Table

Endoparasites	Potential Impact of Ivermectin MDA	Ivermectin Dose (individual treatment)	Ivermectin MDA Schedule for Control	Reduction at recommended Dose (%)[+]	References
Ascaris lumbricoides	yes	200 µg/kg, once		98-100 %	8,103,106
Necator americanus	unclear	Not recommend, two doses of 200 µg/kg 10 days apart		0 – 33% single dose of 200 µg/kg: 68% two doses of 200 µg/kg 10 days apart	8,103,105,106
Ancylostoma duodenale	unclear	Not recommend*;		*	*
*Strongyloides stercoralis***	yes	200 µg/kg once; or multiple several days apart (d1, 2, 15, and 16)		83 – 96%	8,103,106,107, 108, 109
*Trichuris trichiura****	yes	200 µg/kg, for 3 days[#]; 200 µg/kg twice 10 days apart		11 – 88%***; 81.7 - 84% for 200 µg/kg twice 10 days apart	8,103,105,109,110
Enterobius vermicularis	yes	200 µg/kg once, plus repeat after 14 days		52.6 – 89%	105,109
Onchocerca volvulus	yes		150 - 200 µg/kg biannually or annually	99% reduction in microfilaria (mf) after 1 – 2 months; transmission interruption and elimination after 16-18 years	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 mf using IDA	120–124
Brugia malayi	yes		see *W. bancrofti*		
Brugia timori	yes		see *W. bancrofti*		
Mansonella perstans	unclear	(200 µg/kg - 600 µg/kg once) Not recommended;	400 µg/kg once then 800 µg/kg annually for 3 years; or 400 µg/kg twice then 800 µg/kg every 3 months for 3 years[20]	No effect short term; MDA 85 – 97% reduction	131–135

Mansonella streptocerca	yes	150 µg/kg once		55% - 60% reduction in microfilaria[##];	127,128
Mansonella ozzardi	yes	150-200 µg/kg once		94% - 100% reduction in microfilaria;	128-130
Gnathostoma spp.	yes	200 µg/kg for 2 days		76 – 100%	138,139
Trichinella spiralis	mixed	200 µg/kg once (not recommended)		no effect on encysted form; 80 – 90 % in free living forms[++]	140,141
Ancylostoma braziliense; Ancylostoma canium; Uncinaria stenocephala[+++]	yes	200 µg/kg, 1 – 2 doses depending on the clinical picture		81 – 100%	112,113

Table 1: Ivermectin use for endoparasites; *possibly a similar situation as *N. americanus*, no speciation conducted; **in immunocompetent patients; ***T. trichiura* may consist of several species explaining the geographically different rates in reduction after treatment; [#]unknown evidence; [##]potential effect on macrofiliaria similar to *O. volvulus*; [+]cure rate if not otherwise indicated;[++]only animal model data available; [+++]all responsible for CLM;

Ectoparasites (excl. *Anopheles*)	Potential Impact of Ivermectin MDA	Ivermectin Dose (individual treatment)	Ivermectin MDA Schedule for Control	Reduction at recommended Dose (%)[##]	Parasite Mortality (%) after (N) Days	References
Sarcoptes scabiei var. *hominis* (scabies)	yes	200 µg/kg/day, two weeks apart or one single dose	200 µg/kg/day 1 – 2 weeks apart	83 – 100% at 12 months[#]		8-10,146-149
Pediculus humanus capitis (head louse)	yes	200 to 400 µg/kg/day, one week apart		77.4 – 97.1 % for 400 µg/kg/day; 89.1 – 95% in 200 µg/kg/day		154-162
Pediculus humanus corporis (body louse)	yes	200 µg/kg, day 0,7,14;		78 %		164
Phtirus pubis (pubic louse)	yes	200 µg/kg/day, one to two week apart		100 %		165

Cimex lectularius (common bedbug)	yes	200 µg/kg, once			67 % after 20 days; bloodmeal 3 h post IVM oral: moulting reduced to 0% at 20 days in the same group[+]	171–173
Cimex hemipterus (tropical bedbug)	Unclear**	unclear		unclear	Unclear*	**
Demodex spp.	likely	200 µg/kg		unclear		174–176
Tunga penetrans	no	200 µg/kg				149,168
*Myiasis (*botfly larva*)*	unclear***	200 µg/kg		unclear		169,170**

Table 2: Use of ivermectin use for ectoparasites: [#]topical treatment for children < 15 kg; *expected to be similar to *C. lectularius;* **circumstantial observation; ***recommended only in conjunction with surgery; [##]cure rate if not otherwise indicated

Box 1.

After over 30 years as the mainstay for control and elimination programmes for onchocerciasis and lymphatic filariasis 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 currently donations are unlikely.

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

Title

Broadening the Range of Use Cases for Ivermectin – a Review of the Evidence

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Abstract

Ivermectin is a broad spectrum antiparasitic agent which 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 three decades.

More recently interest in the use of ivermectin to control other neglected tropical diseases 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 mass drug administration as a tool which might aid in the control of both malaria and simultaneously that of several neglected tropical diseases (NTD).

In this review we outline the evidence base to date on these emerging indications for ivermectin mass drug administration 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.

Key Words:

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 (IVM). 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 (APOC), the Expanded Special Project for the Elimination of Neglected Tropical Diseases in Africa (ESPEN) and the Onchocerciasis Elimination Program of the Americas (OEPA). 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* spp.) 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 the 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 SARS-CoV-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 GABA, 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.[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 of 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 is 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 of the human equivalent respectively.[38–40] The relevance of these animal data to humans are therefore questionable and better data is needed. Currently children whose weight or height is below 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 amongst young children.[44–50]

Malaria

Malaria control measures over the past two decades have resulted in a significant reduction in morbidity and mortality, driven by a combination of long lasting insecticidal nets (LLIN), indoor residual spraying (IRS), artemisinin-based combination therapy (ACT) and rapid diagnostic tests (RDT).[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 higher than shown for *Anopheles* spp. Its effect on culicine species such as *Aedes* or *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 (MFA) involve feeding mosquitos on donated blood, either from donors who have taken oral ivermectin, or on blood spiked with ivermectin. Direct feeding assays (DFA) involve feeding mosquitos on volunteers treated with ivermectin. Different *Anopheles* species, such as *An. gambiae* spp. (MFA, DFA), *An. arabiensis* (MFA), *An. aquasalis* (MFA, DFA), *An. minimus* (DFA), *An. campestris* (DFA), *An sawadwongporni* (DFA), *An. dirus* (MFA)*, An. darlingi* (MFA)*, An. farauti* (DFA)*, and An. stephensi* (human MFA, mouse DFA), have all shown high mortality after ingesting blood containing ivermectin levels comparable to the ones reached in humans after an oral dose of 200 - 400 – 600 µg/kg body weight.[58,64–69] The IVERMAL trial found no difference in ivermectin mosquitocidal toxicity between MFA and DFA against *An. gambiae* using placebo (n = 23), 300 µg /kg (n = 24) 600 µg /kg/day (n = 22).[70] Although a trial by Sampaio et al. DFA showed higher mosquitocidal toxicity than MFA, however the number of participants was small (n=6).[64]

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 hours means that these dosing regimens only generate a mosquitocidal effect lasting for about 5 – 6 days[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 therefore the pharmacokinetic profile, and hence the duration of its endectocidal effect, alternative dosages have been suggested: a single dose of 400 µg/kg (1×400 µg/kg) or three consecutive daily doses of 300 µg/kg (3 × 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 days.[73]

In the RIMDAMAL trial 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 three weeks over 18 weeks in the intervention 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 under five years 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/day for three day treatment schedule is now being evaluated ongoing or planned cluster randomized trials: the MASSIV trial (NCT03576313) in the Gambia[77], the 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 has not yet started.

Potential Veterinary Application of Ivermectin as Part of Malaria MDA

Several *Anopheles* species, such as *An. arabiensis* or *An. farauti*, exhibit both anthropophagy and zoophagy, particularly for peridomestic animals such as cattle or 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 *T. 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], whilst 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 for livestock on dung degradation and non-target fauna, which could cause environmental concerns[94–98] and need to be addressed.

Soil Transmitted Helminths (STH)

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

Mass drug administration with benzimidazol derivatives (albendazole and mebendazole) is recommended to reduce the STH burden in a community[102], because these drugs have a significantly higher efficacy compared to ivermectin in most STH species.[103,104] Data on the effect of ivermectin on hookworms show a variable reduction of 0 - 33%[103,105,106], with the most successful application being two doses of 200µg/kg 10 days 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%[103] and 83 - 96%[103,107,108], respectively. Reports on *Trichuris trichiura* are mixed varying between 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 but cause cutaneous larva migrans (CLM) syndrome in humans. Depending on the clinical presentation, 1 – 2 standard doses of ivermectin have been used and 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 STH. 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 seen 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 years interrupts transmission and leads to elimination.[117,118] Recent data have shown that a sterilizing effect on adult onchocercal filaria can be achieved 3-monthly administration over three years..[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 (ALB) 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 (IDA) has shown superior efficacy compared to the dual combination[120,122–124] and is now recommended by WHO 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] *M.*

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* spp..[136,137]

Food-borne Nematodes

For food-borne nematodes such as *Gnathostoma* spp., the recommended daily dosage is 200 µg/kg for 2 - 3 days.[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 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 days post treatment and 78% after 30 days[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*) 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 of scabies, although an animal model in pigs is available.[145] Doses ≤ 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 cure.[143]

Several large-scale trials have demonstrated significant reductions in the prevalence of scabies following MDA with ivermectin. The SHIFT trial in Fiji 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 AIM 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 less than 12.5 kg, showed a 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 also treating individuals with a contra-indication to ivermectin. Currently this is through topical permethrin treatment but increasing safety data on ivermectin in these populations, especially from under 5-year-olds, 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 showed the potential for head lice to also potentially transmit similar pathogens[150] , are a cause of bacterial pyoderma of the scalp [151] and even 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 United Kingdom, Ireland, France, and Israel a dose of 400 µg/kg/day, one 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/day twice ten days apart lead to 16% in the intervention arm being louse free compared to 4% in the

control at 60 days post intervention.[156] Several non-randomized studies from Egypt and Mexico using 200 µg/kg/day showed cures rates of 92.5 – 97% after a second dose 8 days later if the first one failed.[157–159] A study in the Solomon Islands using MDA with a dose of 200 µg/kg/day on day 0 and 7 resulted in a 89% reduction of headlice at day 14 post MDA[160], and a study in Thailand using the same schedule showing 95% reduction at 14 days MDA.[161]

A study from Senegal using 400 µg/kg/day resulted in a 77.4% reduction in the ivermectin arm compared to 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 headlice. 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 is 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 treatment of *Tunga penetrans* with a standard dose of ivermectin did not show efficacy although it may be dependent on seasonality and timing of the applica-tion.[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 available.[171–173] Ivermectin has also been used with variable success for treatment of *Demodex* mites that are associated with a variety

of 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.

Conclusion

Ivermectin has been the mainstay of onchocerciasis and lymphatic filariasis control programmes worldwide. Within the last decade, ivermectin's 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. 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, lymphatic filariasis, 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-cases 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 or 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.

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Conceptualization: CK, JB, MM; Review & Editing: JB, HH, AL, UD, MM; Original Draft Preparation: CK; Analysis and interpretation of data: CK, JB, HH, AL, UD, MM; Read and approved final version: CK, JB, HH, AL, UD, MM

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References

1 Omura S, Crump A. The life and times of ivermectin - a success story. *Nat Rev Microbiol* 2004; 2: 984–9.

2 McArthur MJ, Reinemeyer CR. Herding the U.S. cattle industry toward a paradigm shift in parasite control. *Vet Parasitol* 2014; 204: 34–43.

3 Burgess CGS, Bartley Y, Redman E, *et al.* A survey of the trichostrongylid nematode species present on UK sheep farms and associated anthelmintic control practices. *Vet Parasitol* 2012; 189: 299–307.

4 Chabala JC, Mrozik H, Tolman RL, *et al.* Ivermectin, a new broad-spectrum antiparasitic agent. *J Med Chem* 1980; 23: 1134–6.

5 Glaziou P, Cartel JL, Alzieu P, Briot C, Moulia-Pelat JP, Martin PM. Comparison of ivermectin and benzyl benzoate for treatment of scabies. *Trop Med Parasitol* 1993; 44: 331–2.

