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REVIEW ARTICLE

Broadening the range of use cases for ivermectin – a review of the evidence

Christian Kositz [a,*], John Bradley [b], Harry Hutchins [a], Anna Last [a,c], Umberto D'Alessandro [d], and Michael Marks [a,c]

[a]Clinical Research Department, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, WC1E 7HT, London, UK; [b]MRC International Statistics and Epidemiology Group, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, WC1E 7HT, London, UK; [c]Hospital for Tropical Diseases, Mortimer Market Capper Street, WC1E 6JB, London, UK; [d]Disease Control and Elimination, Medical Research Council Unit Gambia at London School of Hygiene and Tropical Medicine, Atlantic Boulevard, Fajara, The Gambia

*Corresponding author: Tel: +447895855829; E-mail: christian.kositz@lshtm.ac.uk

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Ivermectin is a broad-spectrum antiparasitic agent that interferes with glutamate-gated chloride channels found in invertebrates but not in vertebrate species. Mass drug administration (MDA) with ivermectin-based regimes has been a mainstay of elimination efforts targeting onchocerciasis and lymphatic filariasis for more than 3 decades. More recently, interest in the use of ivermectin to control other neglected tropical diseases (NTDs) such as soil-transmitted helminths and scabies has grown. Interest has been further stimulated by the fact that ivermectin displays endectocidal efficacy against various *Anopheles* species capable of transmitting malaria. Therefore there is growing interest in using ivermectin MDA as a tool that might aid in the control of both malaria and several NTDs. In this review we outline the evidence base to date on these emerging indications for ivermectin MDA with reference to clinical and public health data and discuss the rationale for evaluating the range of impacts of a malaria ivermectin MDA on other NTDs.

Keywords: ivermectin, neglected tropical diseases, malaria, mass drug administration, soil-transmitted helminths

Introduction

Ivermectin is a macrocyclic lactone compound and part of the avermectin family. Avermectins were discovered by Satoshi Omura and William C. Campbell in Japan in the 1970s, during analysis of *Streptomyces avermitilis* compounds, and they subsequently discovered ivermectin. In 2015, both scientists received the Nobel Prize in Physiology or Medicine for their discovery.[1] Since its introduction, the drug's utility has seen its use extended in veterinary medicine and animal husbandry to treat endo- and ectoparasites.[2–4]

Ivermectin is a mainstay in the success of the control and elimination of *Onchocerca volvulus*, the causative agent of river blindness. It has been extensively used by the African Programme for Onchocerciasis Control, the Expanded Special Project for the Elimination of Neglected Tropical Diseases in Africa and the Onchocerciasis Elimination Program of the Americas. Ivermectin is also known to affect a variety of invertebrate species.[5–7] Due to its broad application, it is considered an endectocide, a drug affecting several ecto- and endoparasites, and its use has steadily expanded in the years since its discovery. In recent years ivermectin has been successfully applied on a larger scale against several pathogens/parasites, including scabies mites (*Sarcoptes scabiei*), lice (*Pediculus humanus* sp.) and helminths such as *Strongyloides stercoralis*[8–11] and there is growing interest in its use as a mosquitocidal agent as part of malaria control.

We aimed to summarise data on the use of oral ivermectin in non-immuncompromised patients across a range of emerging indications. We highlight key data on the rationale, dosage considerations and existing evidence supporting the use of ivermectin for each new indication. The pharmacology and mode of action of ivermectin have been extensively reviewed elsewhere[12–16] and we therefore primarily limit this literature review to factors of direct relevance to its extended use. However, a short summary of the mode of action and pharmacology will be given for completeness. Finally, this literature review is restricted to multicellular parasites, excluding suggested but unproven applications in oncology[17] or virology,[18,19] including severe acute respiratory syndrome coronavirus 2.

