Conversation with NTD program leaders: Challenges and Opportunities based on progress of the BOHEMIA Ivermectin for Malaria

November 13th, 2024
Hilton Hotel, New Orleans

Background

The meeting gathered representatives from the NTD community which employ ivermectin in their programs or research activities for disease control. Convened by Regina Rabinovich and Frank Richards, the goal was to provide the results of the BOHEMIA project, testing the concept of ivermectin as a complementary vector control tool for malaria, and to initiate conversations between the two communities on potential integration of implementation mechanisms. The stakeholders, which included participants from the major NTD programs, civil society and academia, as well as members of the BOHEMIA team, engaged in an open discussion about potential synergies and challenges of using ivermectin across different diseases.

Summary

A comprehensive presentation of the two ivermectin for malaria clinical trials conducted in Kwale, Kenya and in Mopeia, Mozambique was provided (Presentation 1). The difference in results of the two trials was explained through the following four parameters: timing of the intervention vis a vis the onset of the rains., the community insecticidal level reached, dependent on dose and efficient distribution of ivermectin, duration of community plasma levels and community blood sources covered.

In Kwale, Kenya, the decision was made not to include the veterinary arm due to concerns about cattle migration. The main outcomes of the trial in Kenya were:

- Coverage: 72%
- Implementation right before the rains and ivermectin delivered synchronically
- Distribution was completed in 10 days
- An incremental 26% of reduction in infection incidence following pre-specified methods in an area with good access, ownership and usage of WHO pre-qualified nets.
- In the ivermectin arm, an increase of 22.5% on time to first infection was observed.
- No safety signals were identified by the DSMB
- Well received and perceived by the community.
- Impact on bedbugs.

In Mopeia, Mozambique, despite the bednets and IRS, the baseline prevalence was higher than in Kwale, Kenya (30%), reaching 59% (RDT) in children less than 5 years of age. The trial was delayed pending resolution between the WHO IRB and the local IRB on the requirement for pregnancy testing. The trial encountered significant operational challenges due to a severe storm which flooded the area, and which led to a cholera outbreak, both which hindered the implementation of the trial.

The main outcomes of the Mozambican trial were the following:

- Coverage below 50%.
- Delayed start (after 80% of the rains had already taken place, thus vectors peaked)
- Asynchronic delivery and slow distribution (30 days per round)
- No measurable effect due to a failed implementation. Important operational lessons.
- No safety signals.
- 80% reduction at 3 months on scabies (om the treated clusters) and headlice (in the treated individuals).

The BOHEMIA project was conducted under Good Clinical Practice sand was reviewed by the Vector Control Advisory Group (VCAG) at WHO. They have indicated the need for two positive trials and WHO will commission a systematic review, before making any recommendation. The meeting also addressed the manufacturing capabilities for Ivermectin, indicating that it can be produced by any WHO pre-qualified company, with nine manufacturers of the fermentation AI identified, eight in China. There are no anticipated supply issues in the near term, as current projections suggest sufficient availability for initial countries if the product receives a positive recommendation.

The discussion underscored the importance of timely interventions and efficient drug distribution to enhance treatment effectiveness and mosquito control. Additionally, the engagement of the Global Fund and other donors in the malaria space was noted as a positive step towards. ensuring sustainable access to this health intervention. The need for integrated, context-specific malaria strategies, balancing transmission interruption goals with overall community health improvement was emphasized.

Challenges and opportunities for a collaboration or integrated implementation with NTDs campaigns were summarized (Presentation 2). Shared logistical challenges and potential innovations include access and scale of the LoaScope, which would allow for targeted, safe treatment in *Loa loa* endemic areas of central Africa, a major impediment for full scaled implementation. Where active NTD ivermectin distribution programs for lymphatic filariasis (LF) and onchocerciasis (river blindness) are being implemented, delivery to the community could be synergistic. It was noted that use of MDA ivermectin by the malaria program could help stimulate larger anticipated MDA for scabies and strongyloidiasis. Challenges identified included the fact that the ivermectin is donated for NTD programs and how to combine donated and purchased product would need to be worked out, as there will not be an extension of the donation program for malaria. Programs for ivermectin MDA for malaria could affect the certification of elimination of onchocerciasis, which requires surveillance without ivermectin for three years. This would need to be worked out, as the NTD leaders acknowledged that impacting on malaria would be important to the community. Finally, it is possible that moxidectin could replace ivermectin for RB and LF in some areas (however, moxidectin will not be donated so use cases are being identified). Moxidectin has no killing effect on mosquitoes, thus synergies between distribution programs for malaria are not as clear.

