IVERMEN Briefing Summary Report

October 21st, 2023
Hyatt Regency Hotel, Chicago

Background and introduction

This report summarizes an overview of the discussions taken place during the ivermen meeting held on November 1st during the 2022 ASTMH congress, as a follow-up to the last Ivermen meeting almost 3 years ago, convened by Carlos Chaccour and Kevin Kobylinski. 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, and lessons learned.

ABSTRACT

The meeting began with introductions and a roll call of attendees, with individuals from various organizations and countries introducing themselves and their work.

The results from the ivermectin trials in Burkina Faso, Guinea Bissao and Mozambique were presented followed by the trials that presented data on animals. In general, the trials implemented in country did not show a statistically significant difference in malaria incidence between the intervention and control arms, but further analysis need to be done with efficacy data and also data pending on entomology and PK data obtained from the trials There was data suggesting that ivermectin had an impact on entomology. The meeting shifted to an innovation session that presented data on long actin ivermectin formulations. The meeting concluded with a discussion on lessons learned and potential improvement for future trials.

1. Updates from human ivermectin trials for malaria

The meeting started with the presentations from the trials in Burkina Faso, RINDAMAL II, Mozambique, BOHEMIA, Guinea Bissao, MATAMAL and Thailand

- *Update on RIMDAMAL II trial results, presented by Dr. Sunil Parikh*

The presentation provided an overview of the RINDAMAL II study conducted in Burkina Faso, between 2019 and 2020, which focused on Seasonal Malaria Chemoprevention (SMC) and Mass Drug Administration (MDA). It was emphasized that all doses during the study were directly observed, ensuring accurate data collection and safety monitoring for up to 24 hours after the last dose of ivermectin. The primary outcomes of the study centred on assessing malaria incidence in children aged 10 and under, while also considering safety and entomology factors.

In terms of the study's design, children aged three to fifty-nine months received SMC, whereas those aged six to ten years were administered either ivermectin or a placebo. The study involved regular household visits by nurses, who assessed malaria cases using a history of fever and

conducted rapid diagnostic tests. Positive cases were promptly treated, and the "time at risk" for these individuals was eliminated for 14 days following treatment. This data collection process continued over a span of two years, with a pharmacokinetic (PK) sub-study being conducted in the final month of the trial.

The results and challenges of the study were discussed, revealing that there was no statistically significant difference in malaria incidence between the intervention and control arms. This suggested that the ivermectin MDA did not effectively reduce malaria incidence in children under ten years old. The discussion of these outcomes highlighted the challenges faced, including a decrease in malaria incidence (compared to RINDAMAL I (2015), there was an 80% drop in malaria episodes per child between 2015-2019) and the introduction of Interceptor-2 bed nets. The distribution of new bed nets during the study may have further contributed to the reduction in malaria incidence, explaining the trial's lack of positive results. The study acknowledged that leveraging SMC and other MDA systems could be an effective way to improve coverage, as they achieved 70% coverage, and ivermectin distribution was efficiently conducted within three days. There were also logistical challenges related to enrolling pregnant individuals from the village.

The regimen 3 by 300 was well-tolerated, with no difference in severe adverse events between the two arms.
A Subgroup analysis is ongoing to assess the impact on five to ten-year-olds compared to those receiving SMC.

In addition to the study results, emerging entomology data was presented. The primary objective here was to evaluate the impact of the decrease in ivermectin exposure over time on mosquito survivorship, parity, and related factors. The data showed that Anopheles gambiae (80%) was the predominant mosquito species, with some other species present. Anopheles gambiae exhibited a predominantly zoophagic (blood meal distribution) behaviour, with approximately 80% of these mosquitoes feeding on humans. The live-caught mosquito data indicated reduced survivorship in ivermectin-treated mosquitoes compared to those in the intervention placebo group in 2019, although the effect was not dramatically pronounced.

