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Endectocides for malaria control

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Abstract

Systemic endectocidal drugs, used to control nematodes in humans and other vertebrates, can be toxic to *Anopheles* spp. mosquitoes when they take a blood meal from a host that has recently received one of these drugs. Recent laboratory and field studies have highlighted the potential of ivermectin to control malaria parasite transmission if this drug is distributed strategically and more often. There are important theoretical benefits to this strategy, as well as caveats. A better understanding of drug effects against vectors and malaria ecologies are needed. In the near future, ivermectin and other endectocides could serve as potent and novel malaria transmission control tools that are directly linked to the control of neglected tropical diseases in the same communities.

The birth of endectocides

Endectocides are drugs with endoparasitocidal and ectoparasitocidal activity. Avermectins, the most effective and well-developed class of endectocides, are 16-membered ring macrocyclic lactones produced from the fermentation broth of an actinomycete. Ivermectin (IVM) is a semi-synthetic avermectin derivative that was first licensed in 1981 as a veterinary drug. It has since become one of the most successful drugs discovered owing to its broad spectrum activity against nematodes and ectoparasites, high potency, long pharmacokinetic persistence in blood and lymph, and excellent safety in vertebrates [1]. IVM is one of the primary drugs used to control the filarioid nematodes *Onchocerca volvulus* and *Wuchereria bancrofti* through human mass drug administrations in endemic areas. The drug alleviates disease in individuals as well as reduces nematode transmission in the community by killing the transmissible microfilaria stages and impairing the development and fecundity of adult worms in the human [2]. IVM accomplishes this by interfering with the neuromuscular physiology of invertebrates (Box 1).

Endectocide activity against vectors

Initial ectoparasitocidal studies with the avermectins focused on biting flies, bot flies, fleas, lice, mange mites and ticks, and many were found susceptible to the drug. Wilson [3]

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provided a detailed review of much of this literature 17 years ago, focusing on the prospects of using avermectins in arthropod vector management. His analysis concluded that reducing the ectoparasite abundance on individual animals is a simplistic way to view the broader promise of endectocides for controlling vector-borne diseases. Instead, he argued that the avermectins need to be assessed for their ability to affect all critical variables of vectorial capacity from a vector population, especially reducing the probability of vector lifespan below the extrinsic incubation period (EIP), and reducing the vector feeding frequency through sub-lethal doses (Box 2). Vertebrate blood meals, then, could deliver anti-vector drugs directly into the midguts of vectors to reduce the likelihood of pathogen transmission from the entire vector population. This concept is predicated on high or strategically-targeted coverage of the host population with the drug, and effective drug pharmacokinetics in the host.

Mosquito studies

Initial mosquito studies with avermectin/IVM demonstrated that *Anopheles* species were highly sensitive to these drugs compared to various *Aedes* and *Culex* species [4–6]. Studies also demonstrated that sub-lethal concentrations of IVM (for the adult mosquito) could reduce female fecundity, the hatch rate of their eggs, and survival of progeny larvae [5–8]. In laboratory membrane-feeding experiments matching mosquito feeding times to IVM concentrations found in human plasma post-MDA (150 µg/kg), we recorded mortality effects, inhibition of re-blood feeding and compounding mortality effects of sub-lethal doses in colonized *Anopheles gambiae s.s.* [9]. Direct human blood feeding experiments using colonized mosquitoes and IVM-dosed humans have been conducted with *Aedes polynesiensis* [10], *Anopheles faurauti* [11], and recently against *An. gambiae s.s.* [12]. These studies demonstrated reduced survival of mosquitoes that blood feed on IVM-dosed humans, but reported variable time periods in which mosquitocidal effects could be maintained after drug administration. Bockarie *et al.* [13] performed the first field demonstration of IVM's effects on wild mosquitoes, focusing on the transmission of *Wuchereria bancrofti*. Wild, engorged, indoor-resting *Anopheles punctulatus* caught from two houses the day after IVM MDA (400 µg/kg) had significantly reduced survivorship compared to those captured from two houses of a control untreated village. In another village, *An. punctulatus* had significantly reduced survival if caught within three days after residents received an IVM (400 µg/kg) plus diethylcarbamazine (6 mg/kg) MDA compared to those caught pre-MDA, but survivorship was not reduced in mosquitoes collected 28 days post-MDA. The authors also found that the number of bites per person per month significantly increased one month after the MDA (see Box 2 for possible explanation). We recently conducted similar experiments following IVM MDAs for onchocerciasis control (150 µg/kg) in southeastern Senegalese villages [14]. IVM MDA significantly reduced the direct survivorship of *An. gambiae s.l.* mosquitoes for six days following MDA in villages from three replicate experiments when only ~80% of the villagers were covered in the MDA. The field data also demonstrated that the true IVM MDA effects lasted three times longer than predicted from our laboratory experiments [9]. These data are likely still to be an underestimate because they did not account for IVM sub-lethal effects such as knockdown and inhibited recovery and re-blood feeding that we know occur in the lab. Modeling the field data demonstrated that the basic reproductive rate of malaria (R_0) could be significantly reduced if MDA were given at monthly intervals or shorter. Lastly, sporozoite rates were analyzed from these same captured mosquitoes. Mean sporozoite rates in mosquitoes captured from treated villages decreased 79% from before to two weeks after MDA, while sporozoite rates from nearby pair-matched untreated villages increased over the same time periods. Logistic regression analysis of treatment by time confirmed the difference between control and treated villages to be significantly different [15].

