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Perspective Piece

Rationale for the Coadministration of Albendazole and Ivermectin to Humans for Malaria Parasite Transmission Control

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Abstract. Recently there have been calls for the eradication of malaria and the elimination of soil-transmitted helminths (STHs). Malaria and STHs overlap in distribution, and STH infections are associated with increased risk for malaria. Indeed, there is evidence that suggests that STH infection may facilitate malaria transmission. Malaria and STH coinfection may exacerbate anemia, especially in pregnant women, leading to worsened child development and more adverse pregnancy outcomes than these diseases would cause on their own. Ivermectin mass drug administration (MDA) to humans for malaria parasite transmission suppression is being investigated as a potential malaria elimination tool. Adding albendazole to ivermectin MDAs would maximize effects against STHs. A proactive, integrated control platform that targets malaria and STHs would be extremely cost-effective and simultaneously reduce human suffering caused by multiple diseases. This paper outlines the benefits of adding albendazole to ivermectin MDAs for malaria parasite transmission suppression.

A CALL FOR ERADICATION, ELIMINATION, AND INTEGRATION

There have been recent calls for the eradication of malaria[1] and suggestions of soil-transmitted helminth (STH) elimination by shifting from morbidity control to transmission control.[2,3] Numerous publications call for the integration of control measures that target malaria and neglected tropical diseases (NTDs) with the same platform.[4–9] The NTDs are a diverse group of infectious diseases including STH infections, lymphatic filariasis (LF), schistosomiasis, onchocerciasis, and at least 13 others, prioritized by the World Health Organization as such, because they promote poverty and have a negative impact on pregnancy, child health and development, and adult worker productivity. Examples of synergism between malaria and NTD control programs include a reduction in LF transmission by the large-scale rollout of long-lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS) with insecticides for malaria control[10,11] and the distribution of LLINs and sulfadoxine-pyrimethamine for intermittent preventive therapy for pregnant women by Community-Directed Treatment (CDT) platforms that have been mobilized by the African Program for Onchocerciasis Control (APOC)[12,13] and the Global Program to Eliminate Lymphatic Filariasis (GPELF)[14] in Africa. Indeed, Nigeria has recently announced a nationwide integration of malaria and LF elimination efforts, which will use the CDT platform to enhance LLIN distribution and communication of education messages that promote LLIN use. However, reports of successful integration of malaria elimination and STH control efforts are lacking.

Both the APOC and GPELF in Africa have strategically used mass drug administration (MDA) by CDT with ivermectin to deliver more than 300 million treatments annually (www.mectizan.org) to suppress the transmission of *Onchocerca volvulus* and *Wuchereria bancrofti* microfilariae to their respective insect vectors. Ivermectin MDA to all eligible persons in a given area offers promise as a potential vector-targeted measure to reduce *Plasmodium* transmission because of the lethal and sublethal effects of ivermectin against numerous *Anopheles* vectors.[15] Sustained *Plasmodium* transmission suppression would likely require repeated ivermectin MDAs spaced across transmission seasons.[16,17] In Nigeria, annual APOC-coordinated ivermectin MDAs have shown a significant reduction in prevalence of the STHs *Ascaris lumbricoides* and *Trichuris trichiura* but not hookworm.[18] Ivermectin exerts strong activity against *Ascaris*, moderate activity against *Trichuris*, and minimal to no effect against hookworm. Albendazole, a benzimidazole anthelmintic, has strong effect against *Ascaris* and hookworm and moderate effect against *Trichuris*.[19] The combination of both ivermectin and albendazole is superior to either drug alone for the treatment of the STHs, especially *Trichuris*.[19–23] Gutman and others[18] conclude that the addition of albendazole to ivermectin MDAs would increase effects against STHs, because the MDA would have a greater impact against hookworms. Indeed, part of the rationale for the addition of albendazole for LF elimination by the GPELF was the secondary effects on STHs.[24] In support, analysis of health records in Zanzibar showed that six rounds of GPELF-coordinated ivermectin and albendazole MDAs led to dramatic reductions in reported STH and scabies infections.[25] The coadministration of albendazole and ivermectin is safe and well-tolerated, and the combination is given to millions of people annually by the GPELF in Africa.[26]

