Summary:

In November 2014, the APMEN Vivax Working Group held a 2 day workshop entitled “Analysis and Interpretation of Vivax Antimalarial Efficacy Studies” in Siem Reap, Cambodia.

This workshop was attended by researchers involved in the APMEN funded clinical antimalarial studies and researchers with expertise in clinical trial design and analysis. The aim of the workshop was to exchange experiences and discuss approaches to data analysis and presentation of these trials. Datasets from studies in Bhutan, Malaysia, Vanuatu and Bangladesh were analysed.

Preliminary data analysis showed that the current first line treatments in Bhutan and Bangladesh work well, whereas reduced efficacy of first line treatments has been found in the studies in Malaysia and Vanuatu.

Participants discussed the need to review clinical study design and objectives in the light of decreasing number of cases. Greater focus on case detection and management and a focus on adherence and effectiveness could address this problem.

1. Background:

The APMEN VxWG group technical grant program funded three clinical studies around efficacy and safety of treatment against vivax malaria in Bhutan, Malaysia and the Solomon Island and Vanuatu. Additional funding was obtained for two pharmacovigilance studies, one ongoing in Bangladesh and another site to be determined.

Map of sites:
Researchers undertaking these four studies were invited to meet and exchange experience in study design and conduct of the respective trials, to develop a statistical, to perform some preliminary analyses and discuss the implications of preliminary results for further research and program managers. Participants had time to discuss specific issues and challenges with regards to the study design and their implementation. Group work was conducted using 4 different datasets from Bhutan, Malaysia, Vanuatu and Bangladesh. Participants also discussed the implication that the preliminary results may have for further research and program managers in the respective countries.

2. The workshop

The agenda of the workshop contained three different overarching topics each including a series of sessions. Most sessions were divided into presentations and round table discussions or group work. In brief:

**TOPIC 1: Exchange experience**
- Session 1: Study Protocol
- Session 2: Challenges

**TOPIC 2: Data Cleaning**
- Session 3: Data cleaning

**TOPIC 3: Data Analyses**
- Session 4: Statistical Analysis Plan (SAP)
- Session 5: WWARN Report
- Session 6: Data analyses
- Session 7: Implications

**Participants:**
- Kinley Penjor, Tobgye Drukpal, Sonam Wangchuk (Bhutan study)
- Matt Grigg and Giri Rajahram (Malaysia study)
- Wasif Khan (Bangladesh study)
- Harin Karunajeewa (WEHI), Lyndes Wini, Lawrence Boe, Esau Naket (Sols & Vanuatu study)
- Lorenz von Seidlein (MORU)
- Kevin Baird (EOCRU)
- Ric Price, Kamala Ley-Thriemer (Menzies)
- Lek Desoley (NMCP Cambodia)

**Exchange experience:** In the first session participants from the four studies gave an overview of their study protocols. The second session was dedicated to the challenges that researchers faced when implementing their studies. Challenges described were mainly around difficult access to remote sites, and problems recruiting patients due to political instability and low number of patients with clinical malaria in pre-elimination settings.

**Data Cleaning:** The session started with a presentation by Ric Price, focusing on how a database should look like and a brief introduction on how to merge different data files. This was followed by group work where participants assessed their own datasets and checked the need for further verification with the source data.
Data Analyses: The last topic started with a session on how to prepare a statistical plan (SAP) for an antimalarial clinical trial by Kamala Ley-Thriemer. Participants then broke into 4 groups to develop their own SAPs. This was followed by a short feedback session to the entire group. The second session within this topic was dedicated to the automated WWARN reports. Participants had uploaded their data into the WWARN system for curation and preparation of a vivax specific report, which is currently developed by WWARN. Ric Price started the session with a short presentation and overview of the WWARN curation system. Participants then received the automated reports for their specific studies and had time for review. This was followed by more group work to start preliminary data analyses on issues not covered in the WWARN report (for more details on specific studies please see the result section). Participants reported their results back to the group before starting a final wrap up round table discussion looking at the implication the results have for future research (please see the conclusion section).

3. Results

3.1. Bhutan
Aim: To assess the therapeutic response of chloroquine (CQ) plus primaquine (PQ) treatment for uncomplicated vivax malaria in Bhutan
Study Type: Observational, single arm study
Treatment: CQ 3 days followed by PQ 14 days, directly observed therapy (DOT)
Follow up: 1 year
Status: 24 patients enrolled
Preliminary results showed CQ+ PQ works well in Bhutan, with no recurrences within 28 days.

3.2. Malaysia
Aim: To determine whether the fixed combination of mefloquine+artesunate (MAS) is superior to chloroquine for the treatment of uncomplicated P. vivax infection in adults and children in Sabah, Malaysia
Study type: randomized trial
Treatment: MAS +PQ versus CQ+PQ, in both cases PQ delayed until day 28.
Follow up: until day 42, via phone until 1 year
Status: 77 patients enrolled
Preliminary results show evidence for significant chloroquine resistance, but excellent response with MAS.

3.3. Solomon Island & Vanuatu
Aim: to define and compare the efficacy of standard and high-dose primaquine in preventing early relapses from P. vivax in Solomon Islands and Vanuatu. Primaquine was added to the current standard schizontocidal treatment regimen artemether-lumenfantrine (AL)
Study type: randomized trial
Treatment: AL+PQ (0.25mg/kg/day) versus AL+PQ (0.5mg/kg/day) versus AL
Follow up: 3 months
Status: 35 patients enrolled in Vanuatu
Preliminary analyses suggested lack of efficacy of high dose primaquine that could reflect a number of factors such as adherence, reduced metabolism of lumefantrine and drug quality. Investigations are ongoing to address these.

3.4. Bangladesh
Aim: To assess safety unsupervised PQ treatment in *P. vivax* and *P. falciparum* patients in Bangladesh (Pharmacovigilance study)
Study type: Observational
Treatment: CQ + PQ (14 d) for vivax and AL+PQ (single dose) for falciparum. PQ on day 3
Follow up: 28 days after PQ start
Preliminary analyses showed that CQ+PQ (14d) is still effective treatment for *P. vivax* infection and that AL + single dose PQ is effective in *P. falciparum*.

4. Conclusions

The workshop highlighted some of the challenges in delivering and interpreting antimalarial efficacy of *P. vivax*, particularly in the pre-elimination setting. Participants discussed the need to review clinical study design and objectives in the light of decreasing number of cases in all the participating countries. Suggestions included putting greater focus on case detection and management and shift the focus more to adherence and effectiveness studies than traditional efficacy trials. Drawing from the experiences in the Bangladesh study the way forward maybe to include patients with all plasmodium species (e.g. all patients who will be treated with antimalarials) into trials to create synergisms and maximise programmatic information. Subsequent subgroup analysis would help to provide a more conventional analysis for antimalarial efficacy.

Similar standard operating procedures (SOPs), clinical record forms (CRFs) and collection methods (e.g. databases) throughout different studies will greatly help in analysis and ultimately pooling data for a regional overview.

Poor drug quality and issues of adherence and absorption are critical when interpreting treatment efficacy. Discussions emphasised the importance of including pharmacokinetic and molecular analyses into clinical trials. Trials to rationalise radical cure and the efficacy of different primaquine regimens will require randomised control trials with prolonged follow up and large numbers of patients. These would be extremely difficult for single site studies and will require a multicentred approach.