<table>
<thead>
<tr>
<th>Endoparasites</th>
<th>Potential Impact of Ivermectin MDA</th>
<th>Ivermectin Dose (individual treatment)</th>
<th>Ivermectin MDA Schedule for Control</th>
<th>Reduction at recommended Dose (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ascaris lumbricoides</em></td>
<td>yes</td>
<td>200 µg/kg, once</td>
<td></td>
<td>98-100 %</td>
<td>8,103,106</td>
</tr>
<tr>
<td><em>Necator americanus</em></td>
<td>unclear</td>
<td>Not recommend, two doses of 200 µg/kg 10 days apart</td>
<td></td>
<td>0 – 33% single dose of 200 µg/kg; 68% two doses of 200 µg/kg 10 days apart</td>
<td>8,103,105,106</td>
</tr>
<tr>
<td><em>Ancylostoma duodenale</em></td>
<td>unclear</td>
<td>Not recommend*;</td>
<td></td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td><em>Strongyloides stercoralis</em>**</td>
<td>yes</td>
<td>200 µg/kg once; or multiple several days apart (d1, 2, 15, and 16)</td>
<td></td>
<td>83 – 96%</td>
<td>8,103,106,107, 108, 109</td>
</tr>
<tr>
<td><em>Trichuris trichiura</em>**</td>
<td>yes</td>
<td>200 µg/kg, for 3 days*; 200 µg/kg twice 10 days apart</td>
<td></td>
<td>11 – 88%***; 81.7 - 84% for 200 µg/kg twice 10 days apart</td>
<td>8,103,105,109,110</td>
</tr>
<tr>
<td><em>Enterobius vermicularis</em></td>
<td>yes</td>
<td>200 µg/kg once, plus repeat after 14 days</td>
<td></td>
<td>52.6 – 89%</td>
<td>105,109</td>
</tr>
<tr>
<td><em>Onchocerca volvulus</em></td>
<td>yes</td>
<td>150 - 200 µg/kg biannually or annually</td>
<td></td>
<td>99% reduction in microfilaria (mf) after 1 – 2 months; transmission interruption and elimination after 16-18 years</td>
<td>117–119</td>
</tr>
<tr>
<td><em>Loa Loa</em></td>
<td>yes</td>
<td>Not recommended</td>
<td></td>
<td></td>
<td>125</td>
</tr>
<tr>
<td><em>Wuchereria bancrofti</em></td>
<td>yes</td>
<td>Ivermectin monotherapy not recommended</td>
<td></td>
<td>94% reduction in mf using IDA</td>
<td>120–124</td>
</tr>
<tr>
<td><em>Brugia malayi</em></td>
<td>yes</td>
<td>see <em>W. bancrofti</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Brugia timori</em></td>
<td>yes</td>
<td>see <em>W. bancrofti</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mansonella perstans</em></td>
<td>unclear</td>
<td>(200 µg/kg - 600 µg/kg once) Not recommended;</td>
<td></td>
<td>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</td>
<td>131–135</td>
</tr>
<tr>
<td>Parasite</td>
<td>Treatment</td>
<td>Ivermectin Dose (individual treatment)</td>
<td>Ivermectin MDA Schedule for Control</td>
<td>Reduction at recommended Dose (%)##</td>
<td>Parasite Mortality (%) after (N) Days</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------</td>
<td>----------------------------------------</td>
<td>------------------------------------</td>
<td>-----------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td><em>Mansonella streptocerca</em></td>
<td>yes</td>
<td>150 µg/kg once</td>
<td></td>
<td>55% - 60% reduction in microfilaria##</td>
<td></td>
</tr>
<tr>
<td><em>Mansonella ozzardi</em></td>
<td>yes</td>
<td>150-200 µg/kg once</td>
<td></td>
<td>94% - 100% reduction in microfilaria;</td>
<td></td>
</tr>
<tr>
<td><em>Gnathostoma spp.</em></td>
<td>yes</td>
<td>200 µg/kg for 2 days</td>
<td></td>
<td>76 – 100%</td>
<td></td>
</tr>
<tr>
<td><em>Trichinella spiralis</em></td>
<td>mixed</td>
<td>200 µg/kg once (not recommended)</td>
<td></td>
<td>no effect on encysted form; 80 – 90 % in free living forms**</td>
<td></td>
</tr>
<tr>
<td><em>Ancylostoma braziliense</em>;</td>
<td>yes</td>
<td>200 µg/kg, 1 – 2 doses depending on the clinical picture</td>
<td></td>
<td>81 – 100%</td>
<td></td>
</tr>
<tr>
<td><em>Ancylostoma canium</em>;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Uncinaria stenocephala</em>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 macrofilaria similar to *O. volvulus; *cure rate if not otherwise indicated; **only animal model data available; ***all responsible for CLM;
<table>
<thead>
<tr>
<th></th>
<th>frequency</th>
<th>treatment</th>
<th>effect duration</th>
<th>notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cimex lectularius</strong> (common bedbug)</td>
<td>yes</td>
<td>200 µg/kg, once</td>
<td>67% after 20 days; bloodmeal 3 h post IVM oral; moulting reduced to 0% at 20 days in the same group*</td>
<td>171–173</td>
</tr>
<tr>
<td><strong>Cimex hemipterus</strong> (tropical bedbug)</td>
<td>unclear**</td>
<td>unclear</td>
<td>unclear</td>
<td>Unclear* **</td>
</tr>
<tr>
<td><strong>Demodex spp.</strong></td>
<td>likely</td>
<td>200 µg/kg</td>
<td>unclear</td>
<td>174–176</td>
</tr>
<tr>
<td><strong>Tunga penetrans</strong></td>
<td>no</td>
<td>200 µg/kg</td>
<td></td>
<td>149,168</td>
</tr>
<tr>
<td><strong>Myiasis (botfly larva)</strong></td>
<td>unclear***</td>
<td>200 µg/kg</td>
<td>unclear</td>
<td>169,170**</td>
</tr>
</tbody>
</table>