In sub-Saharan Africa, there is extensive overlap in the distribution of STHs and *P. falciparum*,[27–29] which provides opportunities to target STHs and malaria with the same ivermectin and albendazole MDA platform. In addition to STHs, expanded ivermectin and albendazole MDAs for malaria elimination would aid onchocerciasis control and LF elimination

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efforts as well as affect numerous other NTDs found worldwide, including strongyloidiasis,[30] gnathostomiasis,[31] pediculosis, and scabiasis.[32] Targeting multiple diseases with the same MDA platform will likely help maintain high compliance levels, because treated individuals will readily observe direct personal effects[33] in addition to the community-level effect of reduced *Plasmodium* transmission. This paper will outline the proposed benefits of adding albendazole to ivermectin MDAs for malaria and STH parasite transmission elimination efforts.

STHS MAY FACILITATE *PLASMODIUM* TRANSMISSION

There is mounting evidence that infection with STHs is associated with increased risk for malaria infection. A recent meta-analysis of the published malaria and STH coinfection literature found that hookworm infection is a risk factor for malaria in pregnant women and that any STH infection is a risk factor for malaria in school-aged children.[34] *Ascaris* infection was found to be a risk factor for *P. falciparum* infection in school-aged children in Nigeria,[35] pregnant women in Ghana[36] and Gabon,[37] and people of all ages in Ethiopia.[38] *Trichuris* infection was a risk factor for *P. falciparum* infection for all ages in Ethiopia.[38] Hookworm infection was a risk factor for *P. falciparum* infection in pre–school-aged children, adults,[39] and pregnant women[40] in Uganda, people of all ages in Colombia,[41] and school-aged children in Cote d'Ivoire,[42] Zimbabwe,[43] and Ghana,[44] and it was a risk factor for pregnant women along the Thai–Myanmar border for both *P. falciparum* and *P. vivax* infection.[45] Any STH infection was a risk factor for *P. falciparum* in pre–school-aged and school-aged children in Senegal,[46] school-aged children in Nigeria,[35] and people of all ages in Ethiopia.[38] In Thailand, people infected with a single STH had a higher risk of *P. falciparum* infection, and this risk increased as the number of STH species per person increased.[47] This finding was also true in Ethiopia for *Ascaris* and *Trichuris* coinfections and *Ascaris*, *Trichuris*, hookworm, and *Schistosoma mansoni* coinfections.[48] Although numerous publications have documented no increased risk of *Plasmodium* infection associated with STH infection, there have been only two published negative associations that we are aware of including, *P. falciparum* and *Ascaris* infections in pregnant women along the Thai–Myanmar border[45] and *P. falciparum* and hookworm infections in young, non-pregnant women in Cote d'Ivoire.[42]

Aside from coinfection risk factors, there may be other consequences of STH infection that could enhance *Plasmodium* transmission. *Ascaris*-infected people were more likely to have contemporaneous and successive mixed species infections of *P. falciparum* and *P. vivax*,[49] which may increase *Plasmodium* transmission, because coinfections increase the frequency of *P. falciparum* gametocyte carriage.[50–52] *Trichuris*-infected individuals were more likely to have multiple *P. falciparum* clones,[53] which may affect *Plasmodium* transmission to mosquitoes. Any STH infection was shown to be associated with increased *P. falciparum* gametocyte carriage rates, and an increasing number of STH species in infected people may be associated with increased gametocyte carriage rates.[54] It has been suggested that STH-infected individuals in resource-poor settings may not seek medical treatment even when coinfected with *Plasmodium* parasites, thus acting as a low-profile transmission hub for gametocytes. Because much of this research has been performed in clinical settings, future field trials in various ecological settings will be required to assess whether STHs do enhance *Plasmodium* transmission from asymptomatic individuals.[55]

These studies show that STH infection might influence *Plasmodium* transmission, which suggests that STH control alone may reduce *Plasmodium* transmission. Indeed, in Nigeria, it was shown that albendazole MDA every 4 months for 12 months to children (12–59 months old) reduced the prevalence and intensity of *A. lumbricoides*,[56] and although both albendazole and placebo-treated groups had an increase in *Plasmodium* infection odds over time, this increase was significantly slower in the albendazole-treated group.[57] This work suggests that albendazole MDA may impact malaria transmission, possibly by reducing *A. lumbricoides* prevalence and intensity. Thus, integration of malaria and STH elimination programs may accelerate regional malaria elimination efforts.

