The vivax working group met on Monday 9th May 2011 directly preceding the yearly APMEN meeting. The working group meeting consisted of three parts:

1. An overview of the activities of the working group since the last meeting in Sri Lanka in 2010.
3. Discussion of the work plan of the vivax working group in the coming 12 months.

The first and the last part of the meeting were closed business session. The discussion of the knowledge gaps was open to other participants at the APMEN meeting.
1. **Review of the first year of VxWG activities**

Lorenz von Seidlein summarised the activities of the Vivax Working Group (VxWG) in 2010-2011:

- A brief review of the objectives and governance as well as the terms of reference was presented. Both documents are published on the APMEN website. The research priorities established during the first meeting of the working group in Kandi, Sri Lanka were reviewed.
- The recruitment of the VxWG management committee and the administrative relationship between Menzies and UQ were outlined.
- Reviews of research activities were presented. The first component of these review activities has been in the form of a landscape analysis which has been published in the Malaria Journal. A second research paper is currently in preparation.
- The current vivax research small grants program was described. There was a call for research proposals in July 2010. The working group received 16 pre-proposals all of which were invited to submit full proposals. The working group received 15 full proposals. The proposals were reviewed by 2 reviewers. Funding was decided by a panel based on the reviews. 11 proposals were approved for funding and 4 proposals were deferred. The challenges encountered by the coordinating team during the first round were summarised.
- The coordinating team has conducted three site visits (Malaysia, Indonesia, and China) during the first year to review the projects funded by the working group and to discuss future work with and for the working group. Further site visits are planned for 2011-2012.
- The working group convened a workshop on genotyping preceding the working group meeting to arrive at consensus methods for six grant recipients working on genotyping. Besides interested partners of the working group and six grant recipients the working group invited 4 international guest speakers to provide background information and guidance.
- The current links with other networks were described. The working group is collaborating with the malaria atlas project (MAP) as well as the world wide antimalarial resistance network WWARN.

**Action Points:**

- The delegates voted to approve the activities of VxWG in 2009-2010, including ratifying the review process adopted for the small grants and the decision on the 11 grants selected for funding.
- The group suggested that aspects of the review process could be revised, in particular the feedback form. Biannual calls for applications are not feasible and thus calls for proposals

---

3. Trends in malaria research in 11 Asian Pacific countries: an analysis of 2700 peer-reviewed publications over two decades by Andersen et al. Malaria Journal 2011 [http://www.malariajournal.com/content/10/1/131](http://www.malariajournal.com/content/10/1/131)
4. Operational research needs for elimination of Plasmodium vivax in the Asia Pacific; Hsiang M. et al.
5. George Snounou, Qin Cheng, John Reeder, Olivo Miotti
6. [http://www.map.ox.ac.uk/](http://www.map.ox.ac.uk/)
should be once per year. There will be no more need for pre-proposals, applicants will be asked to submit one “final” proposal.

- Research groups from member countries are eligible to apply for funds, but projects should be agreed upon in advance by the VxWG country representative to ensure local operational relevance.

2. Discussion of 2nd Year Activities of the Vivax working group

The discussion of the 2nd year of activities followed three presentations on vivax knowledge gaps (see appendix).

- In view of limited funds the VxWG agreed to prioritise activities towards operational research where the highest impact is most likely. The working group agreed on two research themes for the next funding period:

  1) Diagnostics and Surveillance.
     - G6PD deficiency. Prevalence mapping and new diagnostics were regarded priority areas. A reference centre to standardise G6PD testing was discussed.
     - RDTs to detect *P. vivax* infections were considered important.
     - New diagnostic technologies specifically LAMP were considered highly relevant.
     - Sero-epidemiologic studies could be useful to define temporal and spatial trends in *P. vivax* transmission if current limitations of serology can be overcome.
     - Case investigations seem to work in practice. Research into case investigations including cluster randomized trials would allow optimisation of such interventions and wider applicability throughout the region, though the feasibility of such large trials is a major limitation.

  2) Treatment trials of *P. vivax*. The two high priority questions in this theme are:
     - What is the optimal treatment of blood stages?
     - What is the optimal treatment of hypnozoites?

*Allocation of Available Resources.* The group discussed a balance in multiple site studies spread across the region, to a single or small number of multi-centred studies coordinating research activities across the network. It was agreed to use approximately half of the available research funding to continue the small grants programme. The other half should be used to start a multicentre study hoping to use the existing funding to leverage additional funding. It was agreed that a multicentre trial should offer all APMEN countries an opportunity to participate. Such a trial should build research capacity specifically in countries with less research experience. The drafting of the proposal should be inclusive, with all countries encouraged to discuss and shape the protocol. The trials organizers will provide GCP training to all participating countries and such create a platform for future trials in the country. This approach will build important clinical trials capacity.

- Several topics of research were prioritised. The delegates were asked to rank which research questions had the greatest relevance for their operational programs towards elimination.
<table>
<thead>
<tr>
<th>Rank</th>
<th>Research question</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A comparison of primaquine regimes: Multicentre efficacy and effectiveness antirelapse studies</td>
</tr>
<tr>
<td>2</td>
<td>Blood Stage RDTs: Sensitivity and specificity in field studies</td>
</tr>
<tr>
<td>3</td>
<td>G6PD: Testing new diagnostics, prevalence mapping</td>
</tr>
<tr>
<td>4</td>
<td>A comparison of schizonticidal regimes: ACT vs Cq Clinical Trial</td>
</tr>
<tr>
<td>5</td>
<td>The relapse pattern of vivax cases in different transmission settings: a cohort study</td>
</tr>
<tr>
<td>6</td>
<td>A cluster randomized trial to compare the effectiveness of case investigations</td>
</tr>
<tr>
<td>7</td>
<td>Risk of Haemolysis following primaquine administration in relation to G6PD status</td>
</tr>
<tr>
<td>8</td>
<td>Mapping the vivax transmission intensity using serological studies</td>
</tr>
<tr>
<td>9</td>
<td>A randomised clinical trial of Primaquine antirelapse after P. falciparum monoinfections</td>
</tr>
</tbody>
</table>

The treatment of hypnozoites was overall highest ranked among the respondents. It was recommended to address other questions such as blood stage RDTs and G6PD testing in the framework of a large multicentre trial. A work shop to plan such a multicentre trial will be convened by the working group later this year.

**Summary decisions by the working group:**

- Focus activities on **two priority themes** for the coming year:
  - Diagnostics and surveillance
  - Treatment trials
- Research funding should be split between small grants and a **multicentre trial**.
  - The multicentre trial should compare primaquine regimens for the radical cure of *P. vivax*.
  - A consensus protocol should be developed at a workshop to take place later in 2011.

**Actions Points:**

- Convene a workshop to develop a multicentre clinical trial and draft protocols.
- A second call for small grant research proposals.
- Site visits planned to Philippines, Vanuatu, and Solomon Islands.

***
Appendix

Public Meeting on Knowledge Gaps in Vivax Malaria

1) Knowledge gaps in management *P. vivax*: diagnostics for *Pv* and G6PD

(Prof. Qin Cheng, Australian Army Malaria Institute)

**Introduction**

The role of malaria diagnostics changes with decreasing malaria transmission in elimination settings. In high transmