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Short Report: Ivermectin Mass Drug Administration to Humans Disrupts Malaria Parasite Transmission in Senegalese Villages

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Abstract. Ivermectin mass drug administration (MDA) to humans is used to control onchocerciasis and lymphatic filariasis. Recent field studies have shown an added killing effect of ivermectin MDA against malaria vectors. We report that ivermectin MDA reduced the proportion of *Plasmodium falciparum* infectious *Anopheles gambiae* sensu stricto (s.s.) in treated villages in southeastern Senegal. Ivermectin MDA is a different delivery method and has a different mode of action from current malaria control agents. It could be a powerful and synergistic new tool to reduce malaria transmission in regions with epidemic or seasonal malaria transmission, and the prevalence and intensity of neglected tropical diseases.

Every year, malaria afflicts an estimated 500 million people worldwide and kills more than one million people, most of whom are children in sub-Saharan Africa.[1,2] Malaria parasite transmission control efforts, especially those intending to scale up to elimination programs, are in urgent need of new integrative tools to achieve their goals.[3] Indoor residual spraying and insecticide-treated nets, though highly effective, primarily affect indoor resting and biting *Anopheles* mosquitoes, and their efficacies are threatened by resistance to currently used insecticides.[4] Here, we show that mass drug administration (MDA) of ivermectin to humans in Senegalese villages significantly reduced the proportion of *Plasmodium falciparum* infectious *Anopheles gambiae* sensu stricto (s.s.) relative to those caught from nearby control villages for up to 2 weeks post administration. Ivermectin MDA has a different mode of action from currently used malaria parasite transmission control agents, and a unique delivery method that will target malaria vectors regardless of whether they are exophagic, exophilic, or crepuscular blood feeders. Furthermore, ivermectin MDA integrates well with existing malaria control technologies and synergizes with neglected tropical disease (NTD) control efforts.

Ivermectin MDA to humans has been developed as a safe and effective control strategy for NTDs such as onchocerciasis[5] and lymphatic filariasis,[6] and it can transiently affect the prevalence and intensity of certain soil transmitted helminths.[7–13] Laboratory studies have showed that *An. gambiae* s.s. mosquitoes can be killed by ivermectin concentrations present in human blood after a standard oral dose.[14,15] Results from our field study showed that wild, bloodfed *An. gambiae* s.s. had significantly reduced survivorship for up to 6 days after ivermectin MDA, and reduced adult *Anopheles* survivorship from the MDA was predicted in a model to shift the mosquito population age structure so that the basic reproductive number of malaria (R_0) was temporarily suppressed.[16]

Mosquitoes were sampled from five villages in the Sudano-Guinean phytogeographic zone of Senegal in 2008 and 2009. The villages of Boundoucondi, Nathia, Ibel, Damboucoye, and Ndebou are located along a 12 km stretch of road that extends westward from Kédougou, Senegal (Figure 1). Various villages in this region are treated annually by MDA of ivermectin (Mectizan, Merck and Co. Inc., Rahway, NJ) as directed by the African Program for Onchocerciasis Control and the Senegalese Ministry of Health. During this experiment, three villages were treated by ivermectin MDA: Ibel (August 2008), Ndebou (August 2009), and Damboucoye (October 2009). Three pair-matched villages served as untreated controls, Ndebou (August 2008), Boundoucondi (August 2009), and Nathia (October 2009). Permission to collect mosquitoes surrounding these MDAs was given by the Senegalese Ministry of Health and the populations of each village, and the study was reviewed by the Institutional Review Board at Colorado State University. A topographical map (Figure 1) of the villages was created with ArcGIS version 9.3 (ESRI Inc., Redlands, CA).

Indoor resting mosquitoes were aspirated from the insides of peoples' huts for a concurrent study that assessed the effects of ivermectin on *Anopheles* survivorship and mosquitoes were processed as previously described.[16] *Anopheles gambiae* s.s. that survived 5 days post capture were used for this analysis as they represented the largest group for adequate statistical analysis between treatment and control collections (73.03%, 934/1,279). Individual thoraxes were tested by Taqman polymerase chain reaction for *Plasmodium* spp. sporozoite detection,[17] which used laboratory-confirmed *P. falciparum* sporozoite-infected *An. gambiae* s.s. as postitive controls for calibration.

Using accepted rates of adult blood feeding frequency,[18,19] we conservatively estimated that it would take 3 days for all potentially infectious *An. gambiae* present in the area at the time of MDA to imbibe a blood meal from treated people. Therefore, mosquitoes collected from 14 days before ivermectin MDA to 3 days post treatment were placed in the "before" group, whereas mosquitoes collected from 3 days post treatment to 12 days post treatment were placed in the "after" group. However, post-hoc analyses revealed that significant differences were retained between the "before"' and "after" sporozoite rates even if mosquitoes caught 1, 2, and 3 days post ivermectin MDA were placed in the "after" group.

