Summary of APMEN VxWG meeting in Bangkok, Thailand on 12th and 13th of October, 2015

**Day 1**

1. **Welcome, introduction, PNG country update and WHO technical brief**

*Chair: Dr. Sanchai Chasombat*

**Welcome and introduction**
Country partners were welcomed by Dr Sanchai Chasombat who highlighted the importance of *P. vivax* for the elimination of malaria in the APMEN region. In contrast to *P. falciparum*, *P. vivax* infections in the APMEN region decrease at a much slower rate, rendering the parasite of significant importance to the endgame of malaria. Prof Ric Price introduced attending member country representatives and research partners and introduced the objective of the meeting: to review the research priorities for a future VxWG agenda. The meeting was generously supported by Medicines for Malaria Venture (MMV), who were represented by Dr Penny Grewal Daumerie.

**New APMEN member presentation: Papua New Guinea (PNG)**
Dr Leonard Nawara highlighted the significant public health burden caused by malaria within PNG. The national malaria treatment guidelines mostly follow WHO recommendations and a 14 day primaquine regimen is included in the national malaria treatment guidelines for *P. vivax* and *P. ovale* infections in the absence of routine G6PD testing.

Overall malaria cases have fallen from 205 per 1000 population in 2010/11 to 48 per 1000 in 2013/14. However the burden of malaria remains high in many parts of the country. The distribution of malaria cases and incidence numbers varies considerable between highland inhabitants who are affected much less and inhabitants of the coastal areas who are at greater risk.

**WHO technical brief**
Dr Maria Bustos introduced the recently published WHO technical brief on *P. vivax* ([http://www.who.int/malaria/publications/atoz/9789241509244/en/](http://www.who.int/malaria/publications/atoz/9789241509244/en/)) that was compiled following the WHO acknowledgement in 2012 that the majority of technical guidance was aimed at *P. falciparum* in an African context. The vivax specific technical brief was formulated by a scientific committee which started working in 2013, with several representatives from the APMEN vivax working group involved in the process. The technical brief is divided into 8 technical areas, highlights the challenges associated with *P. vivax* and provides strategies for control and elimination of the parasite.

Prof Kevin Baird, the Chair of the WHO writing committee, highlighted that *P. vivax* is the dominant species throughout much of the Asia Pacific, with large fractions of the population not receiving effective radical cure. In addition there is increasing resistance of the parasite to some of the anti-malarials currently in use. Despite this alarming development vivax malaria has not been considered a serious threat, mostly due to its clinical manifestations. There is increasing evidence that this asymptomatic and mostly sub-patent reservoir contributes significantly to morbidity, mortality and disease propagation and is a major challenge to the eradication of malaria from the APMEN region.
2. G6PD diagnostics

Chair: Dr Effie Espino

Challenges of introducing routine G6PD testing into radical cure
Dr Benedikt Ley gave a brief overview of primaquine as the only hypnozoitocidal drug currently on the market and G6PD deficiency, a considerable risk factor for primaquine induced haemolysis. A potential solution to the dilemma of providing radical cure at the risk of haemolysis or withholding treatment at the risk of a relapse are diagnostic assays to determine the G6PD status. Those tests can be grouped into quantitative and qualitative categories, depending on their output. While operational characteristics of the majority of qualitative diagnostics assays are superior to quantitative test devices, quantitative tests can potentially identify heterozygous women. Concerns were raised that G6PD testing has to be implemented immediately to promote radical cure, whereas quantitative test devices are not ready for implementation yet. Preliminary results of an ongoing qualitative assessment on the key barriers to the implementation of routine G6PD testing were presented. Key barriers are the fear of additional costs, decision makers being unaware of test formats available and neglecting the seriousness of vivax malaria.

RDT G6PD testing in Laos
Dr. Simone Nambanya from the Peoples republic of Laos gave a talk on the potential to integrate the G6PD RDT from Carestart (USA) into routine testing. The test follows a similar format as a malaria RDT and requires a drop of blood. A G6PD normal result triggers a darkening of the test membrane. In contrast to the widely used fluorescent spot test the G6PD RDT does not require any laboratory infrastructure, however is hampered by a maximum temperature range of 32°C, too low for many tropical settings. The question was discussed whether readings made above 32°C can be considered. The test was implemented in the course of a research project that is ongoing at three sites. Preliminary results indicate a G6PD deficiency prevalence ranging from 3.9% to 7.1% across all sites (average 6.5% among 263 participants).

Quantitative G6PD test devices in Bangladesh
Dr Wasif Ali Khan summarized the Bangladeshi malaria control and elimination efforts and pointed out that much of the malaria reduction has been achieved in *P. falciparum* infections and to a much lesser degree in *P. vivax* infections. While primaquine is part of the routine malaria treatment guidelines for *P. vivax* infections, routine G6PD testing is not included in the guidelines. One of the studies conducted by the icddr,b evaluates a set of novel diagnostic devices that could be integrated into routine testing. The study is ongoing and at the time point of presentation only data for the WST 8/ 1 PMS – methoxy (Dojindo, Japan) test were available, which indicate moderate to good correlation to the reference method spectrophotometry. The evaluation of a second, handheld, quantitative device, a Biosensor (Carestart, USA), is pending.

