IVERMEN Briefing Summary Report

November 20th, 2019
Residence Inn, National Harbour, Maryland

BACKGROUND & INTRODUCTION

This report summarizes an overview and discussion of the concept of ivermectin mass drug administration for malaria, and was organized by the Malaria Eradication Scientific Alliance (MESA) as a follow-up to the Ivermen meeting 5 years ago, convened by Carlos Chaccour and Kevin Kobylinski, prior to the current investments in the range of trials ongoing and planned in Africa and Asia. The aim was to brief a range of interested and active stakeholders, including partners, donors, civil society, academia, and industry, on the status of studies from investigators and companies involved in ivermectin for malaria vector control, timelines to reporting results, and identify key questions.

The ivermectin for malaria field is characterized by individually funded trials, in the context of active, long standing programs for onchocerciasis and lymphatic filariasis, and more recently soil transmitted helminths. Ivermectin remains the "wonder drug", and new delivery vehicles for extended, long lasting formulations, as well as new indications for scabies, as well as novel applications as antiviral and cancer treatment, are currently being explored by other researchers.

Regina Rabinovich, Chair of MESA, introduced the functionality of the MESA Track database in expediting the examination of active research projects, which serves as a platform for robust and up-to-date discussions within the malaria space.

Malaria Eradication Science Alliance (MESA) - presented by Maria Tusell

MESA and the MESA Track database are available to remain well informed as results emerge from the various trials and the evidence base evolves. Through its knowledge management tool MESA Track, combined with MESA's collaborative approach towards WHO-led policy development, MESA provides a virtual and physical platform to facilitate global engagement with the current research efforts. Maria Tusell utilized openly data from MESA track to provide an overview of ivermectin for malaria and NTDs.

Updates from Ivermectin trials for malaria

Five trials using ivermectin to reduce malaria transmission and one trial considering the administration of ivermectin were presented (table 1):

1. Mass drug administration of ivermectin and dihydroartemisinin-piperaquine as an additional intervention for malaria elimination (MASSIV) in The Gambia, presented by Dr Jane Achan;
2. Repeat ivermectin mass drug administrations for malaria control II (RIMDAMAL II) in Burkina Faso, presented by Dr Brian Foy;
3. Broad one health endectocide-based malaria intervention in Africa (BOHEMIA) in Mozambique and Tanzania, presented by Dr Carlos Chaccour;
4. Adjunctive ivermectin mass drug administration for malaria control (MATAMAL) in Guinea-Bissau, presented by Dr John Bradley on behalf of Dr Anna Last;

5. Mass drug administration with dihydroartemisinin-piperaquine and primaquine to reduce malaria in a moderate-low transmission setting in Senegal[1], presented by Dr Jimee Hwang; and
6. A novel vector control measure to combat the spread of artemisinin resistance in the GMS, Thailand, presented by Dr Jetsumon Prachusmri.

[1] Pending final decision as to whether the ivermectin arm will be added to the study.

Table 1. Main characteristics of the trials presented.
(DHA-P: Dihydroartemisinin-piperaquine; GMS: Greater Mekong Subregion; IVM: ivermectin; PCR: polymerase chain reaction; PQ: primaquine; RDT: rapid diagnostic test; SMC: Seasonal Malaria Chemoprevention).

Trial name	Country	Primary outcome	Ivermectin dose (µg/kg)	Regimen	Drug combination	Results expected
MASSIV	The Gambia	Prevalence of malaria infection at peak transmission by quantitative PCR in the second year; vector survival (parity)	300-400 x 3 days	Monthly x 3	IVM + DHA-P	2020
RIMDAMAL II	Burkina Faso	Incidence of uncomplicated malaria episodes in cohort children ≤10 years of age as assessed by active case surveillance	300 x 3 days	Monthly x 4	IVM (simultaneous with SMC)	2020
BOHEMIA	Mozambique Tanzania	Infection incidence in the most vulnerable age group (children under 5 years of age in Mozambique and 5-15 in Tanzania) by RDT	400 x 1 day	Monthly x 3	IVM to humans with or without IVM to livestock	2021/2022
MATAMAL	Guinea-Bissau	Population-based malaria prevalence (all ages) by PCR; vector survival (parity)	300 x 3 days	Monthly x 3	IVM + DHA-P	2021
Mass drug administration with DHA-P and PQ to reduce malaria in a moderate-low transmission setting[2]	Senegal	Difference in village-level malaria case incidence between arms	300 x 3 days	Monthly x 3	DHA-P + PQ	2022
A novel vector control measure to combat the spread of artemisinin resistance in the GMS	Thailand	Prevalence of malaria by qPCR	400 x 1 day	Monthly x 3	IVM	2020

[2] Pending final decision as to whether the ivermectin arm will be included in the study.

