Ivermectin mass drug administration to humans as a potential tool for malaria elimination

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Background

Ivermectin is an extremely safe oral drug, with over 300 million treatments distributed annually by mass drug administration (MDA) for onchocerciasis and lymphatic filariasis elimination in Africa and Latin America.

- Ivermectin can reduce the surivorehip of African Anopheles including: An. gambiae (Chaccour et al. 2010, Spylla et al. 2010, Ouédraogo et al. 2014), An. arabiensis (Fritz et al. 2012), and An. funestus (Ouédraogo et al. 2014) suppresses P. falciparum transmission (Kobylinski et al. 2011, Alout et al. 2014) and effects four out of five variables in the vectorial capacity equation (see right figure).

- A recent clinical trial showed that ivermectin is safe and well tolerated when administered with artemether-lumefantrine (Ouédraogo et al. 2014), and modelling efforts predict that ivermectin MDA coupled with artemisinin combination therapy (ACT) MDA in Africa would accelerate elimination efforts (Slater et al. 2014).

- Ivermectin MDA fulfills many of the demands for novel vector control interventions put forth by the Malaria Eradication Research Agenda Consultative Group on Vector Control (Alonso et al. 2011) including: a different mode of action from currently used insecticides, it targets both indoor- and outdoor-feeding mosquitoes, it suppresses both larval and pupal stages, and it alters the mosquito population age structure (Alout et al. 2014).

- Ivermectin MDA directly targets exophagic and endophagic human-feeding Anopheles regardless of feeding status, thus it could be a powerful new tool to aid the current artemisinin-resistance containment in the GMS and malaria elimination efforts worldwide.

Effect of ivermectin in an African context

- Escalating concentrations of ivermectin reduce number of mosquitoes feeding on a single host in one day.
- The 400 µg/kg concentration is extremely safe and well tolerated.
- The 400 µg/kg concentration appears to be ideal as it reaches the LC50 of An. dirus.
- Ivermectin (400 µg/kg) is extremely safe and well tolerated.

![Graph showing the effect of ivermectin concentration on Anopheles](Graph)

Effect of ivermectin in a Greater Mekong Subregion context

- Various concentrations of ivermectin were blood fed to An. dirus, An. australis, An. campesritis, and An. minimus via membrane feeders.
- Mosquito survival was monitored for seven days.
- A non-linear mixed model (Kobylinski et al. 2010) was used to estimate the lethal concentration that killed 50, 25, and 5 percentage of mosquitoes.

![Graph showing lethal concentration of ivermectin that kills GMS Anopheles](Graph)

Sporontocidal impact of ivermectin on P. vivax in An. dirus

- Ivermectin PK data from 23 adult Thai (12 F: 11M) (Na-Bangchang et al. 2006) raw data kindly provided by Dr. Kesara Nabanbangchang.
- Data re-fitted using non-linear mixed-effects modelling (NONMEM).
- Standard dosing of 200 µg/kg was assumed (no individual dose data).
- Simulations (n=500) were performed for a standard person weighing 56 kg (see below).

![Graph showing model estimates for ivermectin concentration](Graph)

Future directions

- Clinical trials to investigate combination of ivermectin and dihydroartemisinin plus piperquine will commence soon.
- Modelling efforts will be used to determine frequency of ivermectin MDAs to maximise impact on transmission.
- Perform repeated ivermectin MDAs with or without ACTs in Africa and the GMS and monitor impacts on entomological (eg. vector density, population age structure, and sporozoite rate) and parasitological (eg. symptomatic and asymptomatic Plasmodium prevalence, and molecular Force of Infection) indices of transmission.

![Graph showing model estimates for ivermectin concentration](Graph)

Funding Sources

The Military Infectious Disease Research Program, US Armed Forces Health Surveillance Center: Global Emerging Infections Surveillance Network, Colorado State University CRC 186117, the Bill & Melinda Gates Foundation OPP1095931 and Grand Challenges Explorations grant 51995, and the National Institute of Allergy and Infectious Diseases grants R21-A1079528 and R01-A1094349-01A1. This research was performed while the author held a National Research Council Research Associateship Award at the Walter Reed Institute of Research—Armed Forces Research Institute of Medical Sciences.

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