Mode of action

In invertebrates, ivermectin interferes with glutamate-gated chloride channels (GluCls), which are not expressed in vertebrates. GluCls play a role in several processes in invertebrates and their inhibition affects motility, feeding and reproduction.[15,20] These effects are shown at nanomolar concentrations. At higher concentrations, ivermectin interacts with a variety of receptors such as γ-aminobutyric acid, glycine, histamine and nicotinic acetylcholine receptors, which are expressed in both invertebrates and vertebrates.[20]

Vertebrates, including humans, express P-glycoprotein (P-gp), also known as multidrug resistance protein 1 (MDR1), in their blood–brain barrier, which functions as a transport efflux pump of ivermectin out of the central nervous system.[16,21] The combination of its receptor specificity and the existence of P-gp is thought to be the major factor behind the safety and side-effect profile of ivermectin. Notably, some species, such as certain dog or horse breeds, do not possess the gene encoding P-gp, and recently a human case was found.[22] Therefore, in specific animal species, the use of ivermectin, especially at high dosages, can lead to drowsiness, coma and death,[23,24] clearly demonstrating the protective role of P-gp in humans.[16]

Safety considerations

Ivermectin has an extremely well-established safety profile, with billions of doses being administered since the inception of the Mectizan Donation Programme by Merck in 1987 for onchocerciasis and filariasis control.[25] Pharmacokinetic dosing studies have suggested that doses of ivermectin up to six times the recommended dose as well as repeated daily or monthly doses[26–32] are well tolerated. There is a well-established risk associated with the use of ivermectin in *Loa loa* (a filariform parasite) endemic areas. In this setting, ivermectin can lead to a rapid die-off of large numbers of *Loa loa* microfilaria in the central nervous system, leading to a potentially fatal encephalopathy.[33,34]

Currently, due to a lack of safety data, ivermectin should not be given to pregnant women[35], however, inadvertent use in control programmes has occurred regularly.[36] The majority of data currently are based on observed teratogenicity from animal models using P-gp-deficient mice[37] or very high doses in rats and rabbits with 10–50 and 7–30 times the human equivalent, respectively.[38–40] The relevance of these animal data to humans is therefore questionable and better data are needed. Currently children whose weight or height is $<$15 kg or $<$90 cm are also not recommended to receive ivermectin. The basis for these restrictions is the unproven concept of an immature 'leaky' blood–brain barrier, for which there is no scientific support.[41–43] In contrast to theoretical concerns, there is an increasing accumulation of real-world data showing safety among young children.[44–50]

Malaria

Malaria control measures over the past 2 decades have resulted in a significant reduction in morbidity and mortality, driven by a combination of long-lasting insecticidal nets, indoor residual spraying, artemisinin-based combination therapy and rapid diagnostic tests.[51] However, the emergence of drug and insecticide resistance, and changes in vector behaviour, such as increased outdoor biting and resting behaviour, is threatening this progress.[52–54] Over the past decade, interest has emerged in the use of ivermectin as an additional tool for the control of malaria.[55,56]

Anopheles mosquitoes predominantly express GluCls in organs and tissues responsible for their sensory and motor function.[14] The same channels exist in the culicine nervous system; however, ivermectin appears to be unable to penetrate into the haemocoel and only exerts an effect at levels 10 times greater than shown for *Anopheles* sp. Its effect on culicine species such as *Aedes* and *Culex* is therefore greatly reduced[57,58] unless the drug is injected directly into the haemocoel.[59]

Several historical studies have explored the use of ivermectin and its impact on mosquito control,[60–62] but significant interest for malaria vector control has re-emerged recently.[63] These studies use different methods to assess ivermectin's effect. Specifically, membrane feeding assays (MFAs) involve feeding mosquitos on donated blood, either from donors who have taken oral ivermectin or on blood spiked with ivermectin. Direct feeding assays (DFAs) involve feeding mosquitos on volunteers treated with ivermectin. Different *Anopheles* species, such as *Anopheles gambiae* (MFA, DFA), *Anopheles arabiensis* (MFA), *Anopheles aquasalis* (MFA, DFA), *Anopheles minimus* (DFA), *Anopheles campestris* (DFA), *Anopheles sawadwongporni* (DFA), *Anopheles dirus* (MFA), *Anopheles darlingi* (MFA), *Anopheles farauti* (DFA), and *Anopheles stephensi* (human MFA, mouse DFA), have all shown high mortality after ingesting blood containing ivermectin levels comparable to those reached in humans after an oral dose of 200, 400 and 600 μg/kg body weight.[58,64–69] The IVERMAL trial found no difference in ivermectin mosquitocidal toxicity between MFAs and DFAs against *A. gambiae* using placebo (n=23), 300 μg/kg/d (n=24) or 600 μg/kg/d (n=22).[70] Although DFAs showed higher mosquitocidal toxicity than MFAs in a trial by Sampaio et al.,[64] the number of participants was small (n=6).

