding sites, but they will need to be carefully calibrated against HLCs so that the number of flies caught can be reliably interpreted in terms of biting rates, and the samples obtained usable for vector identification and further dissection/molecular analysis for evaluation of infection/infectivity rates. (To this end, further research into optimal, durable glues that do not interfere with visual and olfactory cues, and that permit extraction of intact flies, is crucial.)

Since patterns of (age, sex, and individual) human exposure to vector bites are essential components of transmission dynamics models [27,30], novel immunoassays have recently been developed to quantify antibody levels to *S. damnosum s.l.* saliva in human populations [63,64], with the expectation that their use can help to interpret the results of blackfly collections by HLCs, EWTs, or HDTs, and assist the monitoring of vector control interventions.

Sibling species of *S. damnosum s.l.* are generally considered anthropophagic, with estimates of the human blood index ranging from 0.44 for *S. squamosum* E to 0.92 for the Beffa form of *Simulium soubrense* [65].

Early studies showed that forest species of *S. damnosum s.l.* respond to human odour. Thus, traps baited with human odour collected eight times as many blackflies as a non-baited trap, whereas the same trap baited with CO_2 attracted two-thirds as many as a human-baited trap [66]. Thompson [66,67] realised that human sweat contains some attractants, and traps baited with worn clothes collected significantly more flies than non-baited traps. By contrast, the North American species *Simulium arcticum* is more zoophagic, and silhouette traps collected significantly more flies when they were baited with whole cattle odour or just cattle urine [68]. Other studies aimed to identify relevant semiochemicals. In Liberia, biconical traps baited with octenol tripled the catches of *Simulium sanctipauli* and *S. yahense* [69], whereas in Canada, catches of *S. arcticum* increased in the presence of CO_2 and acetone [68]. The development of EWT has provided new tools to conduct field trials. EWT baited with CO_2 and a blend of octenol, acetophenone, hexanal, and ammonium bicarbonate doubled the catches of *Simulium ochraceum s.l.* (vector in the now eliminated onchocerciasis foci of Mexico and Guatemala), compared with a trap baited with CO_2 only. Similar results were obtained using a blend of different carboxylic acids, ketones, aldehydes, and bicarbonates [70] (Table 1).

Host-seeking behaviour of *Chrysops*

The *Chrysops silacea* and *Chrysops dimidiata* loiasis vectors inhabit West and Central Africa, although the genus is distributed worldwide. They rest among the branches of the canopy formed near freshwater bodies. The oviposition sites have been described to be over water and on substrates such as vegetation and stones near the shore, in permanent swamps, and in small swampy patches formed throughout the rainforest during the wet season. After hatching, the larvae leave the substratum to sink in the mud covered with shallow, slowly running water, and decaying leaves [71].

Female *Chrysops* use olfactory and visual cues to locate their hosts [72]. In Hungary, Horváth *et al*. [73] concluded that different tabanid species seemed responsive to polarised light when observing their responses to black and white surfaces. They hypothesised that this behaviour might increase the probability of blood-seeking females to locate their hosts when visiting water bodies, and of males to encounter females that are looking for blood hosts.

Table 1. Summary of the main visual and olfactory responses of different vector groups[a]

Genus	Group	Disease	Main visual responses	Main olfactory responses
Glossina (tsetse)				
	Savannah	rHAT[b] Nagana	Big objects [104]	CO_2 [105]
			Blue and dark colours [104]	Octenol [105]
			Horizontal oblongs [104]	Phenols [105]
			Movement [103]	Acetone [105]
				Cattle odours [103]
	Riverine	gHAT[c]	Small objects [95]	CO_2 [96,97]
			Blue colour [95]	Lizard odours (*Glossina fuscipes*) [96]
Simulium (blackflies)				
	Old Word	Onchocerciasis[d] Nodding syndrome[e] Blackfly fever[f]	Blue and dark colours [36,55]	CO_2 [67]
				Human odours [67]
				Octenol [69]
	New World	Onchocerciasis[g] Vesicular stomatitis virus Blackfly fever	Blue and dark colours [51,53]	CO_2 [68]
				Cattle odour [68]
				Cattle urine [68]
				Acetone [68]
				Octenol [74]
Chrysops (deerflies)				
	Old World	Loiasis[h]	Horizontal polarised light [73]	Octenol [74]
			Black colour [73]	Acetone [74]
			Blue colour [74]	Smoke [75,76]
	New World		Blue colour [74]	Octenol [74]