3. Realigning Priorities

Chair: Prof Ric Price

Research priorities were identified in two parallel sessions. Country partners were asked to generate an agenda of high and low priorities and in parallel research partners were asked to do the same. The outcome of the respective sessions was subsequently compared and discussed by all partners in a joint round (for an overview of the identified priorities see appendix 1).
Day 2

4. Malaria Diagnostics

Chair: Dr Benedikt Ley

Sub – microscopic *P. vivax* infections and molecular detection

Dr Qin Cheng presented studies showing that decreasing numbers of microscopic *P. vivax* malaria infections do not result in lower numbers of sub-microscopic infections, the relative proportion of sub-microscopic infections increases with decreasing burden of disease. On average (with great geographical variations) approximately 70% of all true vivax infections worldwide are sub-microscopic. It has been shown that sub-microscopic *P. vivax* infections contribute to transmission dynamics, however the extent and exact relation will require further studies. While overlap is not 100%, the great majority of patients suffering from sub-microscopic infection is asymptomatic. The very large fraction of sub-microscopic and asymptomatic infections due to *P. vivax* call for the wide distribution of highly sensitive, molecular, diagnostic methods. Ideally methods such as LAMP are made available for field use.

Malaria Microscopy Quality Control in Research

Dr Mehul Dhorda gave a presentation highlighting the importance of quality assurance in times where most research and malaria programs consist of multiple actors that can potentially introduce an error into diagnostic and data collection pathways. Quality assurance therefore aims to provide reproducible and comparable results on a standardised basis. A detailed description of the proposed malaria microscopy quality control mechanisms can be found online under [http://www.who.int/tdr/publications/microscopy_detec_ident_quantif/en/](http://www.who.int/tdr/publications/microscopy_detec_ident_quantif/en/) (last accessed on 20.10.2015).

5. Roadblock on the way to elimination: sub-microscopic malaria

Chair: Dr Lorenz von Seidlein

Estimating the reservoir of asymptomatic and sub-microscopic malaria infections

Prof Arjen Dondorp highlighted the large asymptomatic and sub-microscopic malaria reservoir within malaria endemic areas and the danger of promoting drug resistance if interventions to eliminate malaria are not conducted in a timely manner. The question remains whether DNA at very low levels of detection indicates very low parasitaemia or just the presence of DNA fragments from an overcome malaria episode. A recent study found a very good correlation between parasite counts done by DNA based and RNA based diagnostic molecular methods, indicating that live parasites can be found at very low densities in the human host. Sub-microscopic infections, also at very low parasite densities, represent a considerable fraction of malaria infections and contribute to transmission. Specifically in pre-elimination settings the danger to select for drug resistant malaria parasites among sub-microscopic infections is high, addressing the sub-microscopic reservoir is therefore of utmost importance. Any elimination approach will have to rely on a comprehensive set of strategies including treatment, testing and a good infrastructure to detect and respond to malaria cases. Addressing this reservoir will among other measures have to include a well working infrastructure to test, treat and track affected individuals, and consider physical barriers as prophylactic measures.

The sub-microscopic parasite reservoir in study sites in Myanmar, Cambodia and Vietnam
Dr Lorenz von Seidlein highlighted that the proportion of sub-microscopic vivax infections increases with decreasing slide positivity rate, the more advanced a setting is in malaria elimination, the more prominent this reservoir becomes. Dr von Seidlein and his team had conducted targeted malaria elimination programs in three countries across South-East Asia providing an ACT and PQ to identified populations at high risk. The study populations were followed up for 12 months. Among 7355 residents a RDT prevalence rate of 4%, microscopy prevalence rate of 5% and a qPCR prevalence rate of 20% was observed.

**Roadblocks on the way to elimination: sub-microscopic malaria**

Dr Tom Peto presented the results of a longitudinal study from Pailin, Cambodia. Five cross sectional surveys were conducted in three villages with 1500 inhabitants over the period of one year and participants were tested for malaria by microscopy, RDT, qPCR and nested PCR. Participants who were parasitaemic at enrolment were followed on a monthly basis and assessed for the presence of parasitaemia. Key findings of the study were the presence of a large hidden sub-microscopic malaria reservoir within the study population and the finding that sub-clinical *P. falciparum* infections do not persist, whereas *P. vivax* infections do.

**Prospects for malaria elimination in SE Asia**

Dr Ricardo Aguas presented results of modelling efforts underlining findings from the field presented earlier. In summary these findings include the importance to address sub-microscopic infections in order to achieve malaria elimination, radical cure as an essential part of any elimination strategy and that due to logistical constraints mass drug administration programs appear to be more feasible than any other malaria elimination approach.