The discussion identified concerns about how new ivermectin MDA strategies could lead to shifts in program "ownership" and resource allocation. New funding for ivermectin for malaria could facilitate its integration with other NTD campaigns. Tools like the LoaScope were highlighted for their potential synergy in central Africa, although scaling and production will require additional funding. Integrating MDA programs efforts with other interventions, such as vaccines, also requires coordination with overburdened community health workers and/or volunteers. However, the current landscape presents challenges as some NTD programs are scaling down MDA as they achieve elimination, and RB and LF MDA are held up in central Africa by the Loa issue; and that RB requires stopping MDA in order to demonstrate transmission interruption by WHO guidelines. Additionally, it is essential to recognize that in an integrated implementation scenario, the data collected may not remain within malaria-specific systems but instead might be distributed across different data systems. Lessons learned from NTD programs underline the need for adaptable and collaborative approaches to scaling interventions.

Pediatric considerations were also addressed, particularly the mismatch in age groups for seasonal malaria chemoprevention and the need for studies on pediatric ivermectin dosing for children below 5 years of age. Ongoing trials for children weighing less than five kilograms suggest safety and potential for expanded coverage. Other challenges that implementation of ivermectin for malaria indication could present, included the lack of clear guidelines on ivermectin use during pregnancy and the logistical barriers of pregnancy testing.

Some suggestions to start building opportunities with the NTD community include targeting populations and identifying which of these are implementing ivermectin for NTDs. This approach should consider not only the cost-effectiveness but also the country-specific effectiveness of interventions. It could be particularly relevant in countries like Ethiopia or Uganda, where there is great interest in exploring ivermectin as a tool to reduce what has been a recent increase in malaria transmission, and in the case of Ethiopia, expansion of *Anopheles stephensi*. The experience of the NTD communities in engaging the communities and effectively delivering MDA can be of great relevance to the malaria programs.

Conclusions

The meeting concluded highlighting the importance of good and continued transparency and communications between the malaria and NTD communities considering using ivermectin MDA. Effective planning and sharing of data will be essential to avoid tensions and unintended impact on ongoing programs. Simplifying ivermectin delivery through fixed-dose formulations was highlighted as a potential way to address logistical challenges and increase efficiency. However, clear and careful communication will be needed to mitigate any negative perceptions. It was also noted that the free ivermectin provided by Merck for LF and RB programs will not be reformulated, as the company is unlikely to consider bearing additional costs for such changes. Continued exploration of new projects in high-burden regions and more research in the veterinary impact as well as long-acting ivermectin and a combined ivermectin/albendazole tablet, or azithromycin will be important components for sustainable implementation of these interventions. The meeting concluded with encouragement to continue discussions and explore synergies with this community.

List of Participants

Alan Brooks, Bridges to Development
Carlos Chaccour, Barcelona Institute for Global Health (ISGlobal)
Elisa Serra-Casas, MESA Alliance, Barcelona Institute for Global Health (ISGlobal)
Frank Richards, Consultant
Greg Noland, The Carter Center
Joana Furnival-Adams, Barcelona Institute for Global Health (ISGlobal)
Julie Guttman, Centers for Disease Control and Prevention (CDC)
Michael Marks, London School of Hygiene and Tropical Medicine
Nana Aba Williams, MESA Alliance, Barcelona Institute for Global Health (ISGlobal)
Patrick Lammie, The Task Force for Global Health- Cor-NTD
Paul Cantey, Centers for Disease Control and Prevention (CDC)
Philip Downs, Sightsavers
Regina Rabinovich, Barcelona Institute for Global Health (ISGlobal)
Simon Bland, CEO GLIDE project (Abu Dhabi)
Sonia Tomas, Barcelona Institute for Global Health (ISGlobal)