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Ivermectin: a complimentary weapon against the spread of malaria?

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Abstract

Introduction—Ivermectin has transformed the treatment of parasitic diseases and led to incommensurable benefits to humans and animals. Ivermectin is effective in treating several neglected infectious diseases and recently it has been shown to reduce malaria parasite transmission.

Areas covered—Malaria control strategies could benefit from the addition of ivermectin to interrupt the transmission cycle if it is a long lasting formulation or repeatedly administered. In turn, this will help also to control neglected infectious diseases where the elimination goal has been slower to achieve. Despite the relevance of using ivermectin for integrated and sustained disease control, there are still essential questions that remain to be addressed about safety and practicality. The efficacy in various malaria ecologies and the interaction between control tools, either drugs or insecticides, are also important to assess.

Expert commentary—Overlapping distribution of several infectious diseases reveals the benefit of integrating control programs against several infectious diseases into one strategy for cost effectiveness and to reach the elimination goals. The use of ivermectin to control malaria transmission will necessitate development and testing of long-lasting formulations or repeated treatments, and implementation of these treatments with other disease control tools may increase the chance of successful and sustained control.

Keywords

Ivermectin; malaria; mass drug administration; neglected infectious diseases; integrated control strategy; lymphatic filariasis; vector control; trials

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Declaration of interest

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1. Introduction

Ivermectin (IVM) is a semi-synthetic macrocyclic lactone molecule derived from natural avermectin compounds produced by the soil actinomycete *Streptomyces avermitilus*. IVM's potency and broad anti-parasitic activity, along with an exceptional safety profile in mammals, fostered its use to control widespread parasitic diseases in humans and other animals, for which its discoverers recently won the Nobel Prize in Medicine [1]. The drug was developed by a partnership between the Kitasato Institute in Japan and Merck, Sharpe and Dohme research laboratories in the US in the late 1970's and early 1980's, when it was discovered to be active not only against parasitic nematodes, but also on many ectoparasitic arthropods [2]. Ivermectin's mode of action is to agonize inhibitory chloride channels gated by glutamate, and also GABA, in invertebrate neuromuscular systems [3,4]. It was soon brought to the veterinary market and its effect on veterinary medicine has been profound, helping to control mange and dermatitis from mites, equine filarial dermatitis, dog heartworm, disease from gastrointestinal roundworms and lungworms, and grub and lice infestations [5]. Annual veterinary sales of IVM have been more than $1 billion since, and the drug's success has spawned a large research enterprise for discovery of other veterinary endectocides [5]. It was assessed early on for activity against human vector-borne filarial parasites, the microfilaria of *Onchocera volvulus*, the causative agent of onchocerciasis (river blindness), and eventually also the microfilaria of *Wuchereria bancrofti* and *Brugia spp.*, which cause lymphatic filariasis (LF). Many clinical trials conducted in tropical countries endemic for these diseases in the latter two decades of the 20th century demonstrated the transmission-blocking effect of IVM to the community when given in yearly or bi-yearly mass drug administrations (MDA), and these have been shown to be relatively safe, whereby adverse events were mostly mild to moderate to Mazzoti reactions associated with dying microfilaria in heavily-infected patients. Due to limited safety data, people <15 kg (or <90 cm in height) and pregnant and newly breast-feeding women are generally excluded from these IVM MDA. Despite this, they still are considered safer than using older medicines with more severe side effects (eg. suramin and diethylcarbamazine [DEC]), and more effective than insecticides against blackfly and mosquito vectors of these diseases, and infrequent MDA with IVM (and other drugs) and have allowed for significant reduction in morbidity from these filarial diseases as well as the prospect of eventually eliminating them from large geographic areas. Consequently, onchocerciasis has been eliminated from much of Central and South America and some regions of Africa, but elimination of LF from regions has been slower to achieve [6,7].

As early as 1985, IVM was shown to be highly effective at killing the primary malaria vector mosquito in India, *Anopheles stephensi*, when it ingested blood meals from treated mice [8]. Since that time, many laboratory studies have variously tested membrane feeding assays (MFA) with IVM-spiked blood, MFA with the blood of IVM-treated humans and other animals, and direct feeding assays (DFA) on IVM-treated humans and animals against many different *Anopheles* vector species from around the world (reviewed in [9]). In nearly all cases, the various malaria vector species have been susceptible to IVM concentrations one could achieve in the blood soon after treating humans and animals (orally or by injection) with recommended drug doses that are safe and effective at killing their internal parasites.