The promise and pitfalls of using ivermectin for malaria transmission control

Malaria remains a significant threat to human health in the developing world, and the rapid development of new control strategies is essential. Since the failed global malaria eradication campaign of the early 1960s, it has been acknowledged that malaria can only be controlled and potentially eliminated from specific geographical areas with combinations of tools in integrated malaria management programs [16]. The diverse epidemiology of malaria around the world highlights the need for many different integrated management control tools. Those that synergize with existing tools, as well as existing health infrastructures, will make these integrated programs a reality. IVM MDAs may be a powerful and synergistic new tool for integrated malaria and NTD control in defined areas.

The most effective malaria vector control tools are long lasting insecticide treated nets (LLITN) and indoor residual spraying (IRS), both of which are designed to kill endophagic vectors that enter houses or repel them from houses, although there is some evidence that LLITNs have an effect on malaria transmission by exophagic vectors [17]. Targeting endophilic vectors has been the ‘low-hanging fruit’ for malaria vector control because in-home measures focus on a more controllable environment, but it is increasingly recognized that we must control parasite transmission by both exophagic and exophilic vectors if we are ever to have success in the new malaria elimination and eradication campaigns being championed [18]. IVM offers a novel mode of delivery to a mosquito, an oral mosquitocidal drug that will be in a person’s blood, and so it will reach both endophagic and exophagic vectors. Furthermore, adaptive changes (e.g. shifting to crepuscular biting or exophagy) will not protect these mosquitoes from drug exposure, as they have for control via LLITNs or IRS.

A second benefit of IVM is the low potential for mosquito cross-resistance from current malaria control and agricultural operations. Mass DDT and pyrethroid agricultural applications have contributed to the spread of insecticide resistance into mosquito populations, threatening malaria control applications using the same insecticides [19]. Avermectin-family agricultural pesticides, on the other hand, are relatively expensive and rarely used in outdoor applications in the developing world. Furthermore, macrocyclic lactone drugs have a different molecular target and mode of action than insecticides currently used for LLITN and IRS (Box 1). Lastly, there is no evidence to date that pyrethroid resistance mechanisms in vectors cross-targets IVM [20].

Thirdly, IVM MDAs have potential value to inhibit the development of malaria parasite resistance to drugs targeting asexual and sexual stages in the human host. Any escapee parasites harboring drug-resistant alleles must still develop in the mosquito to be spread to new hosts. If IVM MDAs were concomitantly deployed with MDAs of antimalarials, a potentially resistant parasite strain is likely to die in the mosquito host and never be propagated. Importantly, under the new malaria elimination and eradication agendas, development of antimalarials that can be safely used in MDAs has been identified as an enhanced research priority [21].

In our models, IVM MDAs might be able to significantly reduce malaria parasite transmission in a community if given once a month or more frequently [14] (Box 2). Current onchocerciasis control regimens only require MDA once or twice per year to be effective, and community directed treatment programs are now effectively employed to achieve the highest sustained coverage of endemic communities [2]. The threat of drug resistance by nematodes associated with more frequent IVM MDAs deserves consideration (discussed below). Additionally, the logistical demands and costs associated with more frequent IVM

MDA must be addressed. The community directed treatment models have proven highly efficacious and cost effective [22, 23]; their enhancement by integration with antimalaria measures (more IVM MDAs, bednet distribution) and control of soil-transmitted helminths via more MDAs (see below) is likely to only enhance their cost: benefit ratio. Merck, through its Mectizan Donation Program, currently covers the majority of the cost of IVM MDAs for onchocerciasis control [23]. It is likely that international health and aid agencies would need to step in to bear the added costs if a massive scale up of IVM MDAs for malaria parasite transmission control were to occur. Most obvious to all of these concerns, IVM MDA may be most manageable in areas with seasonal malaria transmission, such as the Sahel and Sudano-Guinean habits, or during epidemics, but may be less tractable in areas with year-round transmission. However, sustained malaria control or elimination from any continental area is expected to require the application of control tools, expanded health infrastructure, and constant malaria surveillance over decades [16], all of which will be expensive and logistically demanding in their own right. When this fact is taken into consideration, the argument that frequent IVM MDAs might be unsustainable under such needed programs seems weak.

The safety of frequent IVM administrations would need to be monitored, but reports of frequently-dosed individuals and communities have not been associated with increases in IVM-related toxicity or severe adverse reactions [24, 25]. The primary health concern of widespread IVM MDA in Africa is associated with the presence of high *Loa loa* microfilaremias in some individuals who may have severe adverse events following drug administration [26]. Current prevention efforts against this rely on a rapid assessment of loasis in endemic areas planned for IVM MDA.

The added benefit of frequent IVM dosing schedules would be the reduction in prevalence and intensities of soil-transmitted helminths (STH) in the same malaria-afflicted communities. IVM is highly efficacious against *Strongyloides stercoralis*, variably active against roundworms (*Ascaris lumbricoides*) and whipworms (*Trichuris trichiura*), and weakly active against hookworms (*Necator americanus* and *Ancylostoma duodenale*) [27]. The most recent evidence from Nigeria points to significant reduction in the prevalence of roundworms and whipworms among children from villages that have participated in yearly IVM MDA for onchocerciasis control for 13 years [28]. Malaria and STHs are co-endemic across large areas of sub-Saharan Africa [29], and both malaria infections and high STH intensities (particularly hookworms) can result in anemia [30]. Co-infections with malaria and intestinal helminths can increase the likelihood of anemia in children and in pregnant women, and co-infections of women can result in significantly greater risks for adverse birth outcomes [31]. The disease synergies between malaria and STHs, and the possibility of combined control of nematodes and malaria with simple MDA regimens should be a powerful incentive to bundle such regimens into integrated health programs of co-endemic areas.

More frequent endectocide exposure would undoubtedly increase selection on nematode populations to develop drug resistance. There are reports of suboptimal responses of *Onchocerca volvulus* to IVM, which seem to be associated with genetic selection [32]. Anthelmintic resistance has been a problem in veterinary helminths, where 100% coverage rates and frequent drug administration of sheep flocks and cattle herds can be common. Differential GluCl and P-glycoprotein alleles are associated with IVM resistance in *Haemonchus contortus* and *Cooperia onchophora* [33, 34]. The most viable option for limiting the potential for drug resistance under a frequent IVM MDA regimen would likely be combination and/or rotational chemotherapy using other anthelmintic drug classes, such as the benzimidazoles. Similarly, frequent IVM MDAs should not be considered as monotherapy treatment programs that would continue indefinitely, but instead as part of a

concerted integrated disease management programs with defined endpoints. Both MDA timing and coverage rates will also influence the selection of resistance alleles in helminths [35]. Human MDAs rarely achieve >80% coverage because of limitations on who can take the drugs, logistics, and non-compliance. This likely creates refugia in untreated people where non-resistant helminths can proliferate, and may out-compete helminths harboring resistance alleles if such alleles confer lower fitness. More frequent IVM MDAs for malaria control might also be limited to the rainy season when mosquitoes are transmitting the most malaria. This season is also when pre-parasitic stages of helminths can best survive outside the host in moist soils, thus better preserving any non-drug selected alleles among the population.