Moreover, data from pharmacokinetic and pharmacodynamic (PKPD) assessments were discussed. Blood samples were collected at various time points, and it was observed that mosquitoes that fed on the blood of individuals treated with ivermectin died within four days. However, this effect diminished by day 14, suggesting that the 3 by 300 intervention did not have a significant impact beyond this point. Preliminary data indicated that five- to ten-year-olds had less impact on mosquitos than older age groups, possibly due to metabolic differences.

Following the presentation, the discussion opened with reflections on what could have been done differently. Participants considered the need for a better assessment of incidence or a method to assess transmission intensity prior to the trial. It was acknowledged that the study's sample size may have been limited due to the low malaria incidence, and even with a larger sample, the observable effect size would likely still be very small based on the existing data. The impact of COVID-19 in 2020 was also acknowledged as an additional challenge that affected the execution of the trial.

Age and drug effects on outcomes were examined during the discussion. It was pointed out that many drugs, especially those metabolized by CYP3A4, might have maturation effects, particularly in younger age groups. Changes in adolescent pubertal development were also considered as potential factors influencing the outcomes.

The discussion then delved into the definition of malaria, with a focus on the criteria used for diagnosis, including fever and rapid diagnostic test (RDT) results. Notably, episodes of malaria occurring within 14 days were eliminated from the analysis to ensure accurate data interpretation.

Lastly, the conversation addressed concerns about vector resistance in the study area, particularly concerning highly resistant vectors that may have been affected by ivermectin MDA pressure and the use of multiple insecticides. Participants suggested the need for further investigation to assess susceptibility in the populations.

- *Progress of the BOHEMIA trial, resented by Dr. Carlos Chaccour*

The BOHEMIA trial, launched in March 2022, faced initial delays due to approvals, regulatory challenges, and other hurdles. The MDA involved approximately 400 personnel.

Shortly after launching, the field team had to be called back due to the impact of a cyclone that resulted in flooding. The trial had a three-arm design, with one arm receiving ivermectin for humans and livestock, another for humans only, and a control arm receiving albendazole. The dosage for ivermectin was 400 micrograms per kilo, administered as a single dose once a month for three months.

The primary objective of the trial was to assess safety and efficacy. The primary outcome measure for efficacy was parasite or infection incidence a cohort of children under five. The study area was situated along the N1 road in Mozambique, and the implementation faced significant challenges due to a fifth cyclone that disrupted operations.
The challenges extended to the fieldworkers who experienced a spike in malaria cases. Cholera outbreaks in the community added to the difficulties, including reporting deaths. This situation, led to a reduction in clusters from 159 to a 100. Approximately 2,500 households were randomized in each arm, totalling almost 8,000 households.

Enrolment and visitation patterns were presented, showing good coverage, reaching 67% to 78% of the total population, and even higher percentages within the eligible population.

Repeated dosage and the number of tablets were initial concerns but were successfully addressed, with the community liaison team playing a pivotal role in community engagement. The presentation highlighted drug distribution processes and a decrease in the time taken for drug distribution over time.

Surveillance results were presented as raw data, indicating a significant reduction in the control arm's incidence rate between VC2 and VC3, with a threefold difference in the human and human-animal arms. Prevalence data also showed similar trends.

The team is processing PCR data for quality assurance and molecular analysis to calculate the molecular reports of infection, but mosquito parity data is awaited. Post hoc analysis is being conducted to gain a deeper understanding of the data. Coverage in the animal population, particularly pigs, is being measured, with concerns about data artifacts due to population fluctuations. The impact on vector distribution is uncertain.

In conclusion, the presented data was raw and lacked p-values or statistical testing, preventing definitive conclusions. The team emphasized the importance of the ongoing Kenya trial to provide more information and clarity.