Pharmacokinetic considerations limit the effectiveness of a single standard dose of ivermectin of 200 μg/kg for malaria control programmes. The half-life of 18 h means that these dosing regimens only generate a mosquitocidal effect lasting for about 5–6 d,[71] which is inadequate for malaria control. Furthermore, vectors from outside the treated areas, especially in open systems on larger landmasses, will quickly repopulate these losses. To improve the pharmacokinetic profile, and hence the duration of its endectocidal effect, alternative dosages have been suggested: a single dose of 400 μg/kg or three consecutive daily doses of 300 μg/kg.[72] The latter regime was investigated in the IVERMAL trial conducted in Kenya and was given once a month for three consecutive months in human volunteers. The treatment had a good safety profile and the mosquitocidal effect lasted for up to 28 d.[73]

In the Repeat Ivermectin Mass Drug Administrations for Control of Malaria: a Pilot Safety and Efficacy Study (RIMDAMAL) conducted in Burkina Faso, villages were randomly assigned to ivermectin (150–200 μg/kg) and albendazole (400 mg) at baseline in both arms followed by the same single doses of ivermectin every 3 weeks over 18 weeks in the intervention arm or no treatment in the control arm. The study aimed to evaluate the effect on

the cumulative incidence of uncomplicated malaria. The results showed evidence of a reduction in incidence in children <5 y of age,[74] although the statistical methods for analysis have been disputed.[75,76]

The results of these relatively small trials have led to the planning of larger trials. The 300 μg/kg/d for 3 d treatment schedule is now being evaluated in ongoing or planned cluster randomized trials: the MASSIV trial (NCT03576313) in Gambia,[77] the Adjunctive Ivermectin Mass Drug Administration for Malaria Control (MATAMAL) trial in the Bijagos Islands, in Guinea Bissau (NCT04844905) and RIMDAMAL II in Burkina Faso (NCT03967054). The BOHEMIA trial is currently planned to be conducted in Tanzania and Mozambique, in which ivermectin will be administered to both livestock and humans. Another trial is planned in Thailand using ivermectin in rubber plantation workers, but it has not yet started.

Potential veterinary application of ivermectin as part of malaria MDA

Several *Anopheles* species, such as *A. arabiensis* and *A. farauti*, exhibit both anthropophagy and zoophagy, particularly for peridomestic animals such as cattle and pigs.[78,79] These alternative feeding sources can therefore sustain the mosquito population and complicate control efforts.[80] Treating livestock therefore offers a possible addition for vector control for malaria transmission and has been shown to be feasible in field studies in Belize, Burkina Faso and Tanzania.[81–83] Veterinary applications of ivermectin allow for higher and repeated dosing than are possible in humans, as well as application of potential long-lasting formulations.[84–86]

Similarly, *Glossina palpalis* and *Glossina morsitans*, the vectors for *Trypanosoma gambiense* and *Trypanosoma rhodesiense*, West and East African sleeping sickness, respectively, take their blood meal from humans, wild animals and livestock alike. Field studies have shown these species exhibit similar susceptibility to ivermectin as *Anopheles* mosquitos. This included dose-dependent reduced lifespan and fecundity.[87–89] Similar data from animal models exist for some triatomine bugs (*Triatoma infestans* and *Rhodnius neglectus*), vectors of *Trypanosoma cruzi*, the causative agent of Chagas disease.[90]

This 'One Health' approach could offer additional advantages by treating animals for endoparasites and ectoparasites, improving the health and economic value of domestic animals,[91] while also providing vector control for malaria and other diseases. The use of ivermectin in animals is restricted by public health policies, such as the withdrawal times for slaughter or milking,[92] which could make this strategy technically challenging.[93] Another important aspect is the effect of ivermectin in livestock on dung degradation and non-target fauna, which could cause environmental concerns[94–98] and needs to be addressed.