The possibility of IVM resistance developing in mosquitoes is currently theoretical. Drug exposure (both in quantity and in duration) of a mosquito population would be far less compared with helminths that live primarily inside the host, and only female adult mosquitoes would be exposed. Furthermore, the drug exposure of females would be lessened if the malaria vector species had some zoophagic tendencies. A laboratory study of selected IVM resistance in *Drosophila* was the result of target site mutations, but the flies also had compromised fitness [36]. There are field reports of abamectin resistance in plant pests arising from intensive abamectin spraying operations [37]. Potentially confounding variables are IVM effects on female fecundity, egg hatch rate and larval survival, and the possibility of resistant alleles already being present in current mosquito populations. However, these potential confounders are negatively countered by the variables of incomplete human coverage during MDA, heterogeneity in mosquito blood meal choice, and some mosquito immigration from untreated MDA border areas. On the whole, we think IVM resistance would be less likely to develop in malaria vectors if a frequent but sufficiently-spaced IVM MDA strategy was deployed, and only on a seasonal basis. For example, if IVM MDA were administered every three weeks over the course of a five month malaria transmission season, it would only require six to seven MDAs that could be conducted through community directed treatment programs. Smaller numbers of dry season and early and late wet-season mosquitoes would reproduce without drug pressure, while young, non-infectious adult mosquitoes in the middle of the wet season would still be able to lay eggs over interval periods when drug is not in human blood. This strategy has some of the properties of the ‘evolution-proof’ malaria control strategies proposed by Read and others [38].

Finally, malaria transmission driven by zoophagic malaria vectors may be particularly amenable to endectocide MDAs. An enhanced zooprophyllaxis strategy [39] might be achieved by administration of avermectin endectocides to livestock kept near domiciles. Indeed, Fritz *et al.* [8] recently demonstrated that IVM administered to cattle significantly affected the survival and fecundity of *An. gambiae* s.s. blood feeding on these cattle. The pharmacokinetics of IVM in livestock has been optimized by delivery strategies that allow for a longer half life of the drug in animals and sustained release into the blood stream, thus allowing for fewer treatments of the cattle. Both direct injection with non-aqueous preparations and sustained-release implants [40] can achieve these results. Additionally, many other avermectin derivatives have been developed by veterinary pharmaceutical companies for use in livestock and pets (eg. selemectin, doramectin, eprinomectin, moxidectin) which have enhanced pharmacokinetic profiles or reduced toxicity to certain breeds, and which have differential activity against malaria vectors (Ned Walker, unpublished). The added benefit of enhanced zooprophyllaxis would be that the owners would have healthier animals by de-worming.

Concluding remarks

We have presented various arguments in favor of developing endectocides, particularly IVM, as novel tools for the control of malaria. These arguments include a novel mode of drug action compared to currently used insecticides, potential to target many vector species regardless of their biting habits, high sensitivity of the vectors to extremely low concentrations of drug, possible reduced potential for developing drug resistance by the mosquito, and cross-activity against intestinal helminths. The arguments against developing these tools include logistical difficulties and higher costs associated with more frequent MDAs, and the potential to foster endectocide resistance in helminth populations. Ultimately, field data must be collected to validate or invalidate the specific arguments, as well as to address unforeseen issues. In our opinion, the promise of endectocides as novel and synergistic malaria control tools is great for many malaria-endemic regions across the globe.