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**6. Post-2015 Asia Pacific Region Malaria Agenda**

*Chair: Dr Sanchai Chasombat*

**Malaria in the Asia Pacific region: post 2015 - global and regional agenda**

Prof Maxine Whittaker gave a talk summarizing the history of the APMEN – Asia Pacific Leaders Malaria Alliance (APLMA) collaboration and gave a brief insight into APLMA’s Malaria Elimination Roadmap that may be presented later this year at the East Asia Summit (EAS) in Malaysia. The talk highlighted the achieved success made in the Asia Pacific to date on malaria elimination and describes a scenario for the future malaria elimination until 2030 according to the APLMA roadmap.

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**7. VxWG Business Meeting**

*Chair: Dr Sanchai Chasombat and Prof Ric Price*

The challenges of ongoing funding for APMEN were raised. There was unanimous support from all country partners on the success and relevance of the vivax working group and achievements it has made in providing a forum for country (CP) and research partners (RP) and collaborating institutions to come together in constructive process. This has resulted in prioritising the efforts of both CPs and RPs to generate the evidence for *P. vivax* elimination at a country level. The small projects grants have informed policy and provided significant building of research capacity in country. Whilst future funding remains unsure, MMV have kindly offered to support a follow up meeting for the Vivax Working Group in 2016.
Appendix 1

Vivax Working Group – Research Priorities

Research priorities identified by the vivax Working Group panel at a round table discussion; 12th-13th October 2015, Bangkok, Thailand.

<table>
<thead>
<tr>
<th>Priority</th>
<th>Theme</th>
<th>Notes</th>
<th>Proposed by</th>
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<tr>
<td></td>
<td><strong>Treatment</strong></td>
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| A        | Access to safe, efficacious and effective radical cure               | • Assess different Primaquine (PQ) treatment regimens (dosing and duration)  
                                                        • The relevance of ACTs with long post treatment prophylaxis          | CP+RP       |
| A        | Overcoming barriers to primaquine use and G6PD testing              | • Highlight benefits of radical cure (anaemia and transmission reduction)  
                                                        • Strategies to improve adherence: DOTS, educational campaigns, tafenoquine  
                                                        • Methods: how to measure treatment adherence  
                                                        • Costing: Assess cost associated to routine radical cure and G6PD testing | CP+RP       |
| A        | Quantify the risk of G6PD activity and primaquine induced haemolysis |                                                                      | CP          |
| B        | Standard methodology for diagnosing chloroquine resistance          |                                                                      | RP          |
| B        | Universal treatment policy for malaria                               | • ACT plus PQ radical cure for all species of malaria                | RP          |
| B        | Special preventive/treatment strategies for at risk populations      | • Pregnant women  
                                                        • Infants  
                                                        • G6PD deficient individuals                                    | RP          |
| B        | PQ mass drug administration                                         | • Develop algorithms to define methodologies for different scenarios  
                                                        • Develop methodologies for best operational conduct of mass treatment | RP          |
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<tr>
<th><strong>Surveillance</strong></th>
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<tbody>
<tr>
<td><strong>A</strong></td>
<td>The contribution of sub-patent and latent <em>P. vivax</em> infections to transmission dynamics and morbidity</td>
<td>• In different settings with varying strains and prevalence rates.</td>
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<tr>
<td><strong>A</strong></td>
<td>Mapping G6PD deficiency</td>
<td>• Prevalence and variants in different settings.</td>
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<tr>
<td><strong>A</strong></td>
<td>Drug quality assessment of anti-malarials</td>
<td>• To detect drugs with low or altered active ingredients used in routine malaria treatment.</td>
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</table>
| **A** | Parasite genotyping | • Understanding the geographic origin of infection  
• Assess transmission intensity, markers of drug resistance and relapse patterns | RP + CP |
| **B** | Sero-prevalence studies | • To gauge the risk of patent and subpatent *P. vivax* infection at a population level (Hot pops) | RP + CP |
| **B** | CYP2D6 surveillance | • To understand if PQ based radical cure is effective  
• Limited by costs: only applicable in areas where supervised PQ treatment is failing | RP + CP |

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<th><strong>Diagnostics</strong></th>
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<tr>
<td><strong>A</strong></td>
<td>Improved RDT for <em>P. vivax</em></td>
<td>• Vivax specific RDTS need to be at least as sensitive as falciparum RDTS</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>Improve available G6PD diagnostics</td>
<td></td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>RDT for <em>P. knowlesi</em></td>
<td>• Knowlesi specific RDTS are not available to date</td>
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<tr>
<td><strong>B</strong></td>
<td>Standardize methods for <em>P. vivax</em> PCR and quality control</td>
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<td><strong>B</strong></td>
<td>Establish LAMP as a field robust diagnostic for reactive case detection</td>
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<tr>
<td><strong>B</strong></td>
<td>Pragmatic considerations for RDTs</td>
<td>• Improved packing of RDT for buffer preservation, cheaper bivalent RDTS</td>
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