Soil-transmitted helminths (STHs)

STHs are among the most prevalent parasitic infections in humans both in tropical and subtropical regions of the globe[99,100] and are associated with broad health impacts including anaemia, stunting and delays in cognitive development.[101]

MDA with benzimidazol derivatives (albendazole and mebendazole) is recommended to reduce the STH burden in a community,[102] because these drugs have a significantly greater efficacy compared with ivermectin in most STH species.[103,104] Data on the effect of ivermectin on hookworms show a variable reduction of 0–33%,[105,106] with the most successful application being two doses of 200 μg/kg 10 d apart reported from Brazil.[8] In comparison, both *Ascaris lumbricoides* and *Strongyloides stercoralis* respond well to a single standard ivermectin dose of 200 μg/kg each, with field studies finding cure rates of 98–100% and 83–96%,[107,108] respectively. Reports on *Trichuris trichiura* are mixed, ranging from 11% in Tanzania to 84% in Peru.[8,103,105,109,110] The reasons for these geographical differences in susceptibility are not yet well understood but could be due to different species.[111] Other nematodes such as *Ancylostoma braziliense*, *Ancylostoma caninum* and *Uncinaria stenocephala* are primarily zoonotic diseases that cause cutaneous larva migrans (CLM) syndrome in humans. Depending on the clinical presentation, one to two standard doses of ivermectin have been used and have been shown to resolve the lesions in 81–100% of cases.[112,113]

Currently there are no published data evaluating the impact of higher-dose multiple treatment regimes, as utilised for malaria control, on STHs. Ongoing malaria MDA provides an additional opportunity to investigate these potential synergistic impacts.

Filarial worms

Filarial infections were the first human disease targeted for control using ivermectin. Widespread roll-out of ivermectin MDA has produced a significant impact on filarial disease–related morbidity, including blindness and severe pruritus caused by *O. volvulus* and lymphatic obstruction and secondary bacterial skin disease caused by *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*.[114–116]

Ivermectin as a single dose administered annually at 150–200 μg/kg for onchocerciasis will reduce the microfilarial load by 99% after 1–2 months and administered over 16–18 y interrupts transmission and leads to elimination.[117,118] Recent data have shown that a sterilizing effect on adult onchocercal filaria can be achieved with administration every 3 months over 3 y.[119]

In lymphatic filariasis (LF), caused by *W. bancrofti, B. malayi* and *B. timori*, ivermectin (200 μg/kg) lacks activity against the adult filaria responsible for the pathology and it is therefore used in combination with either albendazole or diethylcarbamazine citrate (DEC) or as a triple combination of all three outside onchocerciasis areas.[120–122] The latter combination of ivermectin, DEC and albendazole has shown superior efficacy compared with the dual combination[120,122–124] and is now recommended by the World Health Organization for use in many LF-endemic regions.

Ivermectin is used with caution in *Loa loa*-endemic areas with a surveillance system for early detection and management of post-treatment severe adverse events, as it results in rapid killing of microfilaria (mf),[125] which can cause acute encephalitis, leading to disability and even death.[33,34,126] For other common filarial parasites such as *Mansonella streptocerca* and *Mansonella ozzardi*, ivermectin treatment with 150 μg/kg and

150–200 μg/kg, respectively, leads to a reduction of microfilaria and possibly some impact on macrofilaria.[127–130] *Mansonella perstans* was shown not to be affected by a standard single dose of ivermectin,[131–134] with reports of repeated doses being potentially more successful.[32,135] Importantly, ivermectin does not appear to affect the vector of these filaria, *Culicoides* sp.[136,137]

