

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

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Introduction

Malaria affects an estimated 500 million people worldwide, and kills over one million people per annum; many of whom are young children from sub-Saharan Africa. There is currently an urgent need of new integrative tools to improve transmission control efforts to achieve the goals. Indoor residual spraying (IRS) and insecticide treated nets (ITNs) have been extremely effective to date, however these methods primarily target indoor resting and biting *Anopheles* mosquitoes, and development of insecticide resistance are threatening the efficacies of such control methods.

Mass drug administration (MDA) of ivermectin to humans has been a safe and effective control strategy for onchocerciasis and lymphatic filariasis (LF). Laboratory studies indicated that *An.gambiae* sensu stricto (s.s.) mosquitoes can be killed by ivermectin concentrations present in human blood after a standard ivermectin dose. Results from a recent field study showed that wild, bloodfed *An.gambiae* s.s. significantly reduced survivorship for up to six 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. These suggest that ivermectin MDA, as an alternative mode of action to control methods currently used to interrupt malaria parasite transmission and a unique delivery method, would target the mosquito vectors irrespective of the feeding habits.

The current paper reported that ivermectin MDA for LF provided to humans in Senegalese villages significantly reduced the proportion of *Plasmodium falciparum* infected *An.gambiae* (s.s.) relative to those caught from nearby control villages for up to two weeks post administration.

Materials and Methods

Mosquitoes from five villages within the Sudano-Guinean phytogeographic zone of Senegal were sampled in 2008-2009. The villages were located along a 12km stretch of road, extending westward and various villages within this region were treated with annual ivermectin MDA. Three villages received MDA: Ibel (August 2008), Ndebou (August 2009) and Damboucoye (October 2009). Three pair-matched villages served as untreated controls: Ndebou (August 2008), Boudoucondi (August 2009) and Nathia (October 2009).

Indoor resting mosquitoes were caught in people's huts for a concurrent study that assessed the effects of ivermectin on *Anopheles* survivorship. Mosquitoes that survived 5 days post capture were used for this analysis. Individual thoraxes were tested by Taqman polymerase chain reaction for *Plasmodium* spp. sporozoite detection. It was 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. Mosquitoes collected from 14 days prior to MDA to 3 days post treatment were treated as the "before" group. Mosquitoes collected from 3-12 days post treatment were placed in the "after" group.

Results

For the individual replicates, infection rates were analysed using logistic regression with effects for

village (treated, untreated), period (before, after) and village by period interactions. The combined analysis for all three replicates included effects for village, period, and replicate 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 not included to the model as the second replication control village had zero infection rates. SAS Proc GENMOD was used to conduct the computations.

Direct measurements indicated that *Plasmodium* transmission is indeed significantly disrupted after ivermectin MDA and the effect was sustained for at least two weeks. A 79% reduction in the mean proportion of *P.falciparum* sporozoite-infectious *An.gambiae* s.s. collected two weeks after MDA was seen in the villages from three replicates. In contrast, 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, $\chi^2 = 12.18$, $P = 0.0005$, $N = 934$).

Discussion

The study showed that a single round of ivermectin MDA can significantly reduce the proportion of sporozoite-infectious malaria vectors for at least two weeks, however further studies are needed to determine the duration of control. Should ivermectin be distributed more frequently in spaced intervals defined by the duration of control, it may be effective for reducing malaria parasite transmission during epidemics or delineated malaria transmission seasons. As many regions are co-endemic for ivermectin-susceptible NTDs, more frequent ivermectin MDAs would likely enhance NTD and malaria control.

Editor's Comments

This paper attracted worldwide publicity because of the novel approach to killing mosquitoes through swallowing medicine. The *New York Times* gave a very sensational title to their story about this study: '*Human swallows pill. Mosquito bites human. Mosquito dies*'. The systemic lethal effect of ivermectin on mosquitoes feeding on humans that had recently taken the drug is well established. It was first demonstrated in the field about 10 years ago by Prof. Moses Bockarie working in Papua New Guinea. However this lethal effect lasts about a week and is therefore of little value as an intervention strategy because it would require MDA every two weeks to be effective.

This paper is however more about the effect of residual ivermectin in the blood on the development of malaria parasites in the mosquito host. The interpretation of the observations described is that malaria transmission was disrupted. This is however difficult to ascertain through changes in sporozoite rate. The best entomological indicators of transmission intensity are entomological inoculation rates (EIR) and vectorial capacity. The biggest driver of EIR is the human-vector contact rate which was not directly measured in this study. Moreover, transmission of malaria can be highly focal even along a 12 km stretch of road with different vector species remaining fairly isolated. The changes in sporozoite rates observed can also be accounted for by changes in the age-structure of the mosquitoes in the different groups which could have been significantly different at baseline. Unfortunately, parous rate was not measured during this study.

The entomological equivalent of the basic reproductive rate (R_0) is Vectorial Capacity - the average number of inoculations from a single case of malaria in unit time where all vectors biting an infected person become infective. The main drivers of this are the human-vector contact rate and the vector survival rate. Sporozoite rate is therefore the least weighty among entomological indices for measuring transmission intensity and it alone cannot be a reliable measure of the disruption of malaria transmission. Active malaria transmission in areas where sporozoite positive mosquitoes are not detectable in monthly samples is very common.

Recommended readings

Bockarie MJ, Hii JL, Alexander ND, Bockarie F, Dagoro H, Kazura JW, Alpers MP, 1999. Mass treatment with ivermectin for filariasis control in Papua New Guinea: impact on mosquito survival. *Med Vet Entomol* 13: 120-3.

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