IVERMEN Briefing Summary Report

November 16th, 2024
Hotel Hilton, New Orleans

Background and introduction

This report provides an overview of the discussions from the Ivermen meeting held on November 16, 2024, during the ASTMH congress. The meeting followed the previous Ivermen session in Kigali, Rwanda, convened by Carlos Chaccour and Kevin Kobylinski. Its primary goal was to present the results of the BOHEMIA project, including clinical trials conducted in Mopeia, Mozambique, and Kwale, Kenya, while exploring the path forward and key considerations for potential implementation of this tool.
Discussions focused on the potential synergies and challenges of using ivermectin across various neglected tropical diseases (NTDs). The agenda also included presentations on trials for long-lasting ivermectin formulations and findings on the molecular interactions between ivermectin and mosquitoes.
The meeting brought together diverse stakeholders, including partners, donors, civil society, academia, and national programs, to debate the suitability of ivermectin for malaria and one health initiatives, as well as to discuss strategies for integration with other NTD campaigns.

Meeting summary

The results from the BOHEMIA trials in Kwale, Kenya and Mopeia, Mozambique were presented. Opposite results were observed and factors for these divergent results were discussed. The presentation concluded with a list of different items that still need additional data and would be good to investigate further as well as, suggesting a different approach for this tool with a more One-Health context to leverage all the gains and positive consequences providing ivermectin to humans and animals and considering its impact on NTDs

1. Updates from human ivermectin trials for malaria in Mopeia and Kwale

Carlos Chaccour presented the efficacy and safety results of the BOHEMIA trial, which comprised two clinical trials conducted in Mopeia, Mozambique, and Kwale, Kenya. (Presentation 1). The difference in results of the two trials was explained through four parameters: timing of the intervention, 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 tribal and 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, a delay of 22.5% on time to first infection was observed.
- Well received and perceived by the community.
- No safety signals were identified by the DSMB.
- Impact on bedbugs.

In Mopeia, Mozambique, despite the bednets and IRS, the baseline prevalence was higher than in Kwale, Kenya (30%), reaching 59% (by RDT) in children less than 5 years of age. The trial was delayed due to conflicts between the WHO IRB and the local IRB requirement for pregnancy testing. The trial also encountered significant operational challenges due to a severe storm which flooded the area, and which led to a cholera outbreak 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 had peaked)
- Asynchronic delivery and slow distribution (30 days per round)
- No measurable effect due to a failed implementation, although analysis led to important operational lessons that were incorporated into the Kenyan trial.
- No safety signals were identified by the DSMB.
- 80% reduction at 3 months on scabies and head lice.

These findings underscore the importance of timely intervention and efficient distribution to reach higher ivermectin levels in the community, highlighting areas for improvement and adaptation in future trials.

Discussion:

- Primary outcome and testing approaches: The trial's primary outcome was infection incidence based on rapid diagnostic tests (RDTs) with dual markers for pLDH and HRP2. Residual HRP2 positivity following treatment posed challenges in distinguishing new infections from residual markers. A method was used to adjust for this by checking treatment status from previous visits and analyzing pLDH-negative but HRP2-positive cases. Sensitivity analyses using HRP2 or pLDH independently showed varying reductions in infection incidence: HRP2-only analysis showed a 23% reduction, while pLDH-only

showed 58%, both statistically significant (note that this was a planned tertiary analysis).

- Entomological and mosquito outcomes: In the Mozambique trial there was no significant impact in any entomological outcome measure. However, a temporary shift to younger mosquito age structure during ivermectin MDA was noted but reverted after MDA ended. Results on sporozoite rate and blood meal analysis are still pending.
- Targeting gametocytes carrier: Questions arose on whether targeting high gametocyte carriers (likely to infect mosquitoes) could improve outcomes. However, current dosing restrictions limited treatment to individuals over 15 kilograms, leaving children under 5 untreated despite potential contributions to the reservoir. Broader MDA strategies targeting mosquito populations, rather than specific human hosts, were considered more practical given operational challenges.
- Cost-effectiveness outcomes: The cost per DALY averted was estimated at $870, approximately half the GDP per capita of Kenya, suggesting a 70% probability of cost-effectiveness under current conditions. However, this analysis excluded secondary benefits like impacts on other NTDs.
- Further results on RINDAMAL II and PK: The study revealed that ivermectin distributed alongside SMC did not show incidence outcomes but increased haemoglobin levels in children under 10, likely due to reduced malaria or helminth infections. PK findings indicated that a 300-microgram dose resulted in undetectable ivermectin levels by day 14, which could explain its limited impact, as the population lacked measurable levels for half the month.
- The PK400 study, conducted by the BOHEMIA team showed that a 400-microgram dose killed provided a longer and stronger mosquitocidal effect than the 3 x 300 micrograms dose, though the reason for this remains unclear.

