IVERMEN

Background

The *Ivermectin Research for Malaria Elimination Network* (IVERMEN) was formed during the annual meeting of the American Society of Tropical Medicine and Hygiene in New Orleans in November 2014, when a group of academics, members of different NGOs and funding agencies met to discuss the latest evidence on the potential use of ivermectin as a malaria vector control tool.

The main goal of the group is to establish a common research agenda to generate evidence base on whether ivermectin-based strategies can add to the emerging arsenal to interrupt malaria transmission.

Publications

Establishment of the Ivermectin Research for Malaria Elimination Network: updating the research agenda

Abstract: The potential use of ivermectin as an additional vector control tool is receiving increased attention from the malaria elimination community, driven by the increased importance of outdoor/residual malaria transmission and the threat of insecticide resistance where vector tools have been scaled-up. This report summarizes the emerging evidence presented at a side meeting on "Ivermectin for malaria elimination: current status and future directions" at the annual meeting of the American Society of Tropical Medicine and Hygiene in New Orleans on November 4, 2014. One outcome was the creation of the "*Ivermectin Research for Malaria Elimination Network*" whose main goal is to establish a common research agenda to generate the evidence base on whether ivermectin-based strategies should be added to the emerging arsenal to interrupt malaria transmission.

Bellinger AM et al. *Oral, ultra–long-lasting drug delivery: Application toward malaria elimination goals*

Abstract: Efforts at elimination of scourges, such as malaria, are limited by the logistic challenges of reaching large rural populations and ensuring patient adherence to adequate pharmacologic treatment. We have developed an oral, ultra–long-acting capsule that dissolves in the stomach and deploys a star-shaped dosage form that releases drug while assuming a geometry that prevents passage through the pylorus yet allows passage of food, enabling prolonged gastric residence. This gastric-resident, drug delivery dosage form releases small-molecule drugs for days to weeks and potentially longer. Upon dissolution of the macrostructure, the components can safely pass through the gastrointestinal tract. Clinical, radiographic, and endoscopic evaluation of a swine large-animal model that received these dosage forms showed no evidence of gastrointestinal obstruction or mucosal injury. We generated long-acting formulations for controlled release of ivermectin, a drug that targets malaria-transmitting mosquitoes, in the gastric environment and incorporated these into our dosage form, which then delivered a sustained therapeutic dose of ivermectin for up to 14 days in our swine model. Further, by using mathematical models of malaria transmission that incorporate the lethal effect of ivermectin against malaria-transmitting mosquitoes, we demonstrated that this system will boost the efficacy of mass drug administration toward malaria elimination goals. Encapsulated, gastric-resident dosage forms for ultra–long-acting drug delivery have the potential to revolutionize treatment options for malaria and other diseases that affect large populations around the globe for which treatment adherence is essential for efficacy.

Foy BD et al. *Endectocides for malaria control*

Abstract: Systemic endectocidal drugs, used to control nematodes in humans and other vertebrates, can be toxic to *Anopheles spp*. mosquitoes when they take a blood meal from a host that has recently

received one of these drugs. Recent laboratory and field studies have highlighted the potential of ivermectin to control malaria parasite transmission if this drug is distributed strategically and more often. There are important theoretical benefits to this strategy, as well as caveats. A better understanding of drug effects against vectors and malaria ecologies are needed. In the near future, ivermectin and other endectocides could serve as potent and novel malaria transmission control tools that are directly linked to the control of neglected tropical diseases in the same communities.

Slater HC et al. *The potential impact of adding ivermectin to a mass treatment intervention to reduce malaria transmission: a modelling study*

Abstract: Ivermectin (IVM), used alongside mass treatment strategies with an artemisinin combination therapy, has been suggested as a possible tool for reducing malaria transmission. Mosquitoes ingesting a bloodmeal containing IVM have increased mortality, reducing the probability that the parasite completes sporogony.

Smit MR et al. *Safety and mosquitocidal efficacy of high-dose ivermectin when co-administered with dihydroartemisinin-piperaquine in Kenyan adults with uncomplicated malaria (IVERMAL): a randomised, double-blind, placebo-controlled trial*

Abstract: Ivermectin is being considered for mass drug administration for malaria due to its ability to kill mosquitoes feeding on recently treated individuals. However, standard, single doses of 150–200 µg/kg used for onchocerciasis and lymphatic filariasis have a short-lived mosquitocidal effect (<7 days). Because ivermectin is well tolerated up to 2000 µg/kg, we aimed to establish the safety, tolerability, and mosquitocidal efficacy of 3 day courses of high-dose ivermectin, co-administered with a standard malaria treatment.

Alout H et al. *Evaluation of ivermectin mass drug administration for malaria transmission control across different West African environments*

Abstract: Mass drug administration (MDA) of ivermectin to humans for control and elimination of filarial parasites can kill biting malaria vectors and lead to *Plasmodium* transmission reduction. This study examines the degree and duration of mosquitocidal effects resulting from single MDAs conducted in three different West African countries, and the subsequent reductions in parity and *Plasmodium* sporozoite rates.

Malaria Journal Collection: *Ivermectin to reduce malaria transmission*

Hundreds of millions of people have received ivermectin every year in campaigns against onchocerciasis and lymphatic filariasis with excellent safety profile. It is also an endectocide, a drug capable of killing mosquitoes feeding on treated subjects. In the face of the challenges posed by insecticide resistance and residual transmission, mass drug administration of endectocides holds potential as a complementary strategy for malaria elimination. Mounting evidence suggests that mass-treatment of humans (or their livestock) with ivermectin can reduce vector survival and help reduce malaria transmission. There are however numerous knowledge gaps regarding the appropriate dosing, trial design and regulatory pathway for such a novel approach.

This 'Ivermectin to reduce malaria transmission' thematic series in the *Malaria Journal* aims at providing a comprehensive assessment and factors to consider in adapting this tool for a potential new indication.

- Chaccour C et al. *Ivermectin to reduce malaria transmission I. Pharmacokinetic and pharmacodynamic considerations regarding efficacy and safety*

- Chaccour C, Rabinovich NR. *Ivermectin to reduce malaria transmission II. Considerations regarding clinical development pathway*
- Chaccour C, Rabinovich NR. *Ivermectin to reduce malaria transmission III. Considerations regarding regulatory and policy pathways*

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