Importantly, the concentration of IVM in human blood following a standard oral 150 μg/kg dose peaks around 4–8 hours and the half-life in plasma is approximately 12–15 hours, thus the pharmacokinetic profile of treated human blood is relatively short [10], although there is evidence that females can have higher concentrations in their plasma after treatment, possibly due IVM's accumulation in fat tissue and differences in body mass index between females and males [11]. Nevertheless, depending on the specific *Anopheles* species, malaria vectors can suffer significantly reduced survivorship up to a week or more after blood feeding on treated people. These effects have been now confirmed in a series of natural field experiments whereby investigators have monitored wild *Anopheles* spp. survival after blood feeding on humans treated in MDA conducted for onchocerciasis and LF control [12–14]. The mosquitocidal effects from IVM-treated livestock, which often serve as alternative blood meal hosts for certain malaria vector species (even though they are not carriers of human malaria parasites), can be even stronger and longer lasting [15,16]. This is because higher concentrations of various IVM formulations can be injected into livestock, or fed to them by slow-release bolus, thus achieving higher and longer-lasting plasma concentrations of the drug.

Any one treated person (or stock animal) will not significantly affect malaria parasite transmission in a community because of the sheer number of vectors and the remarkable efficiency of vector-borne transmission [68]. However, the daily probability of vector survival is the most influential variable governing malaria vectorial capacity and the basic reproductive number (R_0) of malaria in a population [17], and so even small decreases in the overall survival rate of the vector population can substantially limit malaria parasite transmission by shifting the mosquito population to a younger age structure that is unable to support widespread transmission of *Plasmodium* sporozoites [13]. As IVM is given in MDA to humans that can cover at least 70% of individuals in a community (or whole herds of animals are simultaneously treated), and assuming the drug administration is timed for the high malaria transmission season, most of the blood meal choices of the vector population will be lethal to them for a week or more. This 'pulse' of mosquitocidal blood meals is both predicted in models [9,18], and has been shown empirically [14], to significantly change the mosquito population age structure around treated communities and thus reduce transmission of *Plasmodium* sporozoites. This effect has been observed over moderate to intense seasonal transmission scenarios, but remains to be tested in perennial transmission regions with high transmission.

Such reduction in the transmission of *Plasmodium* sporozoites is a cornerstone of malaria vector control tools, such as indoor residual spraying campaigns (IRS) with insecticides and widespread dissemination and use of insecticide treated nets (ITN), which also primarily target the overall survival rate of vector populations. While transmission control in the absence of widespread administration of antimalarial drugs can only modestly reduce asexual parasite prevalence in humans from highly endemic communities, it is necessary to control the spread of new parasite populations from infectious hosts (gametocyte carriers) to new hosts, and so it is often linked with reduction of malaria episodes in children who are at the highest risk of disease [19]. When applied properly, IRS and ITN can reduce the incidence of malaria episodes in children by more than 50% [20]. When these transmission control interventions are then integrated with therapeutic and chemopreventative measures

that aim to simultaneously reduce the asexual parasite reservoir, malaria can be further controlled and even eliminated from areas, and the transmission control interventions also become key tools to limit the rapid spread of drug-resistant parasites from the treated area.

Though in its infancy compared to IRS and ITN, IVM should be similarly thought of an integrative transmission reduction tool that will likely help to both control and eliminate malaria in specific endemic communities, and also work to limit the spread of drug-resistant *Plasmodium* parasites in places such as the Greater Mekong Subregion (GMS). The modeling that has been published so far suggests IVM MDA added to antimalarial MDA would help to reduce parasitemias in children and significantly delay re-emergence of *Plasmodium* in the community [18]. Trials have already occurred to determine IVM's efficacy and safety when deployed alone or when paired with artemisinin-based combination therapies (ACT), so that we can predict its relative benefits when used in future integrated campaigns (Table 1, [Table 1 near here]). However, we can already speculate on its potential advantages and disadvantages. Because IVM is already a proven and necessary drug for control of LF, onchocerciasis and other neglected infectious diseases (NID), it could be most easily integrated in communities that are afflicted with malaria and these NID [21]. Such communities are prevalent across large swaths of Africa, Asia and the Americas. It also has a strong potential advantage over ITN and IRS in that it is a transmission control tool that should also work against mosquitoes that preferentially bite outdoors [22], and may be very effective in specific scenarios where certain workers and their families are at heightened risk of malaria, such as those working on rubber plantations in the GMS. Using present formulations approved and available to humans, frequently repeated IVM treatment of people in communities would likely be necessary for it to be most effective in areas where transmission lasts more than a month. There are unanswered questions about the safety of such repeated treatment, and whether frequently repeated treatment could directly affect *Plasmodium* parasites in treated humans or drive IVM-resistance in the nematodes and ectoparasites that cause NID. We also still do not know if and how ivermectin interacts with current insecticides used against mosquitoes and if IVM-resistance might occur in the mosquito population. Finally, there are important questions about how IVM might be best deployed spatially, temporally, and to particular humans or to animals, both within and among communities, for maximal effect. These issues and questions are explored further in this review.