2. Potential challenges and opportunities on NTDs programs

The presentation by Frank Richards focused on the potential for integration of ivermectin as a complementary tool for malaria control, exploring its synergy with existing programs in the NTD community (Presentation 2). The discussion highlighted the contrasts between the malaria and NTD communities, particularly regarding the use of ivermectin. While the NTD community has longstanding experience with ivermectin MDA programs for direct treatment of conditions such as river blindness, lymphatic filariasis, and more recently for soil-transmitted helminths, malaria programs are exploring its potential with a focus on mosquito population control.

Key challenges identified include differences in program ownership, resource allocation, and donor-driven versus non-donor-driven product access models. Ivermectin donation programs, such as those funded by Merck for NTDs, have provided decades of consistent delivery, creating expectations in communities. However, there is no expectation of similar donation support for malaria. The

emerging potential of moxidectin, a drug superior to ivermectin for some NTD applications, but still at high cost presents barriers for wide-scale deployment. From the malaria perspective, moxidectin has not effect on mosquitoes and would not drive cross-disease collaborations.

Discussion:

- *Loa Loa* and safety measures*:* A specific focus was given to *Loa loa*, as ivermectin use is associated with severe adverse reactions in individuals with high microfilarial loads. This has led to the development of a "test and not treat" strategy, involving mobile diagnostic devices to screen and identify high-risk individuals. This approach, set to roll out in pilot programs in Cameroon, represents an important step in addressing safety concerns and could provide valuable insights for future malaria-related applications of ivermectin. There are however limited numbers of these diagnostics available. USAID is investing in this strategy.
- Sustainable access to ivermectin: The discussion continued with a reflection on sustainable access to ivermectin, highlighting its overall 35-year safety record and current good safety profile at the BOHEMIA single dose of 400 mcg/kg in about 200,000 individuals. Sourcing ivermectin from donated supply and purchased supply may present challenges.
- The discussion emphasized the importance of timing, as malaria interventions like seasonal malaria chemoprevention (SMC) typically align with the rainy season, while existing NTD programs operate during the dry season. Combining ivermectin distribution with other campaigns, such as vaccine delivery or nutritional supplementation, offers an opportunity to optimize resources and improve community health outcomes. However, complexities arise in aligning schedules, target populations, and delivery logistics.
- Operational challenges and community-centric approaches: Practical challenges, such as cost and logistics, were noted, with a focus on community-driven approaches. The Mozambique example underscored the need for contingency planning, such as pre-positioning drugs before the rainy season. The importance of leveraging existing community health structures was underscored. Senegal's community health worker model, where workers make regular visits to households for testing and intervention delivery, was cited as an effective approach. Such models foster strong community relationships and allow for timely, localized responses to health needs. Providing a community-centric approach was viewed as a positive component to delivery, and the NTD community has used a number of different models to achieve this.
- Timing of intervention: A key theme was the need to optimize the timing of interventions. Achieving a precise delivery schedule, as seen in successful examples from Kenya, is critical for maximizing community benefit. However, the operational realities—such as weather, logistics, and

variability in timing—can often disrupt these plans. The strict schedules, like the 10-day window in Kenya, was contrasted with the flexibility of other interventions, such as SMC, where some delays in delivery still allowed for individual-level protection. The potential for longer-acting formulations of ivermectin was raised as a promising avenue to mitigate the rigidity of current schedules.

- Pk and PD: The discussion also touched upon the importance of understanding the pharmacokinetics (PK) and pharmacodynamics (PD) of ivermectin in the field. While PK data was presented, further exploration of the PD aspect—specifically the relationship between drug concentrations and mosquito mortality—was encouraged.
- Regulatory challenges: ivermectin is only registered in Kenya and Cameroon, and elsewhere in Africa the drug has been distributed as a donation. The potential for ivermectin to treat multiple parasites, including bed bugs and scabies, was emphasized.

3. Innovation

Kevin Kobylinski presented an update on commercially available long-lasting ivermectin for use in livestock and ivermectin-Anopheles GluCI channel interactions (Presentation 3).
The presentation focused on the pharmacokinetics and effectiveness of ivermectin in controlling malaria-carrying mosquitoes. After a single dose, ivermectin peaks sharply and decreases rapidly, with the standard dose for cattle leading to killing about 95% of mosquitoes for up to 10 days. Long-lasting formulations were developed to extend this effect, showing mosquito mortality for up to 45 days.

A study conducted on Sumba Island, Indonesia, involved cattle and buffalo, and was the first to assess the mosquito-lethal effects of ivermectin in Southeast Asian livestock. Cattle showed higher ivermectin concentrations and effective mosquito mortality up to 72 days, while buffalo had lower concentrations but still exhibited significant mosquito mortality.

The long-lasting formulation achieved mosquito mortality for up to 72 days and met the WHO's mosquito mortality hazard ratio criteria. The formulation is more effective in cattle, and a higher dose may improve results in buffalo, which are more attractive to mosquitoes. This promising formulation could become a key tool for malaria control in Southeast Asia, with further testing and dose optimization for different livestock species.

The following presentation focused on the interaction of ivermectin with the glutamate-gated chloride ion channel (Presentation 4). He referred to a 2011 study using C. elegans models, which showed where ivermectin binds to the channel and how it causes flaccid paralysis in the organism. However, the model used may not fully reflect the situation in mosquitoes. The ivermectin structures and their effects on mosquito mortality was studied. It was found that when the sugar rings in ivermectin are altered, the drug's effectiveness decreases significantly. The team

also worked with computational biologists to model the ivermectin interaction in Anopheles mosquitoes, finding novel binding points that may explain ivermectin's partial activity in mosquitoes. This work could also help predict how resistance to ivermectin might develop in the future, given the differences in the binding sequence between C. elegans and Anopheles. The team emphasized the need for further research to clarify the precise mechanisms of ivermectin's action in mosquitoes and to explore the potential for resistance development. The potential for using Drosophila and expression systems to analyze mutations and understand resistance was discussed.

Quiterie de Beauregard from MedinCell presented the development of three-month long-acting injectable formulations for malaria transmission control. (Presentation 4). Supported by Unitaid funding and a consortium involving IRD, CIRDES, and IRSS, the lead formulation candidate was selected in 2021 and received positive feedback from the MHRA for phase one clinical trials, now in preparation.

The formulations, designed to meet WHO-recommended exposure levels, demonstrated promising results. One formulation, chosen for further field testing, was evaluated in Burkina Faso and Mali, focusing on areas with diverse and resistant mosquito species. In Burkina Faso, the study showed a significant impact on mosquito survival, with a hazard ratio of four over three months. Additional trials revealed the formulation's potential to last up to six months, one year, and even two years, showcasing its adaptability.
The team believes that this technology could have a significant impact on malaria epidemiology, particularly by reducing the coverage rate needed for effective malaria control. Longer-lasting formulations would be beneficial in logistical terms, providing longer exposure and reducing the need for frequent treatment cycles. Additionally, the research integrated a One Health approach, assessing the environmental impact of MDA with a focus on cattle studies.

Discussion:

- Ivermectin effectiveness in buffalo vs cows: Discussion highlighted the difference in ivermectin effectiveness between buffalo and cows, noting that buffalo are more muscular, and cows may have more body fat. The researchers acknowledged this and mentioned plans to explore metabolic differences further, specifically looking at liver enzymes. While body fat could potentially influence drug clearance, they suggested that differences in enzyme activity between the species might be a more likely explanation.
- Mosquito attraction to different animals: Field work on Sumba demonstrated that buffalo are more attractive to Anopheles mosquitoes than humans, horses, or cows. Thus, it is important to understand the ivermectin PK-PD relationship and their attractiveness to local vectors for various livestock species present in a given area.

4. General Discussion

The discussion centered on ivermectin's potential as a vector control tool, its challenges, and strategic pathways for implementation. Participants highlighted its promise in addressing outdoor malaria transmission and its broader public health benefits, such as tackling scabies, lice, and bed bugs. However, they underscored that ivermectin would likely serve as a complementary intervention integrated into existing health systems rather than a standalone tool.

Some of the topics that were highlighted during the discussion were the following:

a. Duration of effectiveness and considerations for veterinary use

A key discussion point was the ideal duration for the long-acting formulation, particularly from a veterinary perspective. While a longer-lasting formulation could be beneficial, concerns about the impact on cattle used for milk and meat consumption were raised. Withdrawal periods must be carefully considered,. Around 3 months could be a good duration. Longer durations could complicate cattle management, especially when pregnancy or lactation changes occur.

b. Gender-specific considerations and pregnancy safety

The discussion also touched on gender-specific considerations for the injectable treatment, particularly regarding its safety for women of reproductive age. So far, collected data on pregnancy status from over 111,000 exposures noted that the chances of pregnancy could be operationally assessed based on women's self-report on risk of pregnancy. This data, though not fully analyzed yet, provides insights into how the treatment could be managed for women in different reproductive stages.

c. Exploration of Alternative Molecules for Enhanced Impact

Alvaro Acosta-Serrano briefly presented a compound called nitisinone, which exhibits significant mosquitocidal capabilities. It shows promise in targeting specific vectors without affecting pollinators. Its pharmacological modelling suggests it could be effective in areas with high malaria transmission. The team would welcome any collaboration to test it in the field.

d. Regulatory challenges and use cases

regulatory challenges were pointed out, particularly in countries where ivermectin is not yet registered as a commercial drug, even though it is used in many regions through donation programs. To secure donor and regulatory support, ivermectin needs a clearly defined use case that demonstrates its impact, such as in pre-elimination malaria settings or residual transmission scenarios where existing tools fall short. Aligning with neglected tropical disease programs and framing ivermectin as part of a broader class of endectocides could attract more support.

e. Integration with broader public health goals

Questions were raised about whether ivermectin could achieve elimination in high-transmission settings or whether it is more suited for residual transmission control in lower-prevalence regions. Kenyan regulatory feedback suggested that ivermectin might be better positioned as a multi-purpose parasitic intervention rather than a malaria-specific tool, which would align with broader public health priorities.

The session concluded by emphasizing the importance of community engagement, multi-sector collaboration, and compelling evidence to showcase ivermectin's value as a multi-purpose health intervention. Participants stressed the importance of opening doors for endectocide research by demonstrating ivermectin's efficacy in targeted scenarios. Once established, further generations of endectocides with improved profiles could follow. Advocacy for ivermectin could involve linking its benefits to community priorities, such as controlling bed bugs and scabies, to gain public and governmental support.

5. Closing

The meeting concluded with reflections on the progress and future of ivermectin research and the collective effort that has brought the project this far. The discussion underscored the importance of continuing the work even as the Unitaid BOHEMIA grant comes to an end. It was acknowledged that the year is closing, the BOHEMIA grant will soon be concluded, and key milestones—such as the meta-analysis, and the GDG—are still months away. However, the work on ivermectin began long before the grant, driven by a group of committed investigators who tackled foundational questions such as optimal dosing and use scenarios. This spirit of inquiry and collaboration will continue beyond the formal funding period.
Looking ahead, the coming year is expected to bring new data, insights, and responses from WHO, which will inform the next steps. Whether ivermectin ultimately proves to be a transformative tool or a concept that should be set aside, there is optimism that the effort will yield valuable learnings. The meeting has highlighted the importance of challenging assumptions and refining models based on trial data, reinforcing the critical role of both trials and operational research in advancing understanding. Future work must also engage communities to explore how ivermectin could be delivered effectively, preparing for the moment when a green light is given by countries or WHO.
The meeting closed with gratitude for the support from MESA, which has provided crucial backing from ivermen, and for the participants who brought energy, ideas, and collaboration to the table. The path forward will require securing funding for the next steps, advancing research, and maintaining the momentum.

List of attendees

Abdisalan Noor, Harvard University, USA.
Alex Bowles, GiveWell, Canada
Allan Brooks, Bridges to Development, uSA.
Álvaro Costa-Serrano, University of Notre Dame, USA.
André-Marie Tchouatieu, Medicines for Malaria Venture, Switzerland
Anna Trett, Liverpool School of Tropical Medicine, UK.
Baltazar Candrinho, NCMP, Mozambique.
Brian Foy, Colorado State University, USA.
Carlos Chaccour, Barcelona Institute for Global Health, Spain.

Charlotte Eddis, Population Services International (PSI), Côte d'Ivoire.
Cheick Ouédraogo, Institut de Recherche en Sciences de la Santé, Burkina Faso.
Christopher Lourenco, Population Services International (PSI), USA.
Dale Halliday, Unitaid, Switzerland.
Daniel Worley, Dexcel Pharma, USA.
Edward Thomsen, UCSF, USA
Erin Eckert, Senior Malaria Advisor, Tulane University, USA.
Fabrice Some Anyrekun, Institut de Recherche en Sciences de la Santé, Burkina Faso.
Felix Hammann, Swiss Insel Hospital, Switzerland
Frank Richards, Consultant, USA.
George Jagoe, MMV, Switzerland.
Hanna Koenker, PATH, USA.
Hannah Slater, PATH, USA
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Jackie Cook, London School of Hygiene and Tropical Medicine, UK.
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Tara Seethaler, Clinton Health Access Initiative, USA.
Tom Burkot, James Cook University, Australia.