[a]The main visual (column 4) and olfactory (column 5) stimuli of three different vector genera (column 1), implicated, according to the literature, in host location. The three vector genera are subclassified into groups in column 2 (*Simulium* and *Chrysops* are subclassified by location, and *Glossina* is subclassified by subgenus). The most common diseases and syndromes transmitted by the vectors are listed in column 3.
[b]Rhodesian **Human African trypanosomiasis (HAT)**: acute and zoonotic form (~3%) of HAT; caused by *Trypanosoma brucei rhodesiense* and transmitted by savannah tsetse.
[c]Gambiense HAT (chronic and anthroponotic form (~97%) of HAT; caused by *Trypanosoma brucei gambiense* and transmitted by riverine tsetse.
[d]Yemen and Africa.
[e]Nodding syndrome has been proposed to be in the onchocerciasis-associated epilepsy spectrum or potentially caused by a neurotropic virus transmitted by simuliids [106].
[f]A systemic reaction in humans following blackfly bites that includes headache, nausea, high temperature, and swollen lymph nodes.
[g]Ongoing transmission in the Amazonian focus between Venezuela and Brazil; eliminated in Mexico, Guatemala, Colombia, and Ecuador [107].
[h]Forested areas of West and Central Africa.

Mihok *et al*. [74] analysed, in Africa and North America, the responses of *Chrysops* to odours, including octenol, phenols, and acetone. Although the responses to odours differed in various locations, the results showed that octenol was the most universal attractant.

Unlike other insects, smoke produced in wood fires attracts some *Chrysops* species. Smoke increased the biting rates of *C. silacea* sixfold in Cameroon [75], and up to 8.5-fold in the Republic of the Congo [76], but the effect was negligible for *C. dimidiata*. This effect may explain the

adaptation of *C. silacea* to peridomestic habitats (unlike *C. dimidiata*), and might be related to the release of semiochemicals during combustion, other than CO_2, such as phenols [77] (Table 1).

Control of *Chrysops*

Some methods for *Chrysops* control were suggested by early workers, including the use of repellents at individual level and/or the use of protective screens at household level, clearing the bush around human dwellings, indoor insecticide spraying, and application of larvicides on breeding sites [78]. However, none of these methods are considered to be viable [41]. In fact, the statement 'We do not consider that it would be wise to recommend any radical form of control, involving the clearing of the bush round breeding-places, the canalization of streams, or the extensive use of insecticides, until further studies, both in the field and in the laboratory, have greatly augmented our present meagre knowledge concerning ... the effect of such methods on the density of *Chrysops*', voiced in the Symposium on Loiasis of 1955 [79], resonates, nearly 70 years later, with our call for a better understanding of vector biology towards their sustainable and environmentally sound control.

Capacity strengthening

There is a pressing need to strengthen entomological technical capacity in endemic areas, to facilitate local implementation and rigorous evaluation of vector control.

