IVERMEN Briefing Summary Report

April 24th, 2024
Kigali Convention Centre, Rwanda

Background and introduction

This report summarizes an overview of the discussions taken place during the ivermen meeting held on April 24th during the 2024 MIM congress, as a follow-up to the last Ivermen meeting in Chicago, convened by Carlos Chaccour and Kevin Kobylinski. The aim was to present the results of the BOHEMIA project, including both clinical trials in Mopeia, Mozambique and in Kwale, Kenya and discuss the way forward and elements to be considered for a potential implementation of this tool. Active stakeholders, including partners, donors, civil society, academia, and national programs were invited to debate on the suitability of ivermectin for malaria and discuss an adequate approach.

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 Kwale, Kenya and Mopeia, Mozambique were presented. Opposite results were observed and factors for these divergent results were discussed. The meeting concluded with a list of different items that still need a response 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.

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

Carlos Chaccour presented the results of the BOHEMIA trial, which comprised two clinical trials conducted in Mopeia, Mozambique, and Kwale, Kenya. The outcomes of both trials varied significantly.

In Mopeia, adverse weather conditions, including flooding and a cholera outbreak, delayed the trial's start until after 80% of the rainy season had passed. This delay, coupled with the protracted time taken to administer Mass Drug Administration (MDA) – approximately 3-4 weeks – which likely contributed to the absence of a positive impact of ivermectin on reducing malaria incidence.

Key takeaways from the Mopeia trial include:

- Despite reaching coverage targets, the trial encountered challenges such as a delayed start, smaller buffer zones than planned, and asynchrony in distribution. Distribution also suffered due to the region's high malaria burden, with a prevalence of 60% by RDT.

- Anopheles mosquitoes exhibited a high entomological inoculation rate (EIR) ranging from 20-40 for An. funestus and 10 for An. gambiae, alongside significant metabolic resistance.
- Bio-efficacy studies confirmed the intervention's effectiveness in wild anophelines.
- However, no measurable impact of ivermectin on malaria incidence was detected.

Conversely, the Kwale trial incorporated lessons learned from Mopeia, resulting in improved outcomes. Administering ivermectin just before the onset of heavy rainfall and streamlining MDA delivery to a few days significantly expedited processes.

Key findings from the Kwale trial include:

- Not only did the trial meet its coverage goals, but it also exceeded them.
- Distribution was markedly faster. The trial started just before the 'short rains.'
- Despite a higher-than-expected disease burden – with a 30% prevalence by RDT – the intervention's bio-efficacy was confirmed.
- A measurable impact of 20% on malaria incidence was observed.

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.

Q&A

During the Q&A session led by Carlos, various aspects of the BOHEMIA trial were asked for clarity and depth.

- Field implementation complexities:
  - uniformity of cluster creation and the presence of a 400-meter buffer zone at both sites. It was confirmed that these procedures were consistent across locations.
- Study design: about the demographic specifics of prevalence measurement, revealing differences between Mozambique and Kenya in terms of age groups assessed.
- IRS usage: Concerns were raised about a shift in IRS products from actellic to bendiocarb, prompting reflection on the potential implications of this change and the time when it took place.
- Distribution timeline: Although some impact was discernible when analysing the fastest delivery clusters in certain areas of the Mopeia trial, the observed effect lacked the necessary strength to draw any conclusions.
- Bioassay methodologies, including the number of mosquitoes used per assay and the replication protocol. It was explained that approximately 50 mosquitoes were utilized per assay, with three replicates conducted for each.
- Pharmacokinetic studies: it was clarified that the collection of blood samples to test ivermectin concentration was done during the intervention.

- Dosing considerations: suggestions to explore potential dose increases. However, regulatory constraints posed challenges in implementing such adjustments promptly.
- Decision to proceed with the study despite weather-related challenges in Mopeia. The team defended the decision, citing logistical and regulatory constraints and the impracticality of delaying the trial for another year.

In contemplating the possibility of conducting the study again in Mozambique, discussions revolved around potential alterations in timing and frequency of intervention rounds, as it was applied in Kenya. It was suggested starting the trial in December and conducting five rounds. These changes could yield different outcomes.

2. Design strategies to maintain power in epidemiological malaria cluster randomised trials with large between cluster heterogeneity: a meta-analysis.

Joseph Biggs presented the implications of high heterogeneity between clusters within the trial design, which significantly increases uncertainty regarding the effect size. Joe outlined the key components of sample size calculation, emphasizing the importance of accounting for predicted heterogeneity, which is often estimated due to a lack of prior population data.
To further understand the impact of cluster heterogeneity, a meta-analysis was conducted. By retro-calculating observed k from cluster-level data of prevalence and incidence from 21 trials, along with covariates, it was found that heterogeneity in the data was substantial.