Food-borne nematodes

For food-borne nematodes such as *Gnathostoma* sp., the recommended daily dosage is 200 μg/kg for 2–3 d.[138,139] Caution is advised in infections of the central nervous system, as treatment could cause deleterious inflammation. For trichinellosis, ivermectin was effective in rat and mouse models against the free-living stage in the gut but was ineffective against the encysted stage of the parasite.[140,141]

Other nematodes

Enterobius vermicularis, colloquially known as pinworm/threadworm, is a common cosmopolitan parasite primarily causing anal pruritus and in rare cases appendicitis. It has been successfully treated with a single dose of ivermectin (200 μg/kg), with a study from Peru reporting cure rates of 89% 3 d after treatment and 78% after 30 d,[109] but a study from China showed a lower cure rate of 52.9%.[105]

Ectoparasites

Scabies is a globally occurring skin disease caused by the scabies mite (*Sarcoptes scabiei* var. *hominis*) that is especially common in poor and crowded communities in tropical and subtropical areas[142] and causes both significant morbidity and mortality through its downstream sequelae.[143,144]

There is limited pharmacodynamic data available on the use of ivermectin for scabies, although an animal model in pigs is available.[145] Doses $\leq$150 μg/kg have lower efficacy,[146] and even at standard doses of 200 μg/kg, increased survival times have been found *in vitro* over the last decade.[147] The use of a higher dose and repeated administration may improve the cure rate.[143]

Several large-scale trials have demonstrated significant reductions in the prevalence of scabies following MDA with ivermectin. The Skin Health Intervention Fiji Trial was a three-arm randomised trial in which communities were randomized to standard of care, MDA with topical permethrin or MDA with ivermectin. MDA was superior to other treatment options, with a relative reduction in prevalence of 94% for ivermectin, 62% for permethrin and 49% for standard of care.[9] The Azithromycin Ivermectin Mass Drug Administration trial on the Solomon Islands, a prospective single-arm, before and after community intervention trial using ivermectin and azithromycin in combination and permethrin 5% for pregnant and breastfeeding women and children weighing $<$12.5 kg, showed an 88% relative reduction of baseline scabies prevalence after 12 months.[148] Similar results have been reported from studies in Australia using ivermectin MDA for scabies control in remote aboriginal communities[10] and Brazil using ivermectin as a community intervention for several susceptible parasites.[8,149]

Success of ivermectin-based MDA for scabies control is dependent on treating individuals with a contraindication to ivermectin. Currently this is through topical permethrin treatment, but increasing safety data on ivermectin in these populations, especially for children $<$5 y of age, may increase the proportion of the population who can be treated with ivermectin.

Humans are host to three species of closely related lice: *Pediculus humanus capitis*, *Pediculus humanus corporis* and *Phtirus pubis*. Of these, only the body louse *P. humanus corporis* commonly acts as a vector of potentially life-threatening infectious diseases. However, recent data have shown the potential for head lice to also transmit similar pathogens,[150] are a cause of bacterial pyoderma of the scalp[151] and even cause iron deficiency in heavy infestations.[152] All three of these species cause pruritus and hence morbidity.[153,154]

In a cluster randomized trial including centres in the UK, Ireland, France and Israel, a dose of 400 μg/kg/d 1 week apart resulted in a 97.1% reduction of head lice on day 15.[155] Another randomized household-level trial in Brazil using 200 μg/kg/d twice 10 d apart led to 16% in the intervention arm being louse free compared with 4% in the control arm at 60 d post-intervention.[156] Several non-randomized studies from Egypt and Mexico using 200 μg/kg/d showed cure rates of 92.5–97% after a second dose 8 d later if the first dose failed.[157–159] A study in the Solomon Islands using MDA with a dose of 200 μg/kg/d on days 0 and 7 resulted in a 89% reduction of head lice at day 14 post-MDA[160] and a study in Thailand using the same schedule showed a 95% reduction at 14 d post-MDA.[161]

A study from Senegal using 400 μg/kg/d resulted in a 77.4% reduction in the ivermectin arm compared with 32.3% in the d-phenothrin shampoo arm at day 15. However, 7.4% of the children showed treatment failure to ivermectin[162] and there was some evidence of potential ivermectin resistance in head lice. Additional molecular analysis confirmed a genetic mutation of the GluCl receptor, the primary target of ivermectin in arthropods.[163]