2. Body

2.1. Integration of IVM to control both malaria and NID

Control of NID with IVM (LF, onchocerciasis and soil transmitted helminthiases [STH]) in Africa through community directed treatment (CDT) such as MDA, has been successful in gaining increased financial support and increasing overall NID control coverage [23]. However, many countries continue to have high prevalence of LF and STH [24] (www.thiswormyworld.org) and more intense and sustained efforts in these regions are clearly needed. Importantly, there is extensive overlap in the distribution of NID and malaria [25], which shows the necessity of targeting both diseases with the same integrated control strategy if we are ever to have success in disease elimination and eradication campaigns. In

addition, an integrated strategy could have the potential to either clear infection (i.e. STH), interrupt transmission (i.e. malaria) or both (i.e. LF). Such an integrated strategy, for example, may be highly effective over much of the African Sahel, which has intense but limited rainy seasons and is highly endemic for LF, malaria and STH. Through malaria vector control tools (ITN/IRS), the control of indoor (endophilic/endophagic) mosquitoes will reduce *Plasmodium* and *Wuchereria* transmission, and we have shown that ivermectin MDA uniquely target both indoor and exophilic (outdoor) vectors [14]. Further, IVM effectively clears treated persons of *Wuchereria* (as well as *Onchocerca*) microfilaria, intestinal roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*) and threadworms (*Strongyloides stercoralis*), and has strong activity against lice and scabies mites. Thus integration of IVM with other control tools, such as ITN and antimalarial and antihelminthic drugs has a clear potential to integrate control of LF, STH and malaria. Despite the potential benefits, combining NID and malaria control strategies poses a number a challenges including coordination between health sectors (national malaria control programs and national onchocerciasis/LF control programs), adequate and sustained funding, and political will. These challenges can be overcome as demonstrated for other CDT recommended by the WHO to control infectious diseases, such as Directly Observed Treatment Short-course (DOTS) for tuberculosis (TB) and HIV [26], seasonal malaria chemoprevention (SMC) and intermittent preventive treatment in pregnancy (IPTp) for malaria. Regular and frequent CDT has proven to be one of the most cost-effective ways to treat NID and engage rural villages to sustain their healthcare so integration of disease control strategies may significantly reduce the cost in the mid-term after the implementation phase. In summary, IVM will be best utilized for malaria control as a complimentary and synergistic tool to other measures that target one or more phases of the malaria life cycle and also reduce NID.

2.2. Issues surrounding repeated or long-lasting IVM treatment (in both humans and other animals)

It is certain that repeated IVM MDA is a logistical challenge for health authorities and may also cost more, especially when the frequency interval is short. However, we have previously argued that integration with NID control campaigns and also other vector control and anti-malarial chemoprevention efforts should greatly lessen the logistical and financial costs, and make this a worthwhile endeavor [9,21]. Nonetheless, formal economic investigations into the expected effort and cost savings should be conducted soon to independently evaluate this hypothesis. Frequent repeated IVM MDA also allows for the intervention to be controlled and better monitored by health authorities, for both safety and evaluation of parasite and vector resistance. Repeated IVM has distinct advantages, despite logistical and costs challenge. Firstly, frequent IVM treatment should cause a dramatic reduction in NID prevalence and intensity [27,28] and help to reach elimination threshold in regions where NID is still prevalent. Also, it would potentially limit the spread of antimalarial drug resistance, as well as to reduce *Plasmodium* transmission. Secondly, repeated and/or higher dose of IVM has been performed many times by different investigators over decades in very small trials, which have been shown to be free of increased harms (reviewed in [29]). For humans, IVM is currently indicated at 150–200 μg/kg in MDA, and up to 400 μg/kg in some cases for LF control. As discussed above, the 150–200 μg/kg dose has a moderate C_{max} and

a relatively short half-life, and so it affects the survival of wild *An. gambiae s.l.* for approximately 6 days following an MDA [14]. Therefore, in most instances, more frequent, repeated treatment with 150 to 400 μg/kg will be necessary for sustained malaria transmission control. In the published literature, the safety of frequent, repeated 150–400 μg/kg doses, administered between several times within a single week to every month within a year, has been consistently strong whereby all the studies reported no adverse events or a similar number of adverse events relative to the control groups [27,30–32]. However the numbers of treated participants in these published studies have been relatively few, and so safety will still need to be monitored and evaluated when frequent, repeated doses are given at a larger scale in future trials, some of which are already underway (Table 1).