EXPECTED HEALTH AND DEVELOPMENT IMPACTS ON MALARIA AND STH REDUCTION

Numerous investigations have shown a protective effect of STHs from severe malaria manifestations (e.g., cerebral malaria),[58,59] whereas others have shown exacerbating effects of STHs on severe malaria.[46,60] The protective or exacerbating effects of STHs on development of severe malaria are highly debatable and may be influenced by several factors, including study location and design, the STH species investigated, STH prevalence and intensity, malaria case definitions, or the anthelmintic drugs investigated.[61,62] The argument that the removal of STHs from local populations may exacerbate malaria severity is controversial. If the goal is malaria elimination and this goal is being regionally achieved, then it is not logical to maintain detrimental STH infections in these same populations for the sake of debatable protective effects of STHs on severe malaria.

Concomitant infection with *Plasmodium* and STHs, particularly hookworm, can exacerbate anemia in non-pregnant and pregnant adults,[34,63] which leads to worsened child development[64] and more adverse pregnancy outcomes[36,65] than these diseases would cause on their own. Reduction in malaria and STH prevalence would positively impact child growth rates, school attendance, cognitive development, and adult labor force participation,[20,66,67] which would allow malaria- and STH-afflicted populations a better opportunity to escape the cycle of poverty.[68] In Nepal, albendazole treatment of pregnant women during their second and third trimesters reduced the rate of severe anemia in pregnant women, increased infant birth weight, and reduced infant mortality.[69] Limited studies show that treatment of pregnant women with both ivermectin and albendazole seems to be safe for the mother and the fetus,[70,71] and thus, the benefit of treating STH infections in pregnant women may outweigh perceived risks of treatment with these drugs.

IVERMECTIN AND ALBENDAZOLE MDA IMPACTS ON MALARIA PARASITE TRANSMISSION

Ivermectin binds at subunit interfaces next to the pore of the glutamate-gated chloride (GluCl) ion channels, which distorts the channel from a closed to open state, thus hyperpolarizing

the cell[72] leading to flaccid paralysis of ectoparasite musculature.[73] *Plasmodium* parasites do not have GluCl channels, and ivermectin is not effective against blood-stage *P. falciparum* at human-relevant concentrations either *in vitro*[74] or *in vivo*.[75] However, ivermectin can affect numerous factors of vectorial capacity for *Plasmodium* transmission, including reducing *An. gambiae* s.s. survivorship and recovery after a blood meal,[76–79] delaying mosquito refeeding,[78] and inhibiting the development of *P. falciparum* in the mosquito (i.e., sporontocidal).[80] Furthermore, we have shown that ivermectin MDA to humans in Senegalese villages reduced wild *An. gambiae* s.s. survivorship up to 1 week post-MDA[16] and reduced the proportion of *P. falciparum*-infectious *An. gambiae* s.s. up to 2 weeks post-MDA.[81] Ivermectin MDA fulfills many of the demands for novel vector-targeted interventions put forth by the malaria eradication research agenda for vector control.[15,82] Although there is mounting evidence that ivermectin MDAs may suppress *Plasmodium* transmission, well-designed clinical trials showing sufficient effect in diverse transmission settings must occur before ivermectin MDAs can be recommended for implementation by national malaria control programs and supported by global public health funding agencies.

Albendazole belongs to the class of benzimidazole anthelmintics that are active against blood-stage *P. falciparum in vitro*[83,84] and *P. berghei in vivo*[85,86] but not at human-relevant concentrations. The benzimidazoles are microtubule inhibitors known as colchicine-site binders that bind to β-tubulin, inhibiting its polymerization and subsequent spindle formation during mitosis and thereby interfering with cellular division and schizogony of *Plasmodium*.[87,88] There may be several points during both blood- and mosquito-stage *Plasmodium* cycles at which benzimidazoles may inhibit microtubule assembly, including micro- and macrogametocytogenisis, microgamete exflaggelation, and the development, integrity, and motility of sporogonic forms in the mosquito.[87]