Box 1. Anthelmintics, insecticides, and ligand-gated ion channels

Several classes of both anthelmintic drugs and insecticides selectively target invertebrate ligand-gated ion channels [41, 42]. These members of the Cys-loop ligand-gated ion channel (LGIC) superfamily are located at both synaptic and extrasynaptic sites on invertebrate nerve and muscle cells, and open (or gate) in response to ligands to allow ions to flow across the cell membrane. Each channel exists as a pentamer of subunit proteins, which are comprised of an extensive N-terminal extracellular domain that binds the ligand, and four transmembrane domains (TM1–TM4) [43]. The LGIC genes of insects encode channel subunit families defined by their corresponding ligands, including nicotinic acetylcholine receptors (nAChRs), and glutamate, glycine, histamine and γ -amino butyric acid (GABA)-gated channels [44] (Table I). The nAChRs (not listed in Table I) mediate excitatory neurotransmission in insects by allowing cations (primarily Na^+ and K^+) to pass through their channel, and they have an expanded and distinct gene family [45]; neonicotinoids are important insecticides that agonize these channels. Insect GABA-gated channels are antagonized by established insecticide classes such as the cyclodienes (e.g. dieldrin) and phenylpyrazoles (e.g. fipronil) [42]. These and the other channels in Table I are mostly thought to be permeable to anions (primarily Cl^-) [46], and so they mediate inhibitory signals that act by hyperpolarizing the cell membrane potential; however, Gisselman *et al.* [47] reported that *Drosophila* GRD and LCCH3 subunits can form excitatory heteromultimeric cation channels.

The avermectins specifically hyperpolarize the membrane potential of invertebrate postsynaptic neurons and muscle fibers through agonization of the inhibitory glutamate-gated chloride channels uniquely used by insects to regulate neuromuscular transmission [36]. This causes flaccid muscle paralysis that can lead to death of the insect [48]. There is also evidence that IVM agonizes pHClS in flies and scabies mites [49, 50] and HisClS in flies [51], and some evidence that GABA and GluCl subunits can associate to form heteromultimeric channels [52]. Whether heteromultimeric channels can form in mosquitoes and how such channels would be regulated between two different ligands is not clear. These issues might affect the susceptibility of mosquitoes to IVM and potential cross-resistance between IVM and other insecticides like dieldrin. Furthermore, GluCl and GABA-receptor subunits have splice isoforms stemming from exon 3, which generates the crucial ligand binding domain in the N terminus [53]. Interestingly, GluCl and pHCl exist as single genes in Dipterans, while the GABA-, glycine- and histidine-gated subunit encoding genes have mostly expanded into 2 or more paralogues within species of Diptera (Table I).

One primary reason for the excellent safety profile of IVM is that GluClS do not exist in mammals [48]. GluClS' orthologous mammalian channel subunits are the distantly-

related glycine-gated cation channel subunits, and while these can be activated by IVM at high concentrations [54], they exist only in the central nervous system and are sequestered behind the blood-brain barrier. The blood-brain barrier is not easily crossed by large macrolide molecules like IVM due to their affinity for P-glycoprotein xenobiotic transporters abundant in the brain's vascular endothelium [55].

Box 2. Effects of mass endectocide administration on mosquito populations
Ivermectin MDA directly results in the death of a significant proportion of existing biting *Anopheles* mosquitoes [13, 14], and should increase mortality rates of a proportion of mosquitoes that imbibe a sub-lethal amount of drug [9]. This should have the dual effect of skewing the age structure of the vector population toward the younger age classes that do not participate in transmission and reduce the population density of adult vectors. This was investigated using a previously developed simulation model [14], that incorporated a minor modification of larval density dependence, as described in [56].

$$p_d = \frac{p_0}{1 + (\alpha * L_t)^\gamma}$$

Equation 1

p_0 = survival of larvae in the absence of density dependent regulation, p_d = survival of larvae under density dependent regulation, L_t = number of larvae at time t, α = carrying capacity constant (0.0002) and γ = intraspecific competition constant (1.0) derived from [56].

An ivermectin MDA was simulated to a village in southeastern Senegal covering 80% of the villagers (see text and [14]). The MDA results in the hastened death of a significant proportion of the adult *Anopheles gambiae* females. Coupled with the emergence of new adult females from the standing larval population, the population age structure shifts toward younger age classes for more than 3 weeks post-MDA (Figure IA). Focusing only on abundance, there is a precipitous but temporary drop in the standing adult female mosquito population size (Figure IB) that is most severe one week post-MDA (26% population reduction). The population remains below pre-MDA levels for up to three weeks post-MDA, but by one month post-MDA the population has rebounded to slightly higher (approximately 4%) than pre-MDA levels (Figure IC). The adult replenishment rate will be influenced by local environmental conditions, including the amount of standing water during the MDA, temperature and weather, so this example is meant to be illustrative rather than predictive. The rebound effect and local environmental conditions are likely to explain the increased bites/person/month observed 28 days after a single MDA [13]. However, given that the majority of the adult female mosquito population is young in the month following MDA, regardless of the population size and local environmental conditions, there will be fewer infectious (sporozoite-transmitting) mosquitoes following treatment [15].