Long-lasting formulations also have advantages, but will require time for investigational new drug development and safety testing. Currently, long-lasting IVM formulations are being tested in pets and livestock [33] with promising results. However despite the time needed for development and approval of such formulations in animals and humans, there will be questions regarding the implementation in countries with weaker health infrastructures and acceptability among the populace that will need to be addressed. Another key issue regarding repeated or long-lasting IVM treatment is the increasing exposure of parasites to the drug. This likely would select for mutants that are able to resist IVM treatments and jeopardize the success of control programs. Anthelmintic resistance has been a problem in veterinary helminths, where total coverage of herds and flocks is desired, and frequent drug administrations are common. MDA for LF and onchocerciasis control usually achieves 65–80% coverage because of exclusion criteria, absence of eligible persons, health worker logistics and acceptability issues [34,35]. This could create refugia in untreated people where parasites can proliferate and might outcompete resistant parasites if selected resistant alleles are associated with a fitness cost. The potential selection of resistance to IVM in parasites as well as in malaria vectors needs special attention because early detection of such mechanism is a prerequisite for a sustained disease control strategy. Such surveillance for resistance is commonly expected from MDA programs, such as with SMC implementation programs in the Sahel.

2.3. Is IVM effective against malaria parasites?

The direct effect of IVM on *Plasmodium* parasites has not been clearly characterized and more laboratory and field research is needed. A recent drug screening study initially demonstrated IVM's efficacy against hepatic *P. berghei* stages both *in vitro* and *in vivo* [36], and another recent study [37] demonstrated some evidence that IVM may inhibit development of *P. falciparum in vitro* and *P. berghei in vivo*, possibly via interference with the *Plasmodium* signal recognition particle. However, an older *in vitro* study with *P. falciparum* estimated that the IC_{50} and IC_{90} of IVM was very high compared to blood plasma concentrations resulting from an administration of a single dose against onchocerciasis (150 μg/kg), and thus suggested that IVM serum concentrations expected after a standard dose are unlikely to affect *P. falciparum* growth and development [38]. Published field data on possible anti-*Plasmodium* effects in humans are almost entirely lacking, other than a short comment in Larivière et al. [39] saying they did not observe an effect of IVM (at a dose of 200 μg/kg) on malaria infection in onchocerciasis patients,

however *Plasmodium* parasitemias were not evaluated. In summary, systematic laboratory testing of relevant IVM doses and schedules on distinct human parasite blood stages (exoerythrocytic, trophozoites, schizonts and gametocytes), both *in vitro* and *in vivo*, is required.

In the first tests of IVM for effects on *Plasmodium* sporogony (i.e. development of *Plasmodium* in the mosquito vector), Kobylinski et al. infected a laboratory strain of *Anopheles gambiae* with cultured *P. falciparum* parasites before, concomitantly or after ingestion of a sub-lethal dose of IVM in blood [40]. The data showed an effect on the prevalence of *Plasmodium* stages (oocyst and sporozoite) in mosquitoes predominantly when IVM was ingested concomitantly, 6 and 9 days after infection, but not 3 days after infection. These data suggested that IVM may have a transmission blocking effect. However, there was an absence of an IVM effect on the intensity of infection (i.e. number of *Plasmodium* oocyst stages), which suggested that IVM may not have a direct effect against *Plasmodium* in mosquitoes. Our own unpublished field data suggest similar effects of IVM on *P. falciparum* oocyst prevalence from wild, captured *An. gambiae* mosquitoes, but no effects on oocyst intensity, and we observed no anti-sporogonic effect from blood feeds of laboratory mosquitoes on the IVM-spiked blood of naturally-infected persons in Burkina Faso (Alout & Foy, unpublished). Ouédraogo et al. [11] conducted a clinical trial to assess the safety of treatment with ACT plus IVM, as well as the mosquitocidal effect of IVM. While the study was not powered to assess the anti-sporogonic effect of IVM, the authors reported no effect of IVM on sporogony after ingestion of an infectious blood meal containing IVM+ACT. Lastly, Pooda et al. [16] reported the absence of an IVM prophylactic effect on *P. falciparum* prevalence in *An. coluzzi* that fed on cattle injected with a therapeutic dose of IVM 4 days prior. The lack of concordance of these data highlights differences in methodologies, and shows that it is currently unresolved as to whether IVM has a direct effect on *Plasmodium* parasites in mosquitoes or only an effect on mosquito traits involved in vectorial capacity such as survival and vector competence. Importantly, malaria ecology is very diverse and the effect observed in one combination of mosquito/parasite may be different or ineffective on another. There are five *Plasmodium* species responsible for human malaria which could be transmitted by a large range of *Anopheles* species, *P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi*. Each combination of natural *Plasmodium*-*Anopheles* species is very specific, leading to distinct epidemiology and transmission patterns. For example, in West Africa the primary vectorial system responsible for malaria transmission is *Anopheles gambiae* s.l.-*Plasmodium falciparum*, while in South-east Asia, *Anopheles dirus* (and *An. minimus*)-*P. vivax* is the main vectorial system. In addition, studies have reported local co-adaptation of parasite genotype with mosquito genotype [41–43] indicating that interactions between parasite populations and *Anopheles* populations are very specific within the same species combination. Thus, the effect of IVM needs to be assessed in natural sympatric *Plasmodium*/*Anopheles* combinations to predict its impact in specific field situations. Finally, modeling and field studies have pointed out that the effect of IVM against malaria transmission is mainly driven by its mosquitocidal effect [14,18] but this needs to be tested directly and among the various malaria ecologies.