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-immunocompromised 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 (GluCl\(_s\)), which are not expressed in vertebrates. GluCl\(_s\) 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. 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. Therefore, in specific animal species the use of ivermectin, especially at high dosages can lead to drowsiness, coma and death, clearly demonstrating the protective role of P-gp in humans.

**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. 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 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.
Currently, due to a lack of safety data, ivermectin should not be given to pregnant women\textsuperscript{35}, however, inadvertent use in control programmes has occurred regularly.\textsuperscript{36} The majority of data currently is based on observed teratogenicity from animal models using P-gp deficient mice\textsuperscript{37} or very high doses in rats and rabbits with 10 - 50 and 7 – 30 times of the human equivalent respectively.\textsuperscript{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.\textsuperscript{41-43} In contrast to theoretical concerns there is an increasing accumulation of real-world data showing safety amongst young children.\textsuperscript{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).\textsuperscript{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.\textsuperscript{52-54} Over the past decade interest has emerged in the use of ivermectin as an additional tool for the control of malaria.\textsuperscript{55,56}

Anopheles mosquitoes predominantly express GluCls in organs and tissues responsible for their sensory and motor function.\textsuperscript{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\textsuperscript{57,58} unless the drug is injected directly into the haemocoel.\textsuperscript{59}

Several historical studies have explored the use of ivermectin and its impact on mosquito control\textsuperscript{60-62} but significant interest for malaria vector control has re-emerged recently.\textsuperscript{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
cpecies, 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–
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 days71
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
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* mosquitoes. 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, 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, which could make this strategy technically challenging. Another important aspect is the effect of ivermectin for livestock on dung degradation and non-target fauna, which could cause environmental concerns 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 and are associated with broad health impacts including anaemia, stunting, and delays in cognitive development.

Mass drug administration with benzimidazol derivatives (albendazole and mebendazole) is recommended to reduce the STH burden in a community, because these drugs have a significantly higher efficacy compared to ivermectin in most STH species. Data on the effect of ivermectin on hookworms show a variable reduction of 0 - 33%, with the most successful application being two doses of 200µg/kg 10 days apart reported from Brazil. 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%, respectively. Reports on *Trichuris trichiura* are mixed varying between 11% in Tanzania to 84% in Peru. The reasons for these geographical differences in susceptibility are not yet well understood but could be due to different species. 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.
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.\(^{127-130}\)
perstans was shown not to be affected by a standard single dose of ivermectin\textsuperscript{131–134} with reports of repeated doses being potentially more successful.\textsuperscript{32,135} Importantly, ivermectin does not appear to affect the vector of these filaria \textit{Culicoides} spp..\textsuperscript{136,137}

**Food-borne Nematodes**

For food-borne nematodes such as \textit{Gnathostoma} spp., the recommended daily dosage is 200 µg/kg for 2 - 3 days.\textsuperscript{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.\textsuperscript{140,141}

**Other Nematodes**

\textit{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\textsuperscript{109} but a study from China showed a lower cure rate of 52.9\%.\textsuperscript{105}

**Ectoparasites**

Scabies is a globally occurring skin disease, caused by the scabies mite (\textit{Sarcoptes scabiei} \textit{var hominis}) especially common in poor and crowded communities in tropical and subtropical areas\textsuperscript{142} and causes both significant morbidity and mortality through its downstream sequelae.\textsuperscript{143,144} There is limited pharmacodynamic data available on the use of ivermectin for of scabies, although an animal model in pigs is available.\textsuperscript{145} Doses ≤ 150 µg/kg have lower efficacy,\textsuperscript{146} and even at standard doses of 200 µg/kg increased survival times have been found in vitro over the last decade.\textsuperscript{147} The use of a higher dose and repeated administration may improve cure.\textsuperscript{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 communities10, 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 scalp151 and even iron deficiency in heavy infestations152. 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. 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 MDA160, 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-phenothin shampoo arm at day 15. However, 7.4% of the children showed treatment failure to ivermectin162 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 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 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 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.

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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References


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


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


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.


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


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