6 Wilson ML. Avermectins in arthropod vector management — prospects and pitfalls. *Parasitol Today* 1993; 9: 83–7.

7 Whitworth JAG, Morgan D, Maude GH, McNicholas AM, Taylor DW. A field study of the effect of ivermectin on intestinal helminths in man. *Trans R Soc Trop Med Hyg* 1991; 85: 232–4.

8 Heukelbach J, Wilcke T, Winter B, *et al.* Efficacy of ivermectin in a patient population concomitantly infected with intestinal helminths and ectoparasites. *Arzneimittelforschung* 2011; 54: 416–21.

9 Romani L, Whitfeld MJ, Koroivueta J, *et al.* Mass drug administration for scabies control in a population with endemic disease. *N Engl J Med* 2015; 373: 2305–13.

10 Kearns TM, Speare R, Cheng AC, *et al.* Impact of an ivermectin mass drug administration on scabies prevalence in a remote Australian aboriginal community. *PLoS Negl Trop Dis* 2015; 9: e0004151.

11 Marks M, Gwyn S, Toloka H, *et al.* Impact of community treatment with ivermectin for the control of scabies on the prevalence of antibodies to Strongyloides stercoralis in children. *Clin Infect Dis* 2020; 71: 3226–8.

12 Chaccour C, Hammann F, Rabinovich NR. Ivermectin to reduce malaria transmission I. Pharmacokinetic and pharmacodynamic considerations regarding efficacy and safety. *Malar J* 2017; 16: 161.

13 Omura S. Mode of action of avermectin. In: Macrolide antibiotics: chemistry, biology and practice. New York: Academic Press, 2002: 571–6.

14 Meyers JI, Gray M, Kuklinski W, *et al.* Characterization of the target of ivermectin, the glutamate-gated chloride channel, from Anopheles gambiae. *J Exp Biol* 2015; 218: 1478–86.

15 Laing R, Gillan V, Devaney E. Ivermectin – old drug, new tricks? *Trends Parasitol* 2017; 33: 463–72.

16 Edwards G. Ivermectin: does P-glycoprotein play a role in neurotoxicity? *Filaria J* 2003; 2 Suppl 1: S8.

17 Juarez M, Schcolnik-Cabrera A, Dueñas-Gonzalez A. The multitargeted drug ivermectin: from an antiparasitic agent to a repositioned cancer drug. *Am J Cancer Res* 2018; 8: 317–31.

18 Mastrangelo E, Pezzullo M, De Burghgraeve T, *et al.* Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. *J Antimicrob Chemother* 2012; 67: 1884–94.

19 Heidary F, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. *J Antibiot (Tokyo)* 2020; : 1–10.

20 Wolstenholme AJ, Rogers AT. Glutamate-gated chloride channels and the mode of action of the avermectin/milbemycin anthelmintics. *Parasitology* 2006; 131: S85.

21 Schinkel AH, Smit JJ, van Tellingen O, *et al.* Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. *Cell* 1994; 77: 491–502.

22 Baudou E, Lespine A, Durrieu G, *et al.* Serious ivermectin toxicity and human ABCB1 nonsense mutations. *N Engl J Med* 2020; 383: 787–9.

23 Mealey KL, Bentjen SA, Gay JM, Cantor GH. Ivermectin sensitivity in collies is associated with a deletion mutation of the mdr1 gene. *Pharmacogenetics* 2001; 11: 727–33.

24 Dowling P. Pharmacogenetics: it's not just about ivermectin in collies. *Can Vet J* 2006; 47: 1165–8.

25 History of the program. Mectizan Donation Program. 2018; published online Jan 29. https://mectizan.org/what/history/ (accessed Jan 8, 2021).

26 Guzzo CA, Furtek CI, Porras AG, *et al.* Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol* 2002; 42: 1122–33.

27 Smit MR, Ochomo EO, Aljayyoussi G, *et al.* Safety and mosquitocidal efficacy of high-dose ivermectin when co-administered with dihydroartemisinin-piperaquine in Kenyan adults with uncomplicated malaria (IVERMAL): a randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis* 2018; 18: 615–26.

28 Smit MR, Ochomo EO, Waterhouse D, *et al.* Pharmacokinetics-pharmacodynamics of high-dose ivermectin with dihydroartemisinin-piperaquine on mosquitocidal activity and QT-prolongation (IVERMAL). *Clin Pharmacol Ther* 2019; 105: 388–401.

29 Kamgno J, Gardon J, Gardon-Wendel N, Demanga-Ngangue, Duke BOL, Boussinesq M. Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. *Trans R Soc Trop Med Hyg* 2004; 98: 496–504.

30 Awadzi K, Attah SK, Addy ET, Opoku NO, Quartey BT. The effects of high-dose ivermectin regimens on Onchocerca volvulus in onchocerciasis patients. *Trans R Soc Trop Med Hyg* 1999; 93: 189–94.

31 Awadzi K, Opoku NO, Addy ET, Quartey BT. The chemotherapy of onchocerciasis. XIX: the clinical and laboratory tolerance of high dose ivermectin. *Trop Med Parasitol* 1995; 46: 131–7.

32 Gardon J, Kamgno J, Gardon-Wendel N, Demanga-Ngangue null, Duke BOL, Boussinesq M. Efficacy of repeated doses of ivermectin against *Mansonella perstans*. *Trans R Soc Trop Med Hyg* 2002; 96: 325–6.

33 Kamgno J, Boussinesq M, Labrousse F, Nkegoum B, Thylefors BI, Mackenzie CD. Encephalopathy after ivermectin treatment in a patient infected with *Loa loa* and *Plasmodium* spp. *Am J Trop Med Hyg* 2008; 78: 546–51.

34 Boussinesq M, Gardon J, Gardon-Wendel N, Chippaux J-P. Clinical picture, epidemiology and outcome of Loa-associated serious adverse events related to mass ivermectin treatment of onchocerciasis in Cameroon. *Filaria J* 2003; 2: S4.

35 Nicolas P, Maia MF, Bassat Q, *et al.* Safety of oral ivermectin during pregnancy: a systematic review and meta-analysis. *Lancet Glob Health* 2020; 8: e92–100.

36 Gyapong JO, Chinbuah MA, Gyapong M. Inadvertent exposure of pregnant women to ivermectin and albendazole during mass drug administration for lymphatic filariasis. *Trop Med Int Health* 2003; 8: 1093–101.