2.4. IVM interaction with current insecticides and insecticide resistance

While efforts are made to scale-up coverage of insecticide containing bednets and increase personal and community protection against vector-borne diseases, implementing IVM as a vector/transmission control tool will increase the probability of interaction between IVM and insecticides. IVM targets mainly GluCl channels [3] but also other proteins in the nervous system such as GABA receptors [4]. IVM and insecticides from various chemical families (pyrethroids, organochlorine, DDT and organophosphates) have been shown to interact through binding on the same protein (i.e. GABA receptors [44,45]) or through the same transporter proteins [46]. For instance, modulators of P-glycoproteins (P-gp, encoded by the MDR1 gene), which include verapamil [47], diazinon [48], chlorpyrifos [49], DDT [50] and avermectins (selamectin, ivermectin and related compounds [51]), could affect competitive expression of P-gp and inhibit its efflux activity [52]. As a result, cypermethrin and fenvalerate (pyrethroid), methylparathion (organophosphate) and endosulfan (organochlorine) increase IVM efficacy by competing with P-gps *in vitro* [46]. As P-gps act to eliminate xenobiotic compounds out of the cells, these molecular studies indicated a potential synergy of IVM with insecticide toxicity on mosquito vectors. Buss et al. [53] reported a synergistic effect of verapamil with the toxicity of cypermethrin, endosulfan and ivermectin in *Culex pipiens* larvae, but not with the organophosphate chlorpyrifos, and Yoon et al. [54] demonstrated that verapamil pretreatment significantly enhanced IVM-related toxicity in lice. As avermectins and other insecticides are both modulators of P-gps, they could reciprocally modulate toxicity towards target *Anopheles*. This is an important question that needs to be addressed in order to assess whether the interaction of IVM with commonly used insecticides will be synergistic in field settings. Under the assumption of synergism between insecticides and IVM, combining these control tools could provide a means to prevent the spread of insecticide resistance.

There is now abundant evidence of IVM's mosquitocidal effect against most major malaria vectors. These studies have revealed that all *Anopheles* vector species are relatively susceptible to IVM concentrations found in vertebrate blood during the first days after standard doses used in treatment, and were conducted in the laboratory as well as in the field, including membrane and direct feeding (reviewed in [29]). However, none have yet taken into account the insecticide resistance status of *Anopheles* populations or strains, and as such, the influence of selected resistance mechanisms on IVM susceptibility is not known. We are aware of only our study with permethrin-resistant *Aedes aegypti* populations that demonstrated a slight correlation of permethrin resistance with IVM susceptibility [55]. IVM MDA field studies will be necessary for providing most of this information because bioassays can be conducted on field-collected *Anopheles* that may include a mix of selected and susceptible mosquitoes. In limited analyses of the *kdr* allele frequency in wild mosquitoes collected during IVM MDA studies in Senegal, Liberia and Burkina Faso [14], we found similar frequencies from collections occurring before and after MDA, which did not show any correlation with survival rates following IVM administration (Pearson correlation = −0.151, p=0.849, Table 2, [Table 2 near here]). This suggests that the *kdr* mutation may not provide cross-resistance between pyrethroids and IVM. In contrast, IVM and some insecticides could share similar molecular targets (e.g. P-gp, GABA receptors), which can lead to resistance if overexpressed. Considering that insecticide resistance is

present in most populations of malaria vector species in Africa and elsewhere across the Tropics (IR mapper: www.irmapper.com), it is very important to assess its impact on IVM susceptibility.