The aims and results of the meta-analysis were as follows:

1. **Characterizing Cluster Heterogeneity:**
    - Retro-calculated observed heterogeneity (k) was higher (mean of 0.5) than the mean estimated k 0.3.
    - Stability of k varied, being more consistent in high transmission settings and more variable in low transmission settings.
2. **Impact of Cluster Heterogeneity on Statistical Power:**
    - Predicted k was consistently lower than observed k, indicating underestimation of cluster heterogeneity.
    - Consequently, statistical power was much lower than expected, posing challenges in trial design.
    - Potential solutions were discussed, such as increasing the number of clusters or seeking a larger effect size, though these are complex actions.
3. **Factors Influencing Cluster Heterogeneity:**
    - Endemicity: Less prevalence was associated with lower k.
    - Outcome Measure: Studies with prevalence outcomes had lower k compared to those with incidence as the outcome measure.
    - Seasonality: Higher k was observed in studies conducted during the wet season, although wet season studies also exhibited a higher effect size, offsetting the lower k.

- Intervention Coverage: Overall coverage did not significantly impact k, but further clarification was needed on another factor mentioned.

The conclusion of the presentation was the following:

- Malaria cluster randomized trials (CRTs) exhibit high between-cluster heterogeneity (k), which undermines the desired study power.
- The observed high k compromises the effectiveness of these trials.
- To improve future trials, researchers suggest utilizing study site transmission data (prevalence/incidence) to derive more accurate estimates of k.
- Additionally, future trials should consider factors such as the seasonality of excess sensitivity (XS) surveys and the variability in cluster-level intervention coverage.
- Moving forward, researchers propose investigating whether adaptive or alternate trial designs can help maintain power in malaria CRTs.

Q&A

Questions regarding the presentation were related to:

- Exploring Minimum Detectable Effect Size:
  There was a proposal to utilize data from all trials to calculate the minimum detectable effect size and make decisions based on the results. The consensus leaned towards viewing this as a favorable starting point.
- Assessment of Heterogeneity:
  An inquiry was made into whether heterogeneity (observed k) was considered in the Kwale trial. It was acknowledged that heterogeneity had been assessed, but due to recent unblinding, there was hesitancy to share specific details at that moment.
- Consideration of Sample Size Increase:
  The discussion revolved around the feasibility and potential benefits of increasing the sample size either in space (more clusters) or time (more follow-up visits), with the assumption that cost would not be a limiting factor. It was concluded that while increasing follow-up data might marginally enhance statistical power, low heterogeneity remained a critical factor.
- Evaluation of Hazard Ratios:
  Participants considered the relevance and utility of examining hazard ratios in the context of the trial. While it was noted that hazard ratios could provide insight, it was acknowledged that they alone might not influence the results positively.

- Effectiveness of Existing Interventions:
  Questions arose regarding the effectiveness of existing tools such as IRS and LLINs in addressing malaria burden. There was discussion on the potential challenges in perceiving impact, particularly amidst a significant malaria burden, despite the utilization of proven interventions.
- Approaches to Implementation:
  The group explored potential implementation models, including the SMC model (door-to-door) or NTD model (community). However, concerns were raised regarding distribution timeframes, particularly in the case of the NTD model, where flexibility in delivery schedules might pose challenges.
- Practical Considerations for Implementation:
  Practical considerations for implementation, such as the potential benefits of a shorter distribution period in reducing adverse events related to the program, were discussed. The consensus leaned towards recognizing the importance of shorter distribution periods in minimizing associated risks.

3. Discussion

Carlos opens the discussion with several questions to provoke the reaction of the audience: What do we think is the next step? If we had to collectively design the best trial ever, how would we do it? Is Ivermectin worth testing further, is this interesting? Should the money go somewhere else?

Summary of the debate

1. **Need for Additional Trials** It was commented the need for additional trials to demonstrate efficacy, particularly when focusing on ivermectin without additional interventions- although this is not how ivermectin would be implemented. It was clarified that VCAG needs two positive trials to validate the efficacy of ivermectin, emphasizing the importance of generating comprehensive data for decision-making.
2. **Pathways to increase impact**: There was uncertainty on whether a new a trial could show efficacy above 20%. The team believed that treating livestock could potentially yield higher efficacy outcomes. Increasing the dosage or frequency of ivermectin administration might also enhance its impact on malaria transmission.
3. **One Health Approach**: Participants discussed the potential benefits of a One Health approach, considering both human and animal health, advocating for an integrated approach that addresses multiple health challenges simultaneously (scabies, headslice, healthier animals that lead to more productivity...) However, challenges related to governance and ethics approval were acknowledged. In that sense, a participant noted that Nigeria is bypassing WHO requirements for azithromycin, suggesting that