37 Lankas GR, Wise LD, Cartwright ME, Pippert T, Umbenhauer DR. Placental P-glycoprotein deficiency enhances susceptibility to chemically induced birth defects in mice. *Reprod Toxicol* 1998; 12: 457–63.

38 Merck & Co. Stromectrol. FDA approved Package insert 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050742s026lbl.pdf (accessed Jan 3, 2020).

39 FDA. Center for drug evaluation and research. Approval package for Mectizan. .

40 Campbell WC. Ivermectin and Abamectin. New York, NY: Springer New York, 1989 http://dx.doi.org/10.1007/978-1-4612-3626-9 (accessed Feb 16, 2021).

41 Saunders NR, Dreifuss J-J, Dziegielewska KM, *et al.* The rights and wrongs of blood-brain barrier permeability studies: a walk through 100 years of history. *Front Neurosci* 2014; 8: 404.

42 Ek CJ, Dziegielewska KM, Habgood MD, Saunders NR. Barriers in the developing brain and neurotoxicology. *NeuroToxicology* 2012; 33: 586–604.

43 Lam J, Baello S, Iqbal M, *et al.* The ontogeny of P-glycoprotein in the developing human blood–brain barrier: implication for opioid toxicity in neonates. *Pediatr Res* 2015; 78: 417–21.

44 Levy M, Martin L, Bursztejn A -C., *et al.* Ivermectin safety in infants and children under 15 kg treated for scabies: a multicentric observational study. *Br J Dermatol* 2020; 182: 1003–6.

45 Colebunders R, Wafula ST, Hotterbeekx A, Siewe-Fodjo JN. Ivermectin use in children below 15 kg: potential benefits for onchocerciasis and scabies elimination programmes. *Br J Dermatol* 2020; 182: 1064–1064.

46 Morris-Jones R. Oral ivermectin for infants and children under 15 kg appears to be a safe and effective treatment for scabies. *Br J Dermatol* 2020; 182: 835–6.

47 Wilkins AL, Steer AC, Cranswick N, Gwee A. Question 1: Is it safe to use ivermectin in children less than five years of age and weighing less than 15 kg? *Arch Dis Child* 2018; 103: 514.1-519.

48 Chosidow A, Gendrel D. Tolérance de l'ivermectine orale chez l'enfant. *Arch Pédiatrie* 2016; 23: 204–9.

49 Brussee JM, Schulz JD, Coulibaly JT, Keiser J, Pfister M. Ivermectin dosing strategy to achieve equivalent exposure coverage in children and adults. *Clin Pharmacol Ther* 2019; 106: 661–7.

50 Jittamala P, Monteiro W, Smit MR, *et al.* A systematic review and an individual patient data meta-analysis of ivermectin use in children weighing less than fifteen kilograms: Is it time to reconsider the current contraindication? *PLoS Negl Trop Dis* 2021; 15: e0009144.

51 World Health organization. World malaria report 2019. S.l.: World Health Organization, 2019.

52 Thomsen EK, Koimbu G, Pulford J, *et al.* Mosquito behavior change after distribution of bednets results in decreased protection against malaria exposure. *J Infect Dis* 2017; 215: 790–7.

53 Charlwood JD, Kessy E, Yohannes K, Protopopoff N, Rowland M, LeClair C. Studies on the resting behaviour and host choice of *Anopheles gambiae* and *An. arabiensis* from Muleba, Tanzania: resting in *Anopheles gambiae s.l. Med Vet Entomol* 2018; 32: 263–70.

54 WHO | Insecticide resistance. WHO. http://www.who.int/malaria/areas/vector_control/insecticide_resistance/en/ (accessed Jan 18, 2021).

55 Alout H, Foy BD. Ivermectin: a complimentary weapon against the spread of malaria? *Expert Rev Anti Infect Ther* 2017; 15: 231–40.

56 Chaccour CJ, Kobylinski KC, Bassat Q, *et al.* Ivermectin to reduce malaria transmission: a research agenda for a promising new tool for elimination. *Malar J* 2013; 12: 153.

57 Deus KM, Saavedra-rodriguez K, Butters MP, Black WC, Foy BD. The effect of ivermectin in seven strains of Aedes aegypti (Diptera: Culicidae) including a genetically diverse laboratory strain and three permethrin resistant strains. *J Med Entomol* 2012; 49: 356–63.

58 Kobylinski KC, Deus KM, Butters MP, *et al.* The effect of oral anthelmintics on the survivorship and re-feeding frequency of anthropophilic mosquito disease vectors. *Acta Trop* 2010; 116: 119–26.

59 Meyers JI, Gray M, Foy BD. Mosquitocidal properties of IgG targeting the glutamate-gated chloride channel in three mosquito disease vectors (Diptera: Culicidae). *J Exp Biol* 2015; 218: 1487–95.

60 Bockarie MJ, Hii JL, Alexander ND, *et al.* Mass treatment with ivermectin for filariasis control in Papua New Guinea: impact on mosquito survival. *Med Vet Entomol* 1999; 13: 120–3.

61 Simonsen PE, Pedersen EM, Rwegoshora RT, Malecela MN, Derua YA, Magesa SM. Lymphatic filariasis control in Tanzania: effect of repeated mass drug administration with

ivermectin and albendazole on infection and transmission. *PLOS Negl Trop Dis* 2010; 4: e696.

62 Gardner K, Meisch MV, Meek CL, Biven WS. Effects of ivermectin in canine blood on Anopheles quadrimaculatus, Aedes albopictus and Culex salinarius. *J Am Mosq Control Assoc* 1993; 9: 400–2.

63 Chaccour C, Lines J, Whitty CJM. Effect of ivermectin on Anopheles gambiae mosquitoes fed on humans: the potential of oral insecticides in malaria control. *J Infect Dis* 2010; 202: 113–6.

64 Sampaio VS, Beltrán TP, Kobylinski KC, *et al.* Filling gaps on ivermectin knowledge: effects on the survival and reproduction of Anopheles aquasalis, a Latin American malaria vector. *Malar J* 2016; 15: 491.

65 Kobylinski KC, Escobedo-Vargas KS, López-Sifuentes VM, *et al.* Ivermectin susceptibility, sporontocidal effect, and inhibition of time to re-feed in the Amazonian malaria vector Anopheles darlingi. *Malar J* 2017; 16.

66 Kobylinski KC, Ubalee R, Ponlawat A, *et al.* Ivermectin susceptibility and sporontocidal effect in Greater Mekong Subregion Anopheles. *Malar J* 2017; 16.