It has been noted before that the scale-up of IVM MDA for malaria control would increase the selective pressure exerted by IVM on hematophageous insect vectors and on *Wuchereria bancrofti*, *Brugia* spp. and *Onchocerca volvulus* [9]. IVM resistance can be common in veterinary helminths and is associated with GluCl and P-glycoprotein alleles [56,57]. This is caused by frequent repeated treatment of entire flocks and herds [58]. In contrast, IVM MDA in humans, even if frequently repeated, are unlikely to result in population coverages more than 80% due to exclusion criteria. Nevertheless, IVM resistance has been documented in *Sarcoptes scabiei* from frequently treated individuals [59] and in *Onchocerca volvulus* following treatment failure [60]. Therefore, increasing the frequency of IVM administration is likely to increase the probability of selecting IVM resistance in human parasitic helminths, unless newer triple drug combinations of IVM, DEC and albendazole (ALB) for filariasis control can slow or prevent resistance [61]. However, these added drugs do not affect *Anopheles* vectors [62] and so characterizing and monitoring IVM resistance will still be needed to avoid control failure. Ongoing research programs are monitoring for IVM-resistance in helminths (reviewed in [63]), and smaller efforts have begun to understand the physiological processes underlying mosquito susceptibility to IVM and to determine potential resistance mechanisms in malaria vectors [64].

2.5. How best to test and deploy IVM for malaria transmission control?

It is clear that for malaria transmission control via mosquitocidal activity, IVM should be administered during rainy seasons when mosquitoes are present and biting. For example, in the Sahel, it should be deployed between May to October, and this timing might allow it to integrate well with monthly SMC efforts in the same communities of this region. However this consideration might change if some direct antimalarial activity in the host by IVM is confirmed. Interestingly, IVM MDA during the rainy season are not common in LF and onchocerciasis control programs that occur in many malaria endemic regions because of the complicated logistics of performing MDA in remote villages when dirt roads are sometimes flooded and when villagers are often quite busy during the planting and harvesting season. Where transmission seasons are year-round, the logistics of constant IVM dosing schedules without season breaks may be prohibitive. Another consideration is understanding when precisely in the season to administer IVM relative to the epidemiology of the malaria transmission cycle. Human parasitemias and the diversity of parasite populations are often most limited at the beginning of the season, but mosquitoes are at their peak in the middle of the season, and clinical disease can vary widely throughout the season depending on the area. Future models should account for these factors. Relatedly, the goal of IVM administrations for malaria transmission control should to be carefully considered. As an integrated intervention with a unique chemistry and mode of application relative to current insecticides, it would seem that it would be best used in malaria elimination campaigns in defined geographic areas, or in outbreak response scenarios (e.g. in refugee camps). If integrated with antimalarials, such as SMC in the Sahel or with ACT in the GMS, it may help to limit the spread of *Plasmodium* that develop antimalarial drug resistance. If it were

deployed alone and only for disease suppression/control efforts, the risks of developing resistance might outweigh the benefits. Again, modeling will be key to determining its best use scenarios.

The above considerations of ‘when’ and ‘where’ IVM should be used for malaria control must ultimately be coupled with practical considerations of ‘how’. Thus far, relatively small rural villages have been the primary targets for IVM MDA efforts because these populations are often the most at risk for LF, onchocerciasis, and STH infections. However, it is less acknowledged that small rural village populations may be easier to treat in mass due to their cohesiveness and sense of the collective good fostered by community-wide drug treatments. The same cohesion does not generally exist in more populous towns, town sectors or cities, where people come from diverse backgrounds, hold diverse jobs, and are unlikely to know all of their neighbors. We have heard anecdotal reports from community health workers about the difficulties of achieving MDA coverage targets in more urbanized communities, and this problem could become more frequent as countries in Africa and other tropical malarious regions become more urbanized. Importantly, models show that a large proportion of the human population (>60%) needs to be treated simultaneously with IVM to achieve enough of a mosquitocidal effect to significantly reduce malaria transmission assuming random mosquito biting of the community [13]. However, we know that mosquitoes do not bite randomly [65], and the alternative to full MDA is a more informed, targeted drug administration approach that may enhance the effect of IVM MDA and circumvent the problems of attempting to treat most people in more urbanized communities. This might utilize epidemiological data and predictive models to determine who is most a risk of being bitten by malaria vectors, or who is most at risk of transmitting parasites to mosquitoes, so that these people may be preferentially administered for IVM. For example, it is thought that 5-15 yr old children in African villages may contribute >50% of the human-to-mosquito parasite transmission due to a combination of high gametocytemias and a relatively larger body surface area that would foster more mosquito bites relative to smaller children [66]. Similarly, epidemiological subgroups who have behaviors that foster more mosquito biting, or who live in poor housing or who live in microhabitats around the community (near water) might all be preferentially targeted for IVM administration.