To assess whether albendazole is sporontocidal, two experiments were performed with *An. gambiae* (G3 strain) and *P. falciparum* (NF54 strain) using the previous methodology in the work by Kobylinski and others[80] that showed the sporontocidal effect of ivermectin. We tested albendazole sulfoxide, the primary metabolite of albendazole, because albendazole is rapidly converted to its primary metabolite[89] by the time that night-feeding *Anopheles* would ingest a blood meal from an albendazole-treated person. For the experiment testing only albendazole sulfoxide (Sigma Aldrich, St. Louis, MO), mosquito blood meals contained vehicle alone (control) and either 1,000 or 100 ng/mL albendazole sulfoxide and were fed to mosquitoes concomitantly with *P. falciparum* gametocytes. For the experiment testing the sporontocidal effect of albendazole sulfoxide and ivermectin coingestion, blood meals containing vehicle alone (control), 10.7 ng/mL ivermectin (Sigma Aldrich), or 10.7 ng/mL ivermectin with 100 ng/mL albendazole sulfoxide were fed to mosquitoes concomitantly with *P. falciparum* gametocytes. Kobylinski and others[80] showed a sporontocidal effect of ivermectin at the human-relevant, mosquito-sublethal concentration of 10.7 ng/mL. The concentration of albendazole sulfoxide used in the coingestion experiment was estimated from human pharmacokinetic data at the time point when 10.7 ng/mL ivermectin is present in an orally treated human approximately 21 hours post-ingestion.[89,90]

TABLE 1

Effect of albendazole sulfoxide on *P. falciparum* sporogony in *An. gambiae*

Stage* (DPI)	Control (0)§	ALB SOx (100)	ALB SOx (1,000)
Oocyst (7)			
Prevalence† mean (SEM)	85.19 (3.42)	86.79 (3.29)	73.45 (4.15)
χ^2 value	Reference	0.8269	1.3757
P value	Reference	0.4604	0.2701
N	Reference	219	210
Intensity‡ mean (SEM)	15.60 (1.79)	17.83 (2.02)	17.68 (1.99)
P value	Reference	0.2716	0.4826
N	Reference	184	174
Sporozoite (14)			
Prevalence mean (SEM)	82.61 (3.95)	78.31 (4.52)	77.27 (4.47)
χ^2 value	Reference	1.8260	0.6950
P value	Reference	0.1947	0.4497
N	Reference	176	180

ALB Sox = albendazole sulfoxide; DPI = days post-infection.
P. falciparum stage investigated.
†Prevalence rates compared by Fisher's exact test.
‡Oocyst intensity compared by Mann–Whitney *U* test.
§Treatments (nanograms per milliliter).

Albendazole sulfoxide at 1,000 or 100 ng/mL concentrations did not alter the sporogony of *P. falciparum* in *An. gambiae* (Table 1). Albendazole sulfoxide did not inhibit the sporontocidal effect of ivermectin as oocyst ($\chi^2 = 0.2485$, $P = 0.6912$, $N = 235$), sporozoite prevalence ($\chi^2 = 0.2462$, $P = 0.6635$, $N = 189$), and oocyst intensity ($P = 0.5851$, $N = 133$) did not differ between the ivermectin and ivermectin plus albendazole sulfoxide treatment groups (Table 2). We previously showed that albendazole sulfoxide at human-relevant concentrations did not reduce the survivorship or alter the refeeding frequency of *An. gambiae*,[78] and the addition of albendazole sulfoxide to ivermectin-containing blood meals did not alter mosquito lethal effects of ivermectin at human-relevant concentrations.[91] Although coadministration of albendazole and ivermectin did not seem to enhance the mosquito-lethal, sublethal, or sporontocidal effects of ivermectin, it is important to note that it does not inhibit these phenomena. Because albendazole does not alter the systemic exposure of ivermectin,[92–94] it is likely that coadministration of these drugs

TABLE 2

The effect of ivermectin and albendazole sulfoxide on *P. falciparum* sporogony in *An. gambiae* treatments