IVERMECTIN INNOVATION Projects

MIVEGEC, MEDINCELL- presented by Karine Mouline on behalf of Christophe Roberge

In collaboration with the Ministries of Health in Burkina Faso and Côte d'Ivoire, this is an ivermectin trial aimed to treat all peridomestic animals treated with slow release formulations of ivermectin. So far 8 ivermectin-treated villages and 8 controls have been used to test the efficacy of the formulation prototypes. In Burkina Faso environmental impact is also being assessed. The follow-on trial ANIVERMATE tests the One-Health approach, treating both humans and peridomestic animals.

Mundo Sano- presented by Marcelo Abril

Mundo Sano is working with academic partners to develop a co-formulated tablet of ivermectin with albendazole in order to simplify the use of ivermectin at fixed high doses. They plan to seek prequalification and regulatory approval.

LYNDRA THERAPEUTICS –presented by Jessica Ballinger

Lyndra is developing a long-acting ivermectin formulation using their gastric residence technology which can achieve 14 days of sustained therapeutic ivermectin levels in the blood when taken orally. The platform has already been tested for chronic disease applications and is reported to have good tolerability and safety. A full regulatory plan for the malaria indication is being developed.

DNDi- presented by Belen Pedrique

DNDi is developing paediatric formulations for use of ivermectin in lymphatic filariases (LF), to address the administrative challenge of treating children. Children are excluded in the label and in policy recommendations, not because of high risks noted, but because the appropriate trials have not been conducted. Thus, at this time, around 20% of the population is excluded from active MDA programmes, and this would also be true for malaria. They plan to consult regulatory agencies, implement the development plan, pharmacokinetics and pharmacokinetics modelling and safety studies in infected children.

DISCUSSION

Questions raised during the discussion of the trials and projects included the ongoing evaluation of the effect of ivermectin on the parasite, the understanding of the role of ivermectin metabolites and identification of the mechanism of action of identified metabolites.

While it was noted that methods, designs and outcomes vary across the individually funded and designed trials, a richness of data will be produced over the next 30 months as a result of this heterogeneity. Collaborations among the investigators have focused on modelling and selection of dose and regimen, and evaluation of safety reports in women inadvertently treated during pregnancy.

Potential topics suggested by participants included the potential for sharing safety information as it emerges; better understanding of the nuances of design and endpoint measurement that will make ultimate comparison across trial results better understood; planning for communications as trials conclude. MESA can serve as a platform for needed consultations and

further support from MESA Track may simplify communications externally. It will also be important for the malaria community, assuming this intervention is effective, to begin to discuss the approaches to policy groups and the additional data needed to plan for implementation of intervention at scale.

NEXT STEPS

a) The Ivermectin Roadmap was published latest February 2020 and participants were be informed.
b) MESA Track for ivermectin will be updated, including the listing of active NTD trials.
c) Identified opportunities, such as expanding the pregnancy exposure and safety databases, will be discussed with the trial investigators
d) MESA was asked to plan for a more in-depth and longer meeting, which can engage additional participants, particularly as data emerges over the next 3 years.

LIST OF PARTICIPANTS:

- Abdoulaye Djimdé, University of Bamako
- Arantxa Roca, Malaria Consortium
- Belen Pedrique, Drugs for Neglected Disease initiative (DNDi)
- Brian Foy, Colorado State University
- Carlos Chaccour, Barcelona Institute for Global Health
- Caroline Jones, KEMRI Wellcome Trust Research Programme
- Chris Drakeley, LSTMH
- Christa June, Bill and Melinda Gates Foundation
- Eberé Anosike, MESA Alliance
- Elizabeth Fox, Global Health Bureau
- George Jagoe, Medicines for Malaria Venture, MMV.
- Graham Brown, University of Melbourne
- Hetty Waskin, Merck
- Janice Culpepper, Bill and Melinda Gates Foundation
- Jessica Ballinger, Lyndra Therapeutics
- Jessica Rockwood, International Public Health Advisors (IPHA)
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