Data on ivermectin for the treatment of body lice and pubic lice are scarce and mainly from smaller case series or cohort studies. These data appear to show a significant reduction in prevalence.[164,165] In this context, a potential ivermectin resistance pathway has been described outside of the GluCl receptor, called complexin, a synaptic exocytosis and neurotransmitter release regulator protein.[166] Aside from resistance, reintroduction and re-infestation is a common problem in all three species of lice even after successful MDA.[160,164,167]

Data from Brazil on the treatment of *Tunga penetrans* with a standard dose of ivermectin did not show efficacy, although it may be dependent on seasonality and the timing of the application.[149,168] In myiasis, which is common in tropical communities and can cause significant morbidity, ivermectin has been successfully used to facilitate extraction of larvae.[169,170]

There are only experimental blood feeding data from human studies using ivermectin to treat *Cimex lectularius and Cimex hemipterus*, the cause of bed bugs, a global nuisance. These data show some impact, but real-world data are unavailable.[171–173] Ivermectin has also been used with variable success for the treatment of *Demodex* mites, which are associated with a variety of

Table 1. Ivermectin use for endoparasites

Endoparasites	Potential impact of ivermectin MDA	Ivermectin dose (individual treatment)	Ivermectin MDA schedule for control	Reduction at recommended dose (%)[a]	References
Ascaris lumbricoides	Yes	200 μg/kg, once		98–100%	8, 103, 106
Necator americanus	Unclear	Not recommended, two doses of 200 μg/kg 10 d apart		0–33% single dose of 20 μg/kg, 68% two doses of 200 μg/kg 10 d apart	8, 103, 105, 106
Ancylostoma duodenale	Unclear	Not recommended[b]		[b]	[b]
Strongyloides stercoralis[c]	Yes	200 μg/kg once or multiple several days apart (day 1, 2, 15 and 16)		83–96%	8, 103, 106, 107, 108, 109
Trichuris trichiura[d]	Yes	200 μg/kg for 3 d[e], 200 μg/kg twice 10 days apart		11–88%[c]; 81.7–84% 200 μg/kg twice 10 d apart	8, 103, 105, 109, 110
Enterobius vermicularis	Yes	200 μg/kg once, plus repeat after 14 d		52.6–89%	105, 109
Onchocerca volvulus	Yes		150–200 μg/kg biannually or annually	99% reduction in microfilaria after 1–2 months; transmission interruption and elimination after 16–18 y	117–119
Loa loa	Yes	Not recommended			125
Wuchereria bancrofti	Yes	Ivermectin monotherapy not recommended	200 μg/kg annually in combination with a second drug or as triple therapy	94% reduction in microfilaria using IDA	120–124
Brugia malayi	Yes		see *W. bancrofti*		
Brugia timori	Yes		see *W. bancrofti*		
Mansonella perstans	Unclear	200–600 μg/kg once, not recommended	400 μg/kg once then 800 μg/kg annually for 3 y or 400 μg/kg twice then 800 μg/kg every 3 months for 3 y[20]	No effect short term; MDA 85–97% reduction	131–135
Mansonella streptocerca	Yes	150 μg/kg once		55–60% reduction in microfilaria[f]	127, 128
Mansonella ozzardi	Yes	150–200 μg/kg once		94–100% reduction in microfilaria	128–130
Gnathostoma sp.	Yes	200 μg/kg for 2 d		76–100%	138, 139
Trichinella spiralis	Mixed	200 μg/kg once, not recommended		No effect on encysted form; 80–90% in free living forms[g]	140, 141
Ancylostoma braziliense, Ancylostoma canium, Uncinaria stenocephala[h]	Yes	200 μg/kg, 1–2 doses depending on the clinical picture		81–100%	112, 113

[a]Cure rate if not otherwise indicated.
[b]Possibly a similar situation as *N. americanus*; no speciation conducted.
[c]In immunocompetent patients.
[d]*T. trichiura* may consist of several species explaining the geographically different rates in reduction after treatment.
[e]Unknown.
[f]Potential effect on macrofiliaria similar to *O. volvulus*.
[g]Only animal model data available.
[h]All responsible for CLM.