For individual replicates, infection rates were analyzed by logistic regression with effects for village (treated, untreated), period (before, after), and village by period interactions. A combined analysis for all three replicates included effects for

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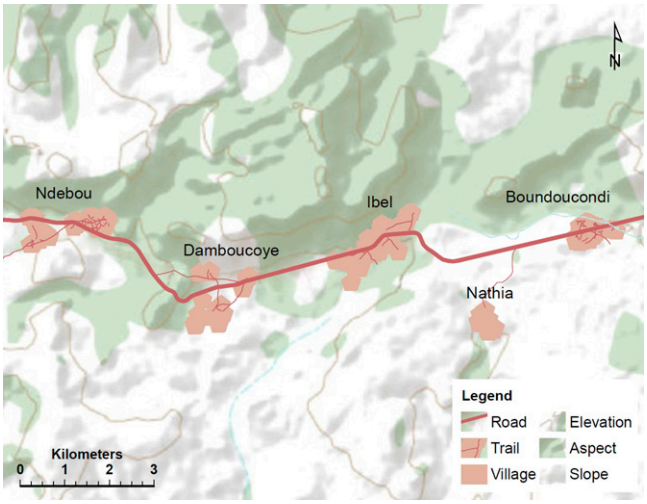

FIGURE 1. Field site map. Topographical map of the five villages where the experiment was conducted in 2008 and 2009.

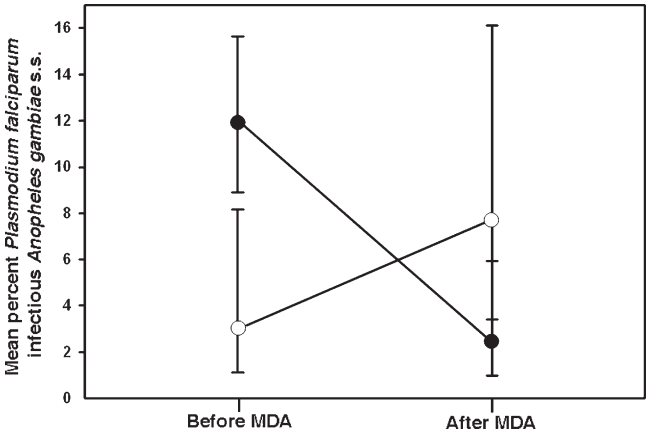

FIGURE 2. The proportion of *Plasmodium falciparum* infectious *Anopheles gambiae* s.s. before and after ivermectin MDAs. The mean percent of *P. falciparum* sporozoite-infectious *An. gambiae* s.s. were estimated from three replicate collections of mosquitoes in treated and pair-matched untreated, control villages in southeastern Senegal. Filled (●) and open (○) circles represent the means of ivermectin treated and untreated control villages, respectively. Error bars represent 95% confidence intervals.

village, period, and replicate, village by period, and village by replicate. In both analyses, the village by period interaction tests whether the change in infection rate over period differs between treated and untreated villages. For estimation of means, the village by replicate interaction was removed from the model because the second replicate control village had zero infection rates. Computations were performed with SAS Proc GENMOD.[20]

Direct measurements presented here show that *Plasmodium* transmission is indeed significantly disrupted after ivermectin MDA and the effect is sustained for at least 2 weeks. Figure 2 shows a 79% reduction in the mean proportion of *P. falciparum* sporozoite-infectious *An. gambiae* s.s. collected 2 weeks following ivermectin MDA in villages from three replicates, whereas there was a 246% increase in the mean proportion of sporozoite-infectious *An. gambiae* s.s. collected in pair-matched control villages at the same time (treatment by period, degrees of freedom [df] = 1, $\chi^2 = 12.18$, $P = 0.0005$, $N = 934$).

This study was conducted on a small spatial scale. All villages are located along a ~12 km stretch of road (Figure 1) where humans, and possibly vectors, moved between treated and control villages, yet there was still a demonstrable effect restricted to treatment villages highlighting that localized *Plasmodium* transmission control that can be achieved in a single village by MDA. The primary activity of ivermectin is to agonize invertebrate glutamate-gated chloride channels, causing flaccid muscle paralysis and death of the nematodes and insects.[21] Insecticides and spatial repellents currently used against malaria vectors do not target these channels,[4] and so cross-resistance is less likely. Ivermectin has not been shown to have antimicrobial effects,[22] however, our field data do not exclude the possibility that sublethal ivermectin concentrations inhibited the development of *Plasmodium* in mosquitoes. If such an effect can occur, it may have contributed to the reduction in sporozoite rates and should be tested further.

This study shows that a single ivermectin MDA can significantly reduce the proportion of sporozoite-infectious malaria vectors for at least 2 weeks; further studies are needed to determine the duration of control. If given more frequently, in spaced intervals defined by the duration of control, ivermectin MDAs may be effective for reducing malaria parasite transmission during epidemics or delineated malaria transmission seasons that occur throughout large regions of Africa and other continents. Because many of these regions are co-endemic for ivermectin-susceptible NTDs, more frequent ivermectin MDAs would likely result in enhanced NTD and malaria control.