MDAs of ivermectin have been occurring for >15 years in many areas of Africa, and Latin America for onchocerciasis control, and so one may question why those areas have not seen obvious signs of reduced malaria parasite prevalence, incidence or associated disease. These programs only administer MDAs once or twice per year, which will not result in a sustained interruption of the malaria transmission cycle. Furthermore, these MDAs often do not coincide with malaria transmission seasons in the same area. Most importantly, asexual parasitemias in humans can be remarkably stable even in the absence of sporozoite transmission, as is seen in parasitological surveys of humans over

transmission seasons [57]. Only sustained reductions in malaria parasite transmission will eventually result in reductions of malaria prevalence or disease.

Acknowledgments

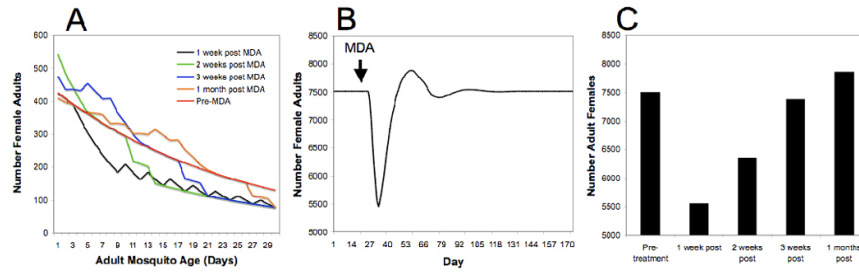
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**Figure I.**

A model of female adult *Anopheles gambiae* age structure and abundance following an ivermectin mass drug administration. **(a)** Models of combined age structure and abundance prior to mass drug administration (Pre-MDA, red line), and 1–4 weeks post MDA (black, green, blue and orange lines, respectively). **(b)** The modeled effect of a single MDA on female adult abundance over time. **(c)** Discrete number output of the abundance model on a weekly timescale. Derived from [14].

Table 1

The ligand-gated ion channel genes (excluding the nAChR family) of Diptera.

Ligand	Paralogue name	<i>Anopheles gambiae</i>	<i>Aedes aegypti</i>	<i>Culex quinquefasciatus</i>	<i>Drosophila melanogaster</i>
glutamate	GlucI	AGAP001434 ^a	AAEL003003	CPIJ010616	FBgn0024963
pH (hydroxyl ions)	pHCl	AGAP005599		CPIJ002294	FBgn0036542
	RDL	AGAP006028	AAEL008554	CPIJ008419	FBgn0004244
GABA	LCCH3	AGAP000038	AAEL010710	CPIJ014518	FBgn0010240
	GRD	AGAP011349		CPIJ006773	FBgn0001134
					FBgn0030707
glycine		AGAP007707	AAEL001568	CPIJ017366	FBgn0029733
			AAEL004513	CPIJ009348	FBgn0036727
					FBgn0039840
histidine	HisC11	AGAP012975	AAEL003028	CPIJ017412	FBgn0037950
	ort	AGAP001913	AAEL012248	CPIJ013943	FBgn0003011
				CPIJ013955	
	HisC12	AGAP001990	AAEL006047	CPIJ006949	
			AAEL015452	CPIJ002292	
			AAEL001272	CPIJ002295	
unknown		AGAP010694	AAEL003958	CPIJ011023	
unknown		AGAP000039	AAEL015091		FBgn0033558

^a Accession numbers for orthologous and paralogous genes were identified in the Vectorbase, Flybase, Ensemble and NCBI databases.

Abbreviations: nAChR, nicotinic acetylcholine receptor; GABA, γ -amino-butyric acid.