Ivermectin as a Complementary Strategy to Kill Mosquitoes and Stop Malaria Transmission?

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(See the Major Article by Ouédraogo et al on pages 357–65.)

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Vector control/killing has been a long and durable strategy for malaria control across the globe. Current efforts to kill or dramatically shorten the life span of female Anopheles mosquitoes have honed the use of insecticides to specifically meet the biology of mosquito biting and resting behaviors, including putting insecticide on long-lasting insecticidal nets (LLINs) where the mosquito lands when trying to reach the person sleeping under the net and indoor residual spraying (IRS) of insecticide on house walls where a blood-fed mosquito often lands and rests before flying off to lay her eggs. There is now much attention focused on methods to kill the mosquitoes that escape these interventions because they bite when people are not yet under LLINs or because they rest or feed outside the sprayed house—but they all must bite to get their blood meals to support egg development and mosquito reproduction. Thus, a systemic endectocidal drug like ivermectin, which can be given to both humans and animals and is toxic to Anopheles mosquitoes when they take a blood meal from a host that has recently received it, provides an intriguing opportunity to kill the remaining mosquitoes that avoid or survive our existing vector control interventions [1, 2].

The results from the randomized controlled trial from Burkina Faso by Ouédraogo et al, reported in this issue of Clinical Infectious Diseases [3], build on a growing body of evidence that demonstrates the safety and efficacy of ivermectin in killing malaria mosquitoes—in this case, Anopheles gambiae and Anopheles funestus, 2 of the most important malaria vectors in Africa—when used as adjunct therapy in patients with uncomplicated falciparum malaria treated with a standard 3-day course of the antimalarial drug artemether-lumefantrine. Of particular note, they used a standard dose (200 μg/kg) of ivermectin that has been used widely for mass drug administration (MDA) in onchocerciasis and lymphatic filariasis control and elimination [4], and they confirmed its safety when used singly or as repeated dosing (2 × 200 μg/kg) in a short 3-day interval. They demonstrated partial but substantial mosquito-cidal efficacy during the week following ivermectin and showed that the killing effect was strongly associated with ivermectin plasma concentrations, which were affected by body mass index and sex (higher in females, possibly due to generally higher body fat content and fat storage of the drug). And, they suggest that the 2-dose ivermectin regimen given during a standard 3-day artemisinin combination therapy (ACTs) could reduce malaria transmission in the protected laboratory setting by approximately 35% during the first week when gametocyte concentrations are highest and onward transmission is most likely [3]. Finally, they demonstrate that a small number of mosquitoes (approximately ≤1%) surviving the ivermectin exposure can become malaria infected and infective after membrane feeding on malaria-infected blood, suggesting that the transmission-blocking properties of ivermectin may be predominantly resulting from its mosquitoocidal effects. In sum, the short-lived but substantial mosquito-killing effect of ivermectin when working against an already fragile transmission environment could have important program intervention benefit, as was suggested in earlier studies with MDA (150 μg/kg) in an area of Senegal where malaria and onchocerciasis are coendemic [5], and by recent models evaluating the potential value of ivermectin when added to ACTs during MDA campaigns for malaria [6]. The impact on the mosquito population under real-life conditions might be greater...
than the 35% transmission reduction observed under the laboratory conditions in this trial [3], as other studies have suggested that surviving *Anopheles* mosquitoes show evidence of lack of movement coordination, lethargy, inability to fly, and even paralysis following ingestion of sublethal concentrations of ivermectin [7].

As the malaria control community considers the added value of ivermectin, recent experience with its safety where >1.3 billion doses have been given as MDA for onchocerciasis and lymphatic filariasis [4] is comforting. The safety and tolerability of repeat dosing at short intervals shown in the current study are particularly helpful and reassuring. This study also highlights some key issues to be addressed. The achievement of high blood concentrations is critical and because ivermectin is rapidly eliminated, it suggests that malaria mosquito killing may be improved with higher and/or more frequent dosing than is currently needed for the control of onchocerciasis and lymphatic filariasis. Repeated doses of up to 800 μg/kg have been used in the treatment of onchocerciasis [8–10]. Furthermore, earlier dose-escalation studies with ivermectin have shown that doses up to 2000 μg/kg (i.e., 5 times the highest US Food and Drug Administration–approved dose) are well tolerated with no indication of central nervous system or general toxicity [11]. Additional dosing during the third day of the ACT treatment (as done in this trial) or at day 7 (and perhaps at day 14) could be considered to provide longer mosquito-killing potential to reduce transmission by the stage 5 gametocytes, which may survive for several weeks after the clearance of the asexual-stage infection. Thus, additional dose-finding studies will help identify optimal treatment regimens for specific control purposes.

The malaria control community is also at a critical juncture where the information from existing studies suggests that now is the time to expand to program-relevant field use, including some specific trials and expanded program use with implementation evaluation. As the study authors suggest, the value of adding ivermectin (possibly with a low-dose primaquine treatment [12]) to the ACT treatment of all malaria infections in areas where artemisinin resistance is established or could be emerging may be critical in protecting the durable efficacy of ACTs. Yet ivermectin use for transmission reduction could expand well beyond this and include a spectrum from high to very low transmission settings. Already control programs have demonstrated marked transmission reduction with LLINs and targeted IRS, but the addition of ivermectin as population-wide treatment in conjunction with LLIN and IRS campaigns may produce dramatic transmission reduction, as each of the 3 interventions addresses a different component of the vector feeding and resting biology. Such malaria transmission reduction might include the deployment of ivermectin with population-wide antimalarial drug treatment programs (e.g., MDA or seasonal malaria chemoprevention) or as part of a complementary strategy for the standard case management of symptomatic cases. In settings where malaria transmission has become very low and few cases exist, programs are often looking for additional interventions to deploy for final elimination. Where detected cases are rare and elicit case investigations, including household and neighborhood screening questions, testing, infection confirmation, and treatment, the use of ivermectin in infected persons (or possibly in all persons residing in the household and immediate vicinity) may be a valuable vector control adjunct along with LLINs or IRS to finally stop local malaria transmission.

The combination of this study by Ouédraogo et al, previous field trials, and the results of recent modeling studies suggests that ivermectin can be a worthy addition to the arsenal of available tools to control and potentially interrupt malaria transmission. Further dose-finding and safety studies will help identify the best regimen(s) required to reach this goal. In addition, ideally using a consolidated approach combining efforts from multiple research groups and program implementation teams, the malaria community could advance this potentially exciting strategy within the coming few years and not wait for decades.

Note

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## References