Stage (DPI)	Control	IVM	IVM and ALB SOx
Oocyst (7)			
Prevalence mean (SEM)	73.96 (4.48)	57.14 (4.54)	60.34 (4.54)
χ^2 value	Reference	8.4717	4.3705
P value	Reference	0.0004*	0.0413*
N	Reference	215	212
Intensity mean (SEM)	14.11 (2.435)	16.38 (2.255)	12.67 (1.371)
P value	Reference	0.0708	0.0641
N	Reference	134	141
Sporozoite (14)			
Prevalence mean (SEM)	76.84 (4.33)	50.0 (5.21)	53.61 (5.06)
χ^2 value	Reference	14.5523	11.4309
P value	Reference	< 0.0001*	< 0.0001*
N	Reference	187	192

ALB Sox = albendazole sulfoxide; DPI = days post-infection; IVM = ivermectin.
*Results are significant.

by MDA would produce the same impact on *Plasmodium* transmission as ivermectin alone but would maximize impact against STHs.

To assess whether albendazole coadministered with ivermectin during MDA alters the mosquito-lethal effect of ivermectin MDA, *An. gambiae* s.l. survivorship data from APOC-coordinated ivermectin (150 μg/kg) MDAs from Senegal in 2008 and 2009[16] were compared with survivorship results from GPELF-coordinated ivermectin (150 μg/kg) plus albendazole (400 mg) MDAs from Liberia and Burkina Faso in 2013. Blood-fed *Anopheles* were collected by backpack aspiration from peoples' huts at multiple time points before and after MDAs and held in an insectary for 5 days post-collection while survivorship was observed daily, which was described in the work by Sylla and others.[16] The survivorship rates of *An. gambiae* s.l. collected before MDA and up to 1 week after MDA were compared using a χ^2 test. Both MDA regimens significantly reduced *An. gambiae* s.l. survivorship: by 31% in ivermectin-treated villages (pre-MDA: 80.99 ± 1.34%; post-MDA: 50.0 ± 2.54%; $\chi^2 = 125.55$, $P < 0.001$, $N = 1{,}240$) and 29% in ivermectin plus albendazole-treated villages (pre-MDA: 85.38 ± 2.04%; post-MDA: 56.29 ± 3.84%; $\chi^2 = 113.03$, $P < 0.001$, $N = 777$). There was not a significant difference in *An. gambiae* s.l. survivorship either before ($\chi^2 = 2.64$, $P = 0.1044$, $N = 1{,}153$) or after ($\chi^2 = 0.45$, $P = 0.503$, $N = 864$) MDAs between the ivermectin- and ivermectin plus albendazole-treated villages. This field evidence shows that ivermectin plus albendazole coadministration does not alter ivermectin-induced *An. gambiae* s.l. mortality.

Although repeated ivermectin MDAs may suppress *Plasmodium* transmission, this administration alone is not enough to clear the infectious human reservoir of *Plasmodium* parasites. Artemisinin-based combination therapies (ACTs) are currently the most effective antimalarial drugs. The combination of ivermectin MDAs with ACT MDA or mass screening and treatment with ACT approaches would maximize *Plasmodium* transmission control efforts by simultaneously targeting vector and human reservoirs. If albendazole were coadministered with ivermectin MDAs for STH and malaria transmission control, then the safety and efficacy of this combination as adjuncts with ACTs must be assessed for both *Plasmodium* and STHs. Coadministration of ivermectin and artemether-lumefantrine was safe and well-tolerated (Bousema T, personal communication); however, no study to date has investigated the safety and efficacy of ivermectin, albendazole, and ACTs in combination. As with all MDA programs, monitoring for adverse and severe adverse events after MDAs should occur, especially when novel drug combinations are used.

IVERMECTIN AND ALBENDAZOLE MDA FOR STH TRANSMISSION CONTROL

Albendazole MDA programs targeting STHs in Kenya, China, and Uganda have shown a significant decrease in intensity and prevalence of STH infections.[95,96] However, sustainable control of STHs is not possible with a single MDA because of high reinfection rates due to the fact that eggs and/or larvae present in soil are not affected by treatment of humans.[97,98] Although MDAs can have an immediate impact on STH prevalence rates,[99,100] reinfection of STHs can occur within 6–9 months post-MDA depending on a multitude of factors, including previous STH prevalence in an area, sanitation infrastructure, community personal hygiene standards, and efficacy of albendazole for the treatment of trichuriasis and hookworm.[101–104] As stated previously, ivermectin MDAs for *Plasmodium* transmission control in many endemic areas will have to be performed repeatedly during malaria transmission seasons to have a sustained impact on *Plasmodium* transmission.[16,17] If albendazole was coadministered with ivermectin during these repeated MDAs for *Plasmodium* transmission control, then this combination could have a dramatic impact on STH transmission as well.