Lastly, we have a very simple understanding of local mosquito movement in and between villages, as well as human movement, and these spatial factors are likely to play a large role in the efficacy of IVM MDA for malaria transmission control. If many mosquitoes in a village targeted for MDA become infected by biting people from nearby, untreated villages, then the effect of IVM will be blunted. Likewise, frequent movement of people in and out of communities targeted for treatment reduces population coverage rates, and can easily introduce new parasite clones in the community shortly after the MDA is administered. We experienced these issues in villages in Burkina Faso where we have been working, whereby many young and old men from the study villages use motorcycles to travel and work in artisanal gold mining camps for several days at a time.

3. Conclusion

Despite the significant advances towards reducing the burden of malaria over the last decade, there are still important efforts to be made to stem the spread of disease and of resistance in malaria parasites and vectors. The broad anti-parasitic drug IVM represents a very promising additional tool for malaria control. We expect that integration of IVM MDA with current malaria control strategies will have several health and economic benefits. However, there are still important questions to investigate to ensure that such integrated strategy is safe and efficient in distinct regions. Other related issues need also to be considered, particularly the potential interactions with other drugs and with insecticides and the potential selection of resistance phenotypes. This type of data will be useful to predict its long-term impact on disease epidemiology and to design future trials.

4. Expert Commentary

The recent demonstration that IVM MDA against onchocerciasis and LF transiently reduces sporozoite rates in African villages by killing local mosquito vectors highlights the potential of adding IVM to the tools for malaria control. Overlapping distribution of NID and malaria reveals the necessity of targeting both diseases with the same integrated control strategy for cost effectiveness and to reach malaria elimination goals. Field studies in Africa have examined the effect of ongoing single IVM MDA on malaria vector survival and parasite transmission. They showed temporary interruption of malaria transmission mediated by a shift in vector population structure towards younger, non-infectious vectors. This has led to the conclusion that IVM is a highly promising partner drug to help control malaria transmission, but will necessitate long-lasting formulations or repeated treatment. New formulations will require time for development and testing, and logistical implementation and population acceptability issues will need to be addressed as early as possible. While repeated and higher doses of IVM have been shown to not increase harms relative to controls in very small trials, safety still needs to be monitored at a larger scale. The efficacy of such strategies should also be determined in different geographical settings. For instance, we suggest that MDA should start before the peak of transmission when the parasite and the vector populations have not yet peaked, but this might be best for areas with seasonal malaria transmission. The optimal start time as well as spacing time between MDA has to be determined for the various malaria ecologies and for various levels of endemicity. Integration of control tools against several infectious diseases into one strategy will probably be best through application of ITNs, IRS, and multi-combination drug therapies (e.g. IVM, ALB, DEC and ACT). Research on the safety of such strategies is ongoing, but such integrated strategies could facilitate elimination of many parasites from many people in communities simultaneously. This will clear infection reservoirs and also halt transmission cycles, increasing the chance of successful and sustained control. Lastly, the integration of repeated IVM MDA with the ITN distribution campaigns will help to increase the coverage of ITN and is likely to be cost-effective. Successive MDA will allow not only to distribute more ITN but also to improve their use through small and local educational programs. There is a lack of evidence of synergy between ITN and IVM from field studies, although it has been shown in a few laboratory studies that IVM increases insecticide toxicity. If this is

confirmed, using IVM for malaria transmission control could reduce the potential threat of insecticide resistance.

5. Five-year view

The prospect of adding IVM to the arsenal of tools to combat malaria becomes clearer despite several important knowledge gaps that need to be filled. The integration of several tools into one strategy should synergize the efforts to improve success as well as cost effectiveness, principally in areas co-endemic for malaria and NID. Several clinical trials are ongoing and will be performed to evaluate various integrative approaches, such as the timing and spacing of repeat IVM MDA, combination with ACT, and integration with ITN distribution. Such studies will allow us to assess the transmission control efficacy of IVM relative to ITN, but fundamental information on the safety of increasing IVM exposure will require constant monitoring. The future of IVM for malaria control will depend on the feasibility and practicality of the intervention and distribution in each geographic location. These should vary greatly in relation to the local malaria epidemiology and transmission patterns, but may have the most success in elimination campaigns undertaken in areas with seasonal transmission. The indirect comparison of these trials will provide information on the efficacy of IVM in distinct malaria ecologies and endemicity. Laboratory research will be an important asset to understand IVM's mode of action and interaction with other drugs and insecticides.