67 Dreyer SM, Morin KJ, Vaughan JA. Differential susceptibilities of Anopheles albimanus and Anopheles stephensi mosquitoes to ivermectin. *Malar J* 2018; 17: 148.

68 Kositz C, Talina J, Diau J, *et al.* Incidental mosquitocidal effect of an ivermectin mass drug administration on Anopheles farauti conducted for scabies control in the Solomon Islands. *Trans R Soc Trop Med Hyg* 2017; 111: 97–101.

69 Sylla M, Kobylinski KC, Gray M, *et al.* Mass drug administration of ivermectin in south-eastern Senegal reduces the survivorship of wild-caught, blood fed malaria vectors. *Malar J* 2010; 9: 365.

70 Smit MR, Ochomo EO, Aljayyoussi G, *et al.* Human direct skin feeding versus membrane feeding to assess the mosquitocidal efficacy of high-dose ivermectin (IVERMAL trial). *Clin Infect Dis* 2019; 69: 1112–9.

71 Chaccour CJ, Rabinovich NR, Slater H, *et al.* Establishment of the ivermectin research for malaria elimination network: updating the research agenda. *Malar J* 2015; 14: 243.

72 Slater HC, Foy BD, Kobylinski K, *et al.* Ivermectin as a novel complementary malaria control tool to reduce incidence and prevalence: a modelling study. *Lancet Infect Dis* 2020; 20: 498–508.

73 Smit MR, Ochomo E, Aljayyoussi G, *et al.* Efficacy and safety of high-dose ivermectin for reducing malaria transmission (IVERMAL): protocol for a double-blind, randomized, placebo-controlled, dose-finding trial in Western Kenya. *JMIR Res Protoc* 2016; 5: e213.

74 Foy BD, Alout H, Seaman JA, *et al.* Efficacy and risk of harms of repeat ivermectin mass drug administrations for control of malaria (RIMDAMAL): a cluster-randomised trial. *The Lancet* 2019; published online March.

75 Bradley J, Moulton LH, Hayes R. Analysis of the RIMDAMAL trial. *Lancet Lond Engl* 2019; 394: 1005–6.

76 Foy BD, Rao S, Parikh S, Slater HC, Dabiré RK. Analysis of the RIMDAMAL trial – Authors' reply. *The Lancet* 2019; 394: 1006–7.

77 Dabira ED, Soumare HM, Lindsay SW, *et al.* Mass drug administration with high-dose ivermectin and dihydroartemisinin-piperaquine for malaria elimination in an area of low transmission with high coverage of malaria control interventions: protocol for the MASSIV cluster randomized clinical rial. *JMIR Res Protoc* 2020; 9: e20904.

78 Pasay CJ, Yakob L, Meredith HR, *et al.* Treatment of pigs with endectocides as a complementary tool for combating malaria transmission by Anopheles farauti (s.s.) in Papua New Guinea. *Parasit Vectors* 2019; 12: 124.

79 Fornadel CM, Norris LC, Glass GE, Norris DE. Analysis of Anopheles arabiensis blood feeding behavior in Southern Zambia during the two years after introduction of insecticide-treated bed nets. *Am J Trop Med Hyg* 2010; 83: 848–53.

80 Waite JL, Swain S, Lynch PA, *et al.* Increasing the potential for malaria elimination by targeting zoophilic vectors. *Sci Rep* 2017; 7: 40551.

81 Dreyer SM, Leiva D, Magaña M, *et al.* Fipronil and ivermectin treatment of cattle reduced the survival and ovarian development of field-collected Anopheles albimanus in a pilot trial conducted in northern Belize. *Malar J* 2019; 18: 296.

82 Pooda HS, Rayaisse J-B, Hien DF de S, *et al.* Administration of ivermectin to peridomestic cattle: a promising approach to target the residual transmission of human malaria. *Malar J* 2014; 13 Suppl 1: 496.

83 Lyimo IN, Kessy ST, Mbina KF, Daraja AA, Mnyone LL. Ivermectin-treated cattle reduces blood digestion, egg production and survival of a free-living population of Anopheles arabiensis under semi-field condition in south-eastern Tanzania. *Malar J* 2017; 16: 239.

84 Chaccour C, Abizanda G, Irigoyen Á, Del Pozo JL. Pilot study of a slow-release ivermectin formulation for malaria control in a pig model. *Antimicrob Agents Chemother* 2017; 61: e02104-16.

85 Lifschitz A, Virkel G, Ballent M, *et al.* Ivermectin (3.15%) long-acting formulations in cattle: absorption pattern and pharmacokinetic considerations. *Vet Parasitol* 2007; 147: 303–10.

86 Lifschitz, Pis, Alvarez, *et al.* Bioequivalence of ivermectin formulations in pigs and cattle. *J Vet Pharmacol Ther* 1999; 22: 27–34.

87 Pooda SH, Mouline K, De Meeûs T, Bengaly Z, Solano P. Decrease in survival and fecundity of Glossina palpalis gambiensis vanderplank 1949 (Diptera: Glossinidae) fed on cattle treated with single doses of ivermectin. *Parasit Vectors* 2013; 6: 165.

88 Langley PA, Roe JM. Ivermectin as a possible control agent for the tsetse fly, Glossina morsitans. *Entomol Exp Appl* 1984; 36: 137–43.

89 van den Abbeele J, D'Haeseleer F, Goossens M. Efficacy of ivermectin on the reproductive biology of Glossina palpalis palpalis (Rob.-Desv.) (Glossinidae: Diptera). *Ann Soc Belg Med Trop* 1986; 66: 167–72.

90 Dias JCP, Schofield CJ, Machado EM, Fernandes AJ. Ticks, ivermectin, and experimental Chagas disease. *Mem Inst Oswaldo Cruz* 2005; 100: 829–32.

91 Chaccour C, Killeen GF. Mind the gap: residual malaria transmission, veterinary endectocides and livestock as targets for malaria vector control. *Malar J* 2016; 15: 24.

92 The Ivermectin Roadmappers, Billingsley P, Binka F, *et al.* A roadmap for the development of ivermectin as a complementary malaria vector control tool. *Am J Trop Med Hyg* 2020; 102: 3–24.