To develop, implement, and monitor the impact of vector control to support onchocerciasis elimination, a cadre of experienced entomologists is required at country level. In the Global Vector Control Response 2017–2030 [80], the WHO highlighted the urgent need to enhance entomological capacity and increase research and innovation in vector control to form the foundation of the response framework. Entomological expertise for malaria has been on the decline since the Global Malaria Eradication Program. During this time, the establishment of a prescribed, global solution for malaria eradication, based on the use of DDT, necessitated experts to shift from being problem solvers to solution implementers [81]. The high reliance on insecticide-treated bed nets in the past 2 decades has only exacerbated the issue. A similar trend has been experienced in onchocerciasis and other NTDs, as vector expertise has become increasingly scarce due to the strong reliance on drug distribution as the primary elimination tool. However, the locally adapted, sustainable approach to vector control advocated by the WHO, the need for **alternative (or complementary) treatment strategies (ATS)** to accelerate and protect EoT [40], and the new WHO roadmap on NTDs for 2021–2030 [1] have rekindled the fillip for a much-needed renaissance of African scientists, medical entomologists, and highly trained technicians specialising in entomological research and the transmission and control of VBDs. For onchocerciasis in particular, the need to recognise and map simuliid breeding sites (for onchocerciasis elimination mapping), identify simuliid species, delineate transmission zones, and refine tools for entomological surveillance (for end-game transmission and infection thresholds), as well as for vector control monitoring, have highlighted the pressing need to strengthen in-country entomological capacity.

This cadre of vector biologists, ecologists, taxonomists, and (field and laboratory) technicians needs to be well networked to enable real change in the capacity of systems to rise to the challenges posed by the demanding goals of achieving onchocerciasis EoT [82], and implementing and monitoring vector control in areas where transmission persists despite prolonged ivermectin MDA. They should be exposed to, and embedded within, interdisciplinary research, so that they can draw on expertise of colleagues in anthropology, social sciences, implementation science, geospatial analysis, molecular analysis, and data management, analysis, and interpretation. They also need to understand the policy-making processes so that they can effectively liaise

with decision-makers and programme managers to ensure that the objectives and results of their work are relevant for programmatic responses to VBDs. They need to grow quickly as leaders with effective management skills to enable an exponential growth in vector expertise, which will permeate the research, government, and private sectors. This will catalyse the establishment of a sustainable cohort of public health entomologists and community health workers who can effectively deliver vector control interventions. Finally, they need to be embedded in high-quality, adequately funded service laboratories, research facilities, and education establishments that have the capacity to offer attractive career pathways.

Several large-scale initiatives are underway to support the development of entomological expertise in Africa. The Partnership for Increasing the Impact of Vector Control (PIIVeC), a capacity-strengthening programme supported by the Global Challenges Research Fund, is investing in promising future VBD research leaders to fill knowledge gaps and ensure the sustainable use of evidence in decision making[i].

Other examples include the Pan-African Mosquito Control Association[ii], with one of its primary pillars being to develop capacity of African entomologists through the organisation of training, exchanges, and dissemination (e.g., conferences) programmes. The Elimination 8[iii], a collaboration of eight countries in southern Africa towards accelerating malaria elimination, has previously offered specialised entomology fellowships. There remains a clear opportunity for southern-led capacity-strengthening initiatives that can generate a cadre of problem-solving vector specialists. To this end, the Global Vector Hub[iv], supported by TDR (the Special Programme for Research and Training in Tropical Diseases), is an open-access community for vector control information and research. It hosts a directory of on-campus and distance-learning courses offered by institutions in all WHO regions intended to promote capacity in medical entomology.

Last but not least, community involvement is a crucial component. Several vector control interventions have relied for their implementation on volunteers from endemic communities [35,83]. Community understanding of the diseases and their vectors improved when some of its members participated actively in vector control activities. In turn, communities' perception of vectors as a biting nuisance provided the necessary collective buy-in for vector control interventions [35,83–87].

Concluding remarks

Ivermectin MDA alone might not be sufficient to interrupt onchocerciasis transmission in 12 endemic countries by 2030, particularly in those with areas of high endemicity, or onchocerciasis–loiasis coendemicity [13]. Not only should EoT be achieved, but also verified within this time framework at a national scale [1]. Vector control can contribute towards achieving the proposed EoT goals, but the prolonged reductions in vector density that are necessary will require sustained and sustainable efforts, particularly where vector biting rates are high. Decreasing vector biting rates below the threshold for endemic transmission [45] will also safeguard elimination once achieved, helping to minimise rates of resurgence or reintroduction of infection. Delineation of transmission zones [12], including onchocerciasis elimination mapping, would benefit from future studies to further test and validate remote-sensing models for identification of *S. damnosum s.l.* breeding sites [88]. Novel (population genomic) approaches to quantify the structure and connectedness of *O. volvulus* populations could also be used to help quantify the movement and dispersal of its simuliid vectors from breeding sites and between endemic communities [89] (see Outstanding questions).