Repeated MDAs on their own are unlikely to result in sustainable control or elimination of STHs. For sustainable, long-term control and eventual elimination of STHs, deworming MDAs need to be combined with access to a safe water supply, provision of adequate sanitation, and improved hygiene behavior.[105] Combining MDAs with water, sanitation, and hygiene (WASH) programs poses a number of challenges, including coordination between the WASH and health sectors, adequate funding, political will, and availability of guidelines for combined strategies that are based on rigorous epidemiological and economic evaluation. The need for improved WASH should not be overlooked in the design of an integrated STH control–malaria elimination program that capitalizes on the synergistic effects of coadministration of albendazole and ivermectin together with more traditional malaria elimination strategies (e.g., LLINs and IRS), and additional research is required to determine the optimal approach for combining these interventions. Comprehensive strategies for community-based WASH programs that incorporate CDT, delivered in concert with hygiene promotion activities, may be ultimately more sustainable and cost-effective than uncoordinated approaches or those that only incorporate drug delivery or only target subgroups, such as school children.

A shift from annual school-based MDAs for morbidity control of STHs to more frequent population-wide MDAs for *Plasmodium* transmission control will increase resistance selection pressure on STHs. Ivermectin is currently not a frontline drug for STH treatment, but it is important to consider possible resistance development in STHs from more frequent ivermectin MDAs for *Plasmodium* transmission control. Coadministration of ivermectin and albendazole may reduce the likelihood of resistance development in STHs to either drug, because these drugs have different modes of action.[106,107] In support, with the model organism *Caenorhabditis elegans*, ivermectin-resistant worms were not cross-resistant to albendazole.[108] In contrast, with the veterinary parasite *Haemonchus contortus*, ivermectin exposure in sheep led to an increase in the frequency of β-tubulin alleles, which are a determinant for benzimidazole resistance.[109] Recently, β-tubulin resistance alleles were identified in human *T. trichiura* that had been treated with albendazole but not ivermectin; however, the study did not compare allele frequency and treatment failure.[110]As with all MDA disease control programs, active and routine monitoring and evaluation must be conducted to ensure that resistance does not develop in the STHs to either ivermectin or albendazole. Novel anthelmintics and drug combinations are needed to handle anthelmintic resistance issues. As these novel drugs and combinations are developed, it would be prudent to test their impact against *Anopheles* survivorship and *Plasmodium* transmission.

The cost of adding albendazole to ivermectin MDAs for *Plasmodium* transmission control should be nominal considering that albendazole costs much less than ivermectin,[111] the MDA costs would have already been accounted for, and the APOC, GPELF, and Mectizan Donation Program have already streamlined delivery methods for the two drugs.[112–114] The apparent association between STHs and malaria infection suggests that targeting populations with high malaria prevalence with both ivermectin and albendazole for a more comprehensive treatment of STHs would be a potentially efficient use of resources. A proactive, integrated control platform that targets malaria and STHs would be extremely cost-effective, especially because malaria control receives a larger portion of donor money compared to NTD control.[68]

CONCLUSIONS

The addition of albendazole to ivermectin MDAs would synergistically integrate STH and *Plasmodium* elimination efforts in the same platform. Albendazole treatment does not seem to inhibit the mosquito-lethal or sporontocidal effects of ivermectin and therefore, could be readily added to ivermectin MDAs for *Plasmodium* and STH transmission control. Repeated longitudinal coadministration of albendazole and ivermectin MDAs would cause dramatic reductions in STH prevalence and intensity, potentially limit STH drug resistance development, and reduce *Plasmodium* transmission rates. The combined effects of ivermectin and albendazole MDAs on malaria and STH transmission could lead to an overall improvement in human health and socioeconomic benefit beyond what would be expected from malaria control alone.

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