countries prioritize interventions based on their own needs and questions rather than solely relying on international recommendations. It was also highlighted that due to the short antimalarials for chemoprevention and the increasing resistance, ivermectin could be used to save current use of antimalarials for chemoprevention, such as ACTs. An increase of insecticide resistance could lead to an increase of outdoor transmission which ivermectin could be beneficial too. A comment was made from a national program perspective, stating that the results of the two trials would not be sufficient for implementing at national level, but as a holistic and one health perspective it could be considered. It was also highlighted the fact that A.Stephensi is zoophilic and ivermectin could pose an additional benefit.

4. **Deployment Considerations:** Concerns were raised regarding the practical deployment of ivermectin and its associated costs. Participants stressed the need for cost-effectiveness analyses and consideration of country-specific needs.
5. **Safety and Adverse Events**: Safety standards and adverse events monitoring were discussed, with reassurance provided regarding compliance with WHO guidelines.
6. **Potential Economic Benefits / Return on Investment (ROI) Analysis**: the potential economic benefits of ivermectin, including its impact on livestock health and productivity, were discussed and suggested the importance of analyzing existing data and conducting cost-benefit analyses to assess the feasibility and impact of One Health interventions. Conducting a ROI analysis on the One Health approach was proposed. This could provide valuable insights into the economic viability of integrated health strategies.
7. **Data Utilization and Analysis**: the importance of analyzing existing data to assess the feasibility and impact of One Health interventions was remarked.

4. Closing

Gina concluded the meeting with final remarks, focusing on the need for another trial that includes a veterinary arm, a different number of rounds and distribution, and with a One Health approach to achieve higher impact.

She also expressed gratitude to the team and partners involved in the project and appreciated the very rich discussions due to diverse background of participants. She acknowledged the complexity of Randomized Control Trials (RCTs), the importance of hearing the country invoice, and announced plans for further discussions at the upcoming ASTMH meeting. She emphasized the need for continued exploration and deeper understanding of the intervention's potential.

List of attendees (falta revisar)

Almudena Sanz, Barcelona Institute for Global Health
Anna Trett Liverpool School of Tropical Medicine
Carlos Chaccour, Barcelona Institute for Global Health
Charlotte Eddis, Population Services International (PSI)
Cheick Ouédraogo, Institut de Recherche en Sciences de la Santé
Cassidy Rist, Virginia Tech
Fabrice Somé, Institut de Recherche en Sciences de la Santé
Felix Hammann, Swiss Insel Hospital
Franck Dongmo, Centre for Research in Infectious Diseases, Cameroon.
Hanna Koenker, PATH
Joseph Challenger, Imperial College
Jackie Cook, London School of Tropical Medicine and Hygiene
Joseph Mwangangi, KEMRI Wellcome
Joel Tarning, Malaria Oxford Tropical Medicine Research Unit
Joseph Biggs, London School of Tropical Medicine and Hygiene
Jessica Rockwood, IPHA
Kevin Baker, Malaria Consortium
Mildred Shieshia, PMI
Emmanuel Sougué, Institute de la Recherche en Sciences de la Santé
MARY MAEL, Barcelona Institute for Global Health
Molly Robertson, The Global Fund
Nicholas Luter, Bill and Melinda Gates Foundation
Nika Gorski, Barcelona Institute for Global health
Nilani Chandradeva, Imperial College
Paula Ruiz-Castillo, Barcelona Institute for Global Health
Regina Rabinovich, Barcelona Institute for Global Health
Thomas Churcher, Imperial College
Ambachew YOHANNES, Unitaid
Abdisalan Noor, University of Harvard
Anna Trett, Liverpool School of Tropical Medicine
Ellie Sherrard-Smith, Imperial College
Hannah Slater, PATH
James Tibenderana, Malaria Consortium
George Jagoe, Medicines for Malaria Venture
Justin Cohen, Clinton Health Access Initiative
Joseph Mwangangi, KEMRI-Wellcome
Milred Shieshia- USAID
Nakul Chitnis, Swiss TPH
Nana Aba Williams, MESA, Barcelona Institute for Global Health
Neil Lobo, University of Notre Dame
Olusa Oresanya- Malaria Consortium
Jimmy Opigo, NMCP Uganda
Rukaari Medard, Malaria Control Division, MoH of Uganda
Tara Seethaler, CHAI
Victor Sumbi, USAID
Nelli Westercamp, PMI