Table 2. Use of ivermectin for ectoparasites

Ectoparasites (excluding *Anopheles*)	Potential impact of ivermectin MDA	Ivermectin dose (individual treatment)	Ivermectin MDA schedule for control	Reduction at recommended dose (%)[a]	Parasite mortality (%) after n days	References
Sarcoptes scabiei var. *hominis* (scabies)	Yes	200 μg/kg/day, 2 weeks apart or a single dose	200 μg/kg/d 1–2 weeks apart	83–100% at 12 months[b]		8–10, 146–149
Pediculus humanus capitis (head louse)	Yes	200–400 μg/kg/d 1 week apart		77.4–97.1% for 400 μg/kg/d, 89.1–95% for 200 μg/kg/d		154–162
Pediculus humanus corporis (body louse)	Yes	200 μg/kg on day 0, 7 and 14		78%		164
Phtirus pubis (pubic louse)	Yes	200 μg/kg/d 1–2 weeks apart		100%		165
Cimex lectularius (common bedbug)	Yes	200 μg/kg once			67% after 20 d; blood meal 3 h after oral ivermectin: moulting reduced to 0% at 20 d in the same group[c]	171–173
Cimex hemipterus (tropical bedbug)	Unclear[d]	Unclear		Unclear	Unclear[e]	[d]
Demodex sp.	Likely	200 μg/kg		Unclear		174–176
Tunga penetrans	No	200 μg/kg				149, 168
Myiasis (botfly larva)	Unclear[f]	200 μg/kg		Unclear		169, 170[d]

[a]Cure rate if not otherwise indicated.
[b]Topical treatment for children <15 kg.
[c]Without molting sexual maturity does not occur.
[d]Circumstantial observation.
[e]Expected to be similar to *C. lectularius*.
[f]Recommended only in conjunction with surgery.

inflammatory skin diseases, including acne, rosacea, blepharitis and peri-oral dermatitis,[174–176] but larger randomized studies are needed to show specific efficacy of ivermectin.

Conclusions

Ivermectin has been the mainstay of onchocerciasis and LF control programmes worldwide. Within the last decade, ivermectin has shown considerable promise for use in a broader range of diseases, in particular for malaria, scabies and as an adjunct for STH control. These diseases have highly overlapping distributions, suggesting that in some circumstances MDA for malaria may also result in additional health and economic benefits through 'off-target' effects.

Ongoing and planned malaria control trials utilising ivermectin MDA provide opportunities to explore these potential synergies (Box 1). Incorporating STH and scabies endpoints into these trials should be strongly considered to more fully capture the potential health impacts of these programmes. On the other hand, current onchocerciasis, LF, STH and scabies dosing schedules are unlikely to have significant impacts on mosquito populations or malaria transmission. A key question is whether the platforms can be coordinated alongside newer malaria control efforts to accelerate progress. The expansion of ivermectin use requires careful consideration of the development of resistance in both on- and off-target organisms. Potential environmental problems could also arise from its use in animals for malaria vector control or its impact on non-target insect species.[94,96]

In summary, as we enter the decade of the Sustainable Development Goals, it appears the role of ivermectin may be expanding not contracting. Data emerging from recently completed, ongoing and future well-designed clinical trials using ivermectin MDA

for malaria control in varied settings, as mentioned in the malaria section, will answer key programmatic questions about its future role in disease control programmes worldwide.

Box 1.

After >30 y as the mainstay for control and elimination programmes for onchocerciasis and LF there is increasing evidence for a range of expanded indications including scabies and malaria control.

Extended use of ivermectin MDA for malaria vector control has the potential to impact several co-endemic parasites by reducing their burden of disease.

There is a need for exploration of reliable affordable generic supply of ivermectin to support expanded applications for which donations are currently unlikely.

Safety data on use in, at present, excluded populations such as pregnant or breastfeeding women and younger children (<5 y of age) is needed.

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