93 Chaccour C. Veterinary endectocides for malaria control and elimination: prospects and challenges. *Philos Trans R Soc Lond B Biol Sci* 2021; 376: 20190810.

94 Mancini L, Lacchetti I, Chiudioni F, *et al.* Need for a sustainable use of medicinal products: environmental impacts of ivermectin. *Ann Ist Super Sanita* 2020; 56: 492–6.

95 Liebig M, Fernandez ÁA, Blübaum-Gronau E, *et al.* Environmental risk assessment of ivermectin: a case study. *Integr Environ Assess Manag* 2010; 6: 567–87.

96 Ishikawa I, Iwasa M. Toxicological effect of ivermectin on the survival, reproduction, and feeding activity of four species of dung beetles (Coleoptera: Scarabaeidae and Geotrupidae) in Japan. *Bull Entomol Res* 2020; 110: 106–14.

97 Pecenka JR, Lundgren JG. Effects of herd management and the use of ivermectin on dung arthropod communities in grasslands. *Basic Appl Ecol* 2019; 40: 19–29.

98 Bloom RA, Matheson JC. Environmental assessment of avermectins by the US Food and Drug Administration. *Vet Parasitol* 1993; 48: 281–94.

99 Singer R, Xu TH, Herrera LNS, *et al.* Prevalence of intestinal parasites in a low-income Texas community. *Am J Trop Med Hyg* 2020; 102: 1386–95.

100 McKenna ML, McAtee S, Bryan PE, *et al.* Human intestinal parasite burden and poor sanitation in rural Alabama. *Am J Trop Med Hyg* 2017; 97: 1623–8.

101 Hotez PJ, Molyneux DH, Fenwick A, *et al.* Control of neglected tropical diseases. *N Engl J Med* 2007; 357: 1018–27.

102 Guideline: preventive chemotherapy to control soil-transmitted helminth infections in at-risk population groups. Geneva: World Health Organization, 2017 http://www.ncbi.nlm.nih.gov/books/NBK487927/ (accessed June 25, 2021).

103 Marti H, Haji HJ, Savioli L, *et al.* A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of Strongyloides stercoralis and other soil-transmitted helminth infections in children. *Am J Trop Med Hyg* 1996; 55: 477–81.

104 Campbell WC. Ivermectin as an antiparasitic agent for use in humans. *Annu Rev Microbiol* 1991; 45: 445–74.

105 Wen L-Y, Yan X-L, Sun F-H, Fang Y-Y, Yang M-J, Lou L-J. A randomized, double-blind, multicenter clinical trial on the efficacy of ivermectin against intestinal nematode infections in China. *Acta Trop* 2008; 106: 190–4.

106 Freedman DO, Zierdt WS, Lujan A, Nutman TB. The efficacy of ivermectin in the chemotherapy of gastrointestinal helminthiasis in humans. *J Infect Dis* 1989; 159: 1151–3.

107 Buonfrate D, Salas-Coronas J, Muñoz J, *et al.* Multiple-dose versus single-dose ivermectin for Strongyloides stercoralis infection (Strong Treat 1 to 4): a multicentre, open-label, phase 3, randomised controlled superiority trial. *Lancet Infect Dis* 2019; 19: 1181–90.

108 Suputtamongkol Y, Premasathian N, Bhumimuang K, *et al.* Efficacy and safety of single and double doses of ivermectin versus 7-day high dose albendazole for chronic strongyloidiasis. *PLoS Negl Trop Dis* 2011; 5: e1044.

109 Naquira C, Jimenez G, Guerra JG, *et al.* Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg* 1989; 40: 304–9.

110 Wimmersberger D, Coulibaly JT, Schulz JD, *et al.* Efficacy and safety of ivermectin against Trichuris trichiura in preschool-aged and school-aged children: a randomized controlled dose-finding trial. *Clin Infect Dis* 2018; 67: 1247–55.

111 Betson M, Søe MJ, Nejsum P. Human trichuriasis: whipworm genetics, phylogeny, transmission and future research directions. *Curr Trop Med Rep* 2015; 2: 209–17.

112 Vanhaecke C, Perignon A, Monsel G, Regnier S, Bricaire F, Caumes E. The efficacy of single dose ivermectin in the treatment of hookworm related cutaneous larva migrans varies depending on the clinical presentation. *J Eur Acad Dermatol Venereol* 2014; 28: 655–7.

113 Caumes E. Treatment of cutaneous larva migrans. *Clin Infect Dis* 2000; 30: 811–4.

114 Ottesen EA, Hooper PJ, Bradley M, Biswas G. The global programme to eliminate lymphatic filariasis: health impact after 8 years. *PLoS Negl Trop Dis* 2008; 2: e317.

115 World Health organization. Progress report 2000-2009 and strategic plan 2010-2020 of the global programme to eliminate lymphatic filariasis. Geneva.: World Health Organization., 2010.

116 World Health Organization (WHO). Onchocerciasis. Geneva, Switzerland; WHO. https://www.who.int/news-room/fact-sheets/detail/onchocerciasis (accessed May 1, 2020).

117 Traore MO, Sarr MD, Badji A, *et al.* Proof-of-principle of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: final results of a study in Mali and Senegal. *PLoS Negl Trop Dis* 2012; 6.

118 Basáñez M-G, Pion SD, Boakes E, Filipe JA, Churcher TS, Boussinesq M. Effect of single-dose ivermectin on Onchocerca volvulus: a systematic review and meta-analysis. *Lancet Infect Dis* 2008; 8: 310–22.

119 Walker M, Pion SDS, Fang H, *et al.* Macrofilaricidal efficacy of repeated doses of ivermectin for the treatment of river blindness. *Clin Infect Dis* 2017; 65: 2026–34.

120 Bjerum CM, Ouattara AF, Aboulaye M, *et al.* Efficacy and safety of a single dose of ivermectin, diethylcarbamazine, and albendazole for treatment of lymphatic filariasis in Côte d'Ivoire: an open-label randomized controlled trial. *Clin Infect Dis*

121 Horton J, Witt C, Ottesen EA, *et al.* An analysis of the safety of the single dose, two drug regimens used in programmes to eliminate lymphatic filariasis. *Parasitology* 2000; 121: S147–60.

122 Thomsen EK, Sanuku N, Baea M, *et al.* Efficacy, safety, and pharmacokinetics of coadministered diethylcarbamazine, albendazole, and ivermectin for treatment of bancroftian filariasis. *Clin Infect Dis* 2016; 62: 334–41.