In *O. volvulus–L. loa* coendemic areas, and in addition to complementary vector control against *Simulium* spp., actions against *Chrysops* could also reduce the loiasis endemicity, and ultimately

Outstanding questions

For vector and parasite identification, can novel tools (e.g., IR spectroscopy and supervised machine learning), developed for mosquito vectors, be adapted and used to optimise identification of *Simulium* spp., their feeding preference and age structure in relation to vectorial capacity for *O. volvulus*?

For onchocerciasis elimination mapping and demarcation of transmission zones, how could identification and mapping of simuliid breeding sites be improved (e.g., by using remote-sensing modelling), and the mobility and dispersion of adult blackfly populations best measured and compared with *O. volvulus* populations (e.g., by using genomic approaches)?

For improving control of adult blackflies, how can existing and novel adult fly trapping methods/devices be used to design experiments to further understand cues that elicit host-seeking responses in *Simulium*, and how can this knowledge be used, in turn, to improve trap effectiveness for vector control?

For entomological monitoring and surveillance of onchocerciasis elimination, how can optimised trapping methods be used to better understand vector density, dispersal from breeding sites, and transmission seasonality, for example, to enhance vector-sampling protocols, inform transmission models, and optimise timing of antiparasitic and/or antivectorial interventions?

For optimising control of simuliid immature stages and the prospects of community-led vector control, how can knowledge of breeding sites in natural substrates and artificial structures (e.g., dams, irrigation systems) be improved to deploy efficacious and seasonally appropriate environmental management interventions (including S&C)?

For the control of loiasis vectors, could the methods and devices being developed/tested for *Simulium* be adapted for use in *Chrysops* to assess the feasibility of designing control and/or monitoring methods against vectors of *Loa loa*, particularly (but not solely) in onchocerciasis–loiasis coendemic areas?

the individual risk of developing SAEs following microfilaricidal treatment [42]. In areas where MDA is likely to achieve EoT on its own, and vector control may not be deemed necessary, quantification of entomological parameters will still provide valuable indicators to monitor progress and verify elimination [90]. Tools such as mid-infrared spectroscopy linked to supervised machine learning, developed for identification of vector and pathogen species, bloodmeal origin, and age structure in mosquitoes [91,92], could be adapted and tested for use in *Simulium* (and ideally also in *Chrysops*).

For the refinement of onchocerciasis transmission models, how can novel adult blackfly trapping (EWT, HDT) methods and anti-blackfly's saliva immunoassays be used to improve understanding of vector biting rates and patterns of human exposure to vector bites?

Affordable, sustainable, and environmentally sound methods of vector control are receiving increasing attention [35,36,83]. Behavioural studies suggested that tsetse, blackflies, and *Chrysops* respond to similar host stimuli [72,74]. The development of tsetse traps and EWT followed different processes but converged towards similar designs [54–56,93], using black and blue fabric panels (Figure 1); HDTs also use black cloth [61]. Therefore, these trapping methods and devices could be used in experimental designs to further understand the cues that elicit olfactory, visual, and thermal responses in *Simulium* and improve trap effectiveness for monitoring progress towards EoT and vector control, as well as to refine transmission dynamics models, which rely on entomological parameters [27,30,46]. This would respond to the pressing need for the development or improvement of vector control tools suitable to be applied by endemic communities at a local scale. Community-directed methods of vector control should be consistent with WHO policy on community participation in NTD programmes [94] and help to strengthen the three pillars of the WHO roadmap on NTDs (accelerating programmatic action, intensifying cross-cutting approaches, and facilitating country ownership [1]).

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Declaration of interests

The authors declare no competing interests.

Resources

[i] www.piivec.org/

[ii] www.pamca.org/

[iii] https://malariaelimination8.org/

[iv] https://globalvectorhub.lshtm.ac.uk/

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