- *MATAMAL : update and preliminary results, presented by Dr. Anna Last*

The project is a fully blinded, cluster-randomized, placebo-controlled trial conducted across multiple islands in Guinea-Bissau. It involves administering ivermectin in combination with dihydro-artemisinin piperaquine through Mass Drug Administration (MDA). The National Malaria Control Programme in the region carries out active case management, insecticide-treated net distribution every three years, and intermittent preventive treatment in pregnancy (IPTp) with slightly lower coverage. Seasonal Malaria Chemoprevention (SMC) is not conducted in this region, with a pilot round in the Bijagos in 2020. The project follows eligibility criteria, resulting in a 15% exclusion rate and a 2% refusal rate. The malaria seasonality in the study site is highly seasonal and stable, with increased vector population in August-September and case incidence in October and November each year.

The intervention assumed a baseline prevalence of 25% malaria in the study area and involved the administration of a 300 microgram per kilo per day dose over three consecutive days on three consecutive months during the transmission season. The goal was to determine if adding ivermectin MDA with dihydro-artemisinin piperaquine (DP) would have a greater impact on malaria transmission during this period (down from 25% to 10% in the DHA-p vs 5% in the combined).

The results of the clinical trial, which aimed to assess the impact of the treatment intervention on malaria prevalence, reported a downward trend in malaria incidence but no significant difference between the intervention and control groups.

During the discussion, different questions were raised about various aspects of the trial, including the baseline prevalence, drug potency, the potential added effect of ivermectin when given together with DP, and the challenge of detecting small differences. There were concerns about the current intervention's effectiveness and suggestions that it might be more effective when combined with other medications or distribution mechanisms. Seasonal variations in data and doubts about the current intervention's effectiveness in its current formulation were also highlighted.

The discussion concluded by emphasizing the evolving landscape of malaria interventions and the need for continued research in this area. It stressed the importance of achieving more durable effects and effective coverage, considering issues like absenteeism, and biting behaviour. The need to explore alternative formulations and combinations was also highlighted to enhance the intervention's effectiveness.

- *Ivermectin Mass Drug Administration in Surat Thani,Thailand, a low transmission setting, presented by Dr. Wang Nguitragool*

During the presentation, several key points were highlighted. First, there was mention of a new cost-effective ivermectin product available for analysis in Bangkok. Additionally, two upcoming paediatric ivermectin trials were introduced, which will evaluate safety, tolerability, pharmacokinetics, and efficacy. An innovative excipient developed at the University of Basel was discussed, showing potential to improve ivermectin administration, particularly in paediatric and geriatric populations.
The results of a study conducted in Surat Thani Island, Thailand, where malaria transmission is low (0,5%-1,5%), were presented. The study involved a cluster randomized trial with 10 treatment and 10 control clusters, starting in 2017 and continuing until

recently, partly due to the COVID-19 pandemic. The major mosquito species is *An. minimus* and the evaluation endpoints are malaria prevalence and mosquito parity rate.

The intervention consisted of monthly doses of ivermectin during the rainy season, accompanied by community preparation and three days of mass drug administration (MDA), followed by seven days of monitoring for adverse events, repeated for three rounds. The MDA achieved good population coverage, with nearly 80% after the first round, over 70% in the second, and about 70% in the third.

The study found no significant impact of ivermectin on malaria prevalence in the treated clusters compared to the control clusters. Potential reasons discussed included uncertainties about ivermectin's impact on the local major vector, variations in coverage between clusters, the fact that *P.vivax* is also present in the area, and the possible influence of parasite reservoirs in the environment.

During the discussion, questions were raised about the alignment of individuals covered by MDA with those getting infected, and whether the trial had sufficient statistical power to detect an impact. The discussion concluded with the understanding that the study did not show a significant reduction in malaria prevalence due to ivermectin treatment in this low transmission setting, raising questions about its effectiveness in such contexts.

- *Field evaluation of long-lasting veterinary ivermectin formulations and paediatric ivermectin by Kevin Kobylinski*

The presentation showed experiments that had been conducted ivermectin and its metabolites to examine the effects of different metabolites on mosquitoes. It was shown that three of these metabolites, produced after ivermectin treatment, had a lethal effect on mosquitoes similar to the parent compound. The study's tests included various mosquito species and yielded consistent results.