123 Dubray CL, Sircar AD, Rochars VMB de, *et al.* Safety and efficacy of co-administered diethylcarbamazine, albendazole and ivermectin during mass drug administration for

lymphatic filariasis in Haiti: Results from a two-armed, open-label, cluster-randomized, community study. *PLoS Negl Trop Dis* 2020; 14: e0008298.

124 Hardy M, Samuela J, Kama M, *et al.* The safety of combined triple drug therapy with ivermectin, diethylcarbamazine and albendazole in the neglected tropical diseases co-endemic setting of Fiji: A cluster randomised trial. *PLoS Negl Trop Dis* 2020; 14: e0008106.

125 Pion SD, Tchatchueng-Mbougua JB, Chesnais CB, *et al.* Effect of a single standard dose (150–200 µg/kg) of ivermectin on Loa loa microfilaremia: systematic review and meta-analysis. *Open Forum Infect Dis* 2019; 6.

126 Chippaux J-P, Boussinesq M, Gardon J, Gardon-Wendel N, Ernould J-C. Severe adverse reaction risks during mass treatment with ivermectin in loiasis-endemic areas. *Parasitol Today* 1996; 12: 448–50.

127 Fischer P, Tukesiga E, Büttner DW. Long-term suppression of Mansonella streptocerca microfilariae after treatment with ivermectin. *J Infect Dis* 1999; 180: 1403–5.

128 Ta-Tang T-H, Crainey JL, Post RJ, Luz SL, Rubio JM. Mansonellosis: current perspectives. *Res Rep Trop Med* 2018; 9: 9–24.

129 de Almeida Basano S, de Souza Almeida Aranha Camargo J, Fontes G, *et al.* Phase III clinical trial to evaluate ivermectin in the reduction of Mansonella ozzardi infection in the Brazilian Amazon. *Am J Trop Med Hyg* 2018; 98: 786–90.

130 Medeiros JF, Vera LJS, Crispim P di TB, *et al.* Sustained clearance of Mansonella ozzardi infection after treatment with ivermectin in the Brazilian Amazon. *Am J Trop Med Hyg* 2014; 90: 1170–5.

131 Richard-Lenoble D, Kombila M, Rupp EA, *et al.* Ivermectin in loiasis and concomitant O. volvulus and M. perstans infections. *Am J Trop Med Hyg* 1988; 39: 480–3.

132 Bregani ER, Rovellini A, Mbaïdoum N, Magnini MG. Comparison of different anthelminthic drug regimens against Mansonella perstans filariasis. *Trans R Soc Trop Med Hyg* 2006; 100: 458–63.

133 Van den Enden E, Van Gompel A, Van der Stuyft P, Vervoort T, Van den Ende J. Treatment failure of a single high dose of ivermectin for Mansonella perstans filariasis. *Trans R Soc Trop Med Hyg* 1993; 87: 90.

134 Asio SM, Simonsen PE, Onapa AW. A randomised, double-blind field trial of ivermectin alone and in combination with albendazole for the treatment of Mansonella perstans infections in Uganda. *Trans R Soc Trop Med Hyg* 2009; 103: 274–9.

135 Kyelem D, Sanou S, Boatin B, Medlock J, Coulibaly S, Molyneux DH. Impact of long-term ivermectin (Mectizan®) on *Wuchereria bancrofti* and *Mansonella perstans* infections in Burkina Faso: strategic and policy implications. *Ann Trop Med Parasitol* 2003; 97: 827–38.

136 Reeves WK, Nol P, Miller MM, Jones GZ. Effects of ivermectin on the susceptibility of Culicoides sonorensis (Diptera: Ceratopogonidae) to bluetongue and epizootic hemorrhagic disease viruses. *J Vector Ecol* 2009; 34: 161–3.

137 Murchie AK, Thompson GM, Clawson S, Brown A, Gordon AW, Jess S. Field evaluation of deltamethrin and ivermectin applications to cattle on culicoides host alighting, blood-feeding, and emergence. *Viruses* 2019; 11.

138 Herman JS, Chiodini PL. Gnathostomiasis, another emerging imported disease. *Clin Microbiol Rev* 2009; 22: 484–92.

139 Kraivichian K, Nuchprayoon S, Sitichalernchai P, Chaicumpa W, Yentakam S. Treatment of cutaneous gnathostomiasis with ivermectin. *Am J Trop Med Hyg* 2004; 71: 623–8.

140 Soliman GA, Taher ES, Mahmoud MA. Therapeutic efficacy of dormectin, ivermectin and levamisole against different stages of Trichinella spiralis in rats. *Turk J Parasitol* 2011; 35: 86–91.

141 Campbell WC, Blair LS, Lotti VJ. Efficacy of avermectins against *Trichinella spiralis* in mice. *J Helminthol* 1979; 53: 254–6.

142 Hay RJ, Steer AC, Engelman D, Walton S. Scabies in the developing world--its prevalence, complications, and management. *Clin Microbiol Infect* 2012; 18: 313–23.

143 Lawrence G, Leafasia J, Sheridan J, *et al.* Control of scabies, skin sores and haematuria in children in the Solomon Islands: another role for ivermectin. *Bull World Health Organ* 2005; 83: 34–42.

144 Chung S-D, Wang K-H, Huang C-C, Lin H-C. Scabies increased the risk of chronic kidney disease: a 5-year follow-up study. *J Eur Acad Dermatol Venereol* 2014; 28: 286–92.

145 Mounsey K, Ho M-F, Kelly A, *et al.* A tractable experimental model for study of human and animal scabies. *PLoS Negl Trop Dis* 2010; 4: e756.

146 Chouela EN, Abeldaño AM, Pellerano G, *et al.* Equivalent therapeutic efficacy and safety of ivermectin and lindane in the treatment of human scabies. *Arch Dermatol* 1999; 135: 651–5.

147 Mounsey KE, Holt DC, McCarthy JS, Currie BJ, Walton SF. Longitudinal evidence of increasing in vitro tolerance of scabies mites to ivermectin in scabies endemic communities. *Arch Dermatol* 2009; 145: 840–1.

148 Romani L, Marks M, Sokana O, *et al.* Efficacy of mass drug administration with ivermectin for control of scabies and impetigo, with coadministration of azithromycin: a single-arm community intervention trial. *Lancet Infect Dis* 2019; 19: 510–8.