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REFERENCES

1. Hay SI, Okiro EA, Gething PW, Patil AP, Tatem AJ, Guerra CA, Snow RW, 2010. Estimating the global clinical burden of *Plasmodium falciparum* malaria in 2007. *PLoS Med 7:* e1000290.
2. Snow RW, Craig M, Deichmann U, Marsh K, 1999. Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. *Bull World Health Organ 77:* 624–640.

3. The malERA Consultative Group on Vector Control, 2011. A research agenda for malaria eradication: vector control. *Plos Med 8:* e1000401.
4. WHO, 2006. Malaria vector control and personal protection. WHO technical report series: no. 936. Geneva: WHO.
5. Amazigo U, 2008. The African Programme for Onchocerciasis Control (APOC). *Ann Trop Med Parasitol 102:* 19–22.
6. Ottesen EA, Hooper PJ, Bradley M, Biswas G, 2008. The global programme to eliminate lymphatic filariasis: health impact after 8 years. *PLoS Negl Trop Dis 2:* e317.
7. Anderson RM, Medley GF, 1985. Community control of helminth infections of man by mass and selective chemotherapy. *Parasitol 90:* 629–660.
8. Beach MJ, Streit TG, Addiss DG, Prospere R, Roberts JM, Lammie PJ, 1999. Assessment of combined ivermectin and albendazole for treatment of intestinal helminth and *Wuchereria bancrofti* infections in Haitian schoolchildren. *Am J Trop Med Hyg 60:* 479–486.
9. Belizario VY, Amarillo ME, de Leon WU, de los Reyes AE, Bugayong MG, Macatangay BJC, 2003. A comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against *Ascaris* and *Trichuris* spp. *Bull World Health Organ 81:* 35–42.
10. Gutman J, Emukah E, Okpala N, Okoro C, Obasi A, Miri ES, Richards FO, 2010. Effects of annual mass treatment with ivermectin for onchocerciasis on the prevalence of intestinal helminths. *Am J Trop Med Hyg 83:* 534–541.
11. Marti H, Haji HJ, Savioli L, Chwaya HM, Mgeni AF, Ameir JS, Hatz C, 1996. A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of *Strongyloides stercoralis* and other soil-transmitted helminth infections in children. *Am J Trop Med Hyg 55:* 477–481.
12. Ranque S, Chippaux JP, Garcia A, Boussinesq M, 2001. Follow-up of *Ascaris lumbricoides* and *Trichuris trichiura* infections in children living in a community treated with ivermectin at 3-monthly intervals. *Ann Trop Med Parasitol 95:* 389–393.
13. Wen LY, Yan XL, Sun FH, Fang YY, Yang MJ, Lou LJ, 2008. A randomized, double-blind, multicenter clinical trial on the efficacy of ivermectin against intestinal nematode infections in China. *Acta Trop 106:* 190–194.
14. Chaccour C, Lines J, Whitty CJ, 2010. Effect of ivermectin on *Anopheles gambiae* mosquitoes fed on humans: the potential of oral insecticides in malaria control. *J Infect Dis 202:* 113–116.
15. Kobylinski KC, Deus KM, Butters MP, Hongyu T, Gray M, da Silva IM, Sylla M, Foy BD, 2010. The effect of oral anthelmintics on the survivorship and re-feeding frequency of anthropophilic mosquito disease vectors. *Acta Trop 116:* 119–126.
16. Sylla M, Kobylinski KC, Gray M, Chapman PL, Sarr MD, Rasgon JL, Foy BD, 2010. Mass drug administration of ivermectin in south-eastern Senegal reduces the survivorship of wild-caught, blood fed malaria vectors. *Malar J 9:* e365.
17. Bass C, Nikou D, Blagborough AM, Vontas J, Sinden RE, Williamson MS, Field LM, 2008. PCR-based detection of *Plasmodium* in *Anopheles* mosquitoes: a comparison of a new high-throughput assay with existing methods. *Malar J 7:* e177.
18. Beier JC, 1996. Frequent blood-feeding and restrictive sugar-feeding behavior enhance the malaria vector potential of *Anopheles gambiae* s.l. and *An. funestus* (Diptera: Culicidae) in western Kenya. *J Med Entomol 33:* 613–618.
19. Briegel H, Horler E, 1993. Multiple blood meals as a reproductive strategy in *Anopheles* (Diptera: Culcidae). *J Med Entomol 30:* 975–985.
20. SAS Institute I, 2002. Cary, NC: SAS.
21. Kane NS, Hirschberg B, Qian S, Hunt D, Thomas B, Brochu R, Ludmerer SW, Zheng Y, Smith M, Arena JP, Cohen CJ, Schmatz D, Warmke J, Cully DF, 2000. Drug-resistant *Drosophila* indicates glutamate-gated chloride channels are targets for the antiparasitics nodulisporic acid and ivermectin. *Proc Natl Acad Sci USA 97:* 13949–13954.
22. Chabala JC, Mrozik H, Tolman RL, Eskola P, Lusi A, Peterson LH, Woods MF, Fisher MH, 1980. Ivermectin, a new broad-spectrum antiparasitic agent. *J Med Chem 23:* 1134–1136.