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* Of interest

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Key issues

- Repeated IVM MDA has the potential to concomitantly control malaria and NID.
- IVM, a potent and broad anti-parasitic drug, is distributed to control onchocerciasis and lymphatic filariasis.
- Control of NID with IVM (LF, onchocerciasis and soil transmitted helminths [STH]) in Africa through community directed treatment (CDT) such as MDA, has been successful in gaining increased financial support and increasing overall NID control coverage.
- IVM is highly effective at killing Anopheles vector species from around the world and single IVM MDA can temporarily disrupt malaria transmission.
- In most scenarios, the potential use of IVM to control malaria transmission will require long-lasting formulations or repeated treatment.
- Long-lasting formulations have advantages, but will require time for investigational new drug development and extensive safety monitoring.
- Safety will also need to be monitored and evaluated when frequent, repeated doses are given at a larger scale in future trials.
- Increased exposure due to repeated or long-lasting IVM treatment may increase the selection of resistance and needs special attention for a sustained disease control strategy.
- The effect of IVM on Plasmodium parasite developmental stages needs to be characterized in human and vector mosquitoes in vivo.
- Testing of IVM efficacy alone or in combination with ACT against Plasmodium parasites in laboratory experiments and ultimately in various field setting will provide relevant information to integrate control strategies.
- It will be advantageous and cost-effective to combine IVM distribution and ITN distribution campaigns to improve bed-net coverage, quality and usage in local populations.
- Implementing IVM as a vector/transmission control tool will increase the probability of interaction between IVM and insecticides, which may be synergistic.
- The potential synergistic interaction between insecticides and IVM may provide a means to prevent the spread of insecticide resistance and stresses the need to investigate this interaction further on mosquito survival and parasite transmission.
- Several clinical trials in Africa and South-East Asia are investigating the safety and the efficacy of several approaches utilizing IVM to control malaria.

- Issues regarding the “when”, “where” and “how” for the deployment of IVM for malaria transmission control need to be addressed by modelling, experimental and observational approaches.
- IVM may be best used in malaria elimination campaigns in defined geographic areas, or in outbreak response scenarios.
- A thorough understanding of the movement in and between villages of local mosquito vectors, human populations, and the spatial and environmental factors involved will help to best design strategies that include IVM for malaria transmission control.

Table 1

Clinical trials using ivermectin for controlling malaria transmission

ID number	Status	Study	Condition	Interventions	Outcomes: Primary (secondary)	Reference
NCT02511353 (ClinicalTrials.gov)	Recruiting	Efficacy and Safety of High-dose Ivermectin for Reducing Malaria Transmission: A Dose Finding Study	Malaria	Drug (3-day course): dihydroartemisinin-piperaquine+placebo; dihydroartemisinin-piperaquine+ivermectin (300 µg/kg/day) ; dihydroartemisinin-piperaquine+ivermectin (600 µg/kg/day))	Mosquito survival (Number of clinical malaria cases, AUC and C_{max} for ivermectin and piperaquine, Hb concentration, Safety)	no
NCT02509481 (ClinicalTrials.gov)	Active, not recruiting	Repeat Ivermectin Mass Drug Administrations for Control of Malaria: a Pilot Safety and Efficacy Study	Malaria, Lymphatic Filariasis	Drug: Ivermectin +Albendazole (1×); Ivermectin+Albendazole (1×) + repeated ivermectin (5× at 3 weeks interval)	Incidence of clinical malaria episodes (Force of infection, Soil-transmitted helminths, EIR, Safety)	no
NCT01603251 (ClinicalTrials.gov)	Completed	Trial of Artemether-Lumefantrine Alone and in Combination With Ivermectin to Reduce Post-Treatment Malaria Transmission	Malaria	Drug: Artemether-lumefantrine combination (3-day course, twice a day) + placebo (1st and 5th dose of AL); Artemether-lumefantrine combination + single dose Ivermectin (200 µg/kg with 1st dose of AL, placebo with 5th dose of AL); Artemether-lumefantrine combination + repeated dose Ivermectin (200 µg/kg with 1st and 5th doses of AL)	Safety (Mosquitocidal activity)	[11]

Search in ClinicalTrials.gov, EU Clinical Trials Register, ISRCTN Registry, Google, Pubmed, Web of Sciences® with keywords: ivermectin + malaria + clinical trial

Table 2

Pyrethroid resistance (*kdr*) frequency and survival rate of field caught *Anopheles gambiae* during the first week following IVM MDA

Study site	Year	Sample size*	f(*kdr*)	Survival rate**
Burkina Faso	2013	86	0.976	0.498
Liberia	2013	88	0.909	0.422
Senegal	2009	53	0.792	0.476
Senegal	2008	47	0.851	0.573

* Presence of the L1014F *kdr*-west mutation was determined using the PCR diagnostic test of Martinez-Torres et al. 1998 [67]

** Data from Alout et al. 2014