It was also presented the work conducted in Sumba Island, where they explored the impact of Ivermectin treatment on cattle and buffalo to control wild Anopheles mosquito populations. An effective, long-lasting Ivermectin formulation was tested, offering potential for future malaria control efforts, with a duration of over two months.

The presentation continued with the upcoming paediatric ivermectin studies aimed at assessing the drug's safety, tolerability, pharmacokinetics, and efficacy in children under 15 kg. A new paediatric Ivermectin formulation being developed at University Basel was presented. The novel excipient is designed to dissolve rapidly, making it more suitable for young children.

During the Q&A session, various topics were discussed, including other malaria control interventions, the cost of treating livestock, the potential synergistic effects of Ivermectin in combination with other interventions, and the challenges of ensuring that animal-based strategies reach all affected villages, considering the diversity of vector species.

- *Ivermectin to domestic animals against malaria in Burkin Faso*

The presentation showcased the work conducted in Burkina Faso to evaluate the effectiveness of a One Health approach in combating malaria. The study focused on using ivermectin to treat domestic animals and assess its impact on malaria transmission. Burkina Faso, where the study

was conducted, was deemed suitable for this approach due to the prevalence of cattle and other domestic animals.

The study featured a complex design with multiple arms evaluating the treatment of various domestic animal species in clusters, 8 clusters per arm, of around 300 individuals. The baseline for the study is defined as an average of one clinical malaria episode per person-year. The Key outcomes included malaria incidence (through passive case detection) to all the participants, malaria case prevalence and infection prevalence to 0-18 years old, while various interventions like indoor residual spraying, larvicides, and education were compared for their impact on malaria control.

The study consisted in monthly injection of the therapeutic recommended dose to cattle, sheep and goats. It also involved collecting mosquitoes that had fed on the treated animals, revealing a significant reduction in malaria prevalence due to ivermectin treatment. Owners of treated animals expressed high satisfaction with the approach and willingness to continue.

Future plans included developing a long-acting ivermectin formulation and seeking trial extensions, with the ultimate goal of WHO recommendation and integration into malaria control programs.

In a follow-up discussion, the speaker emphasized the long-acting ivermectin's efficacy in reducing malaria transmission, particularly in areas with resistant mosquitoes. The results showed sustained efficacy over several months, meeting WHO criteria and potentially addressing logistical challenges associated with multiple doses.

The discussion concluded by highlighting government and donor enthusiasm for cost-effective interventions and collaboration on a research paper to expedite the adoption of long-acting ivermectin in the field.

2. Innovation on ivermectin

- *Long-acting injectable formulation of ivermectin as a new vector control tool to reduce malaria transmission, IMPACT project, by Dr. Patrick Boen*

Patrick Boen presented an update regarding the development of a sustained-release ivermectin formulation by Lyndra Therapeutics. Lyndra Therapeutics, established in 2015, specializes in the creation of extended-release therapeutic solutions using their proprietary Lynx drug delivery platform. This platform is designed to facilitate prolonged drug release, thereby enhancing the efficacy of treatments. The Lynx Drug Delivery Platform operates via a specialized, stomach-dissolvable capsule that releases a drug-forming structure, enabling controlled and sustained drug release over a predetermined duration.

The primary focus of the presentation was the development of a 14-day sustained-release ivermectin formulation with the overarching objective of mitigating malaria infections in regions where the disease is endemic. Lyndra conducted a Phase 1 study to evaluate the safety, tolerability, and pharmacokinetics of this formulation, which encompassed multiple cohorts and entailed the monitoring of gastric retention through medical imaging. Unfortunately, the study had to be terminated prematurely due to lower-than-expected exposure levels.

Results from the pilot cohort indicated an average gastric retention period of approximately 6.8 days, falling short of the intended 14-day target. Nevertheless, subsequent enhancements within the first cohort improved gastric retention, with an average duration of 10.6 days.

Sustained drug release was observed in all participants throughout the 14-day assessment period, and membrane feeding studies were conducted to gauge its impact on mosquito survival.