149 Heukelbach J, Winter B, Wilcke T, *et al.* Selective mass treatment with ivermectin to control intestinal helminthiases and parasitic skin diseases in a severely affected population. *Bull World Health Organ* 2004; 82: 563–71.

150 Amanzougaghene N, Fenollar F, Raoult D, Mediannikov O. Where are we with human lice? A review of the current state of knowledge. *Front Cell Infect Microbiol* 2019; 9: 474.

151 Burgess IF. Human lice and their management. *Adv Parasitol* 1995; 36: 271–342.

152 Burke S, Mir P. Pediculosis causing iron deficiency anaemia in school children. *Arch Dis Child* 2011; 96: 989.

153 Heukelbach J, Wilcke T, Winter B, Feldmeier H. Epidemiology and morbidity of scabies and pediculosis capitis in resource-poor communities in Brazil. *Br J Dermatol* 2005; 153: 150–6.

154 Coates SJ, Thomas C, Chosidow O, Engelman D, Chang AY. Ectoparasites. *J Am Acad Dermatol* 2020; 82: 551–69.

155 Chosidow O, Giraudeau B, Cottrell J, *et al.* Oral ivermectin versus malathion lotion for difficult-to-treat head lice. *N Engl J Med* 2010; 362: 896–905.

156 Pilger D, Heukelbach J, Khakban A, Oliveira FA, Fengler G, Feldmeier H. Household-wide ivermectin treatment for head lice in an impoverished community: randomized observer-blinded controlled trial. *Bull World Health Organ* 2010; 88: 90–6.

157 Ahmad HM, Abdel-Azim ES, Abdel-Aziz RT. Assessment of topical versus oral ivermectin as a treatment for head lice: Topical versus oral ivermectin for head lice. *Dermatol Ther* 2014; 27: 307–10.

158 Ameen M, Arenas R, Villanueva-Reyes J, *et al.* Oral ivermectin for treatment of pediculosis capitis. *Pediatr Infect Dis J* 2010; 29: 991–3.

159 Nofal A. Oral ivermectin for head lice: a comparison with 0.5 % topical malathion lotion: Oral ivermectin vs. malathion lotion for head lice. *JDDG J Dtsch Dermatol Ges* 2010; 8: 985–8.

160 Coscione S, Esau T, Kekeubata E, *et al.* Impact of ivermectin administered for scabies treatment on the prevalence of head lice in Atoifi, Solomon Islands. *PLoS Negl Trop Dis* 2018; 12: e0006825.

161 Singhasivanon O, Lawpoolsri S, Mungthin M, Yimsamran S, Soonthornworasiri N, Krudsood S. Prevalence and alternative treatment of head lice infestation in rural Thailand: a community-based study. *Korean J Parasitol* 2019; 57: 499–504.

162 Leulmi H, Diatta G, Sokhna C, Rolain J-M, Raoult D. Assessment of oral ivermectin versus shampoo in the treatment of pediculosis (head lice infestation) in rural areas of Sine-Saloum, Senegal. *Int J Antimicrob Agents* 2016; 48: 627–32.

163 Amanzougaghene N, Fenollar F, Diatta G, Sokhna C, Raoult D, Mediannikov O. Mutations in GluCl associated with field ivermectin-resistant head lice from Senegal. *Int J Antimicrob Agents* 2018; 52: 593–8.

164 Foucault C, Ranque S, Badiaga S, Rovery C, Raoult D, Brouqui P. Oral ivermectin in the treatment of body lice. *J Infect Dis* 2006; 193: 474–6.

165 Salavastru CM, Chosidow O, Janier M, Tiplica GS. European guideline for the management of pediculosis pubis. *J Eur Acad Dermatol Venereol* 2017; 31: 1425–8.

166 Amanzougaghene N, Fenollar F, Nappez C, *et al.* Complexin in ivermectin resistance in body lice. *PLoS Genet* 2018; 14: e1007569.

167 Munirathinam A, Sunish IP, Rajendran R, Tyagi BK. Impact of ivermectin drug combinations on Pediculus humanus capitis infestation in primary schoolchildren of south Indian rural villages. *Int J Dermatol* 2009; 48: 1201–5.

168 Heukelbach J, Franck S, Feldmeier H. Therapy of tungiasis: a double-blinded randomized controlled trial with oral ivermectin. *Mem Inst Oswaldo Cruz* 2004; 99: 873–6.

169 Shinohara EH, Martini MZ, de Oliveira Neto HG, Takahashi A. Oral myiasis treated with ivermectin: case report. *Braz Dent J* 2004; 15: 79–81.

170 Osorio J, Moncada L, Molano A, Valderrama S, Gualtero S, Franco-Paredes C. Role of ivermectin in the treatment of severe orbital myiasis due to Cochliomyia hominivorax. *Clin Infect Dis* 2006; 43: e57–9.

171 Sheele JM, Anderson JF, Tran TD, *et al.* Ivermectin causes Cimex lectularius (bedbug) morbidity and mortality. *J Emerg Med* 2013; 45: 433–40.

172 Baraka GT, Nyundo BA, Thomas A, Mwang'onde BJ, Kweka EJ. Susceptibility status of bedbugs (hemiptera: Cimicidae) against pyrethroid and organophosphate insecticides in Dar es Salaam, Tanzania. *J Med Entomol* 2020; 57: 524–8.

173 Dang K, Doggett SL, Veera Singham G, Lee C-Y. Insecticide resistance and resistance mechanisms in bed bugs, Cimex spp. (Hemiptera: Cimicidae). *Parasit Vectors* 2017; 10: 318.

174 Brown M, Hernández-Martín A, Clement A, Colmenero I, Torrelo A. Severe demodexfolliculorum–associated oculocutaneous rosacea in a girl successfully treated with ivermectin. *JAMA Dermatol* 2014; 150: 61–3.

175 Salem DA-B, El-Shazly A, Nabih N, El-Bayoumy Y, Saleh S. Evaluation of the efficacy of oral ivermectin in comparison with ivermectin-metronidazole combined therapy in the treatment of ocular and skin lesions of Demodex folliculorum. *Int J Infect Dis* 2013; 17: e343-347.

176 Chen W, Plewig G. Human demodicosis: revisit and a proposed classification. *Br J Dermatol* 2014; 170: 1219–25.