The presentation concluded that suboptimal drug release was the primary factor contributing to the lower-than-expected exposure levels. Lyndra Therapeutics is actively engaged in refining the formulation through various strategies, such as enhancing solubility and optimizing the drug's solid form to enable more extended drug segments. The company maintains confidence in achieving the target concentrations for prolonged durations, and a second Phase 1 study is planned to finalize the initial phase of the project.

During the final discussion, participants acknowledged the potential utility of Ivermectin as a tool for controlling malaria transmission. They also engaged in conversations regarding the challenges encountered and lessons learned in the development process.

- *Exploiting insect tyrosine metabolism for vector control, by Álvaro Acosta*

The presentation focused on the potential repurposing of a compound called Nitisinone for combating mosquito-borne diseases such as malaria. This chemistry was originally produced as a herbicide by Syngenta and then FDA-approved to treat human diseases involved in tyrosine catabolism. The compound targets an enzyme, HPPD, which is essential an conserved across various species of arthropods vectors but has no effect on sugar feeder insects. Experiments indicate that nitisinone exhibits significant mosquitocidal capabilities and can be used either orally, or as insecticide or in attractive targeted sugar baits. Challenges include the high cost, which is currently addressed through partnerships, and the need for further field testing. Finally, the successful HPPD based gene knockout experiments, conducted in collaboration with mosquito genetics expert Tony Nolan, offered promise for future gene-drives applications.

3. Final discussion

The discussion opened with a message of appreciation for the participants, encompassing researchers, experts, and funders who have collectively contributed to the discussion.

The conversation progressed into an examination of the various challenges encountered in previous studies, with a focus on the design and execution of these studies and the potential improvements that could be made in future initiatives.

Key points discussed during the meeting included:

1. Cost reduction trough collaboration: Participants discussed the need for cost-effective strategies that could make Ivermectin more accessible for vector control programs. Collaborative efforts between research organizations and funders were suggested as means to reduce the financial burden of such initiatives.
2. Safety and side effects: Concerns were raised regarding the safety of Ivermectin, especially when considering its prolonged use in vector control programs. Participants emphasized the importance of ensuring that any intervention involving Ivermectin should prioritize the safety of both the targeted population and the environment.

3. Selective lethality to blood-fed mosquitoes: Some participants highlighted the unique feature of Ivermectin, its ability to selectively affect blood-fed mosquitoes. This specificity was seen as a potential advantage, as it could potentially minimize harm to non-target organisms while still reducing mosquito populations.
4. Timing and dosing challenges: The discussion delved into the timing of interventions and the complexities of dosing Ivermectin, especially in regions where mosquito populations exhibit seasonal fluctuations. The challenges of administering Ivermectin when these populations vary over time were discussed in detail.
5. Coverage and eligibility: Some participants expressed concerns about the limited coverage of the population, as many individuals are either ineligible or absent during intervention programs. This led to a debate on the definition of effective coverage for vector control initiatives.
6. Gene-drive technology: the meeting touched on the prospects of combining Ivermectin with gene-drive technology to more effectively reduce mosquito populations. This approach was considered as a potential way to achieve lasting effects in vector control.
7. Long-Acting Formulation: Participants discussed the potential benefits of a long-acting Ivermectin formulation and its relevance for malaria control.
8. Combination with other drugs: The combination of Ivermectin with other antimalarial drugs, such as DP (Dihydroartemisinin-Piperaquine), was explored. It was suggested that Ivermectin's benefits might be more evident in those who didn't receive DP.

4. Closing

The discussion ended with words of appreciation for the participants and an invitation to continue the conversation.

In conclusion, the meeting brought to light the multifaceted nature of ivermectin-based vector control strategies and the associated challenges. The conversation underscored the importance of ongoing research and adaptation to enhance the efficacy of these interventions. As additional analyses of the trials are conducted, participants were encouraged to engage in further deliberations.

LIST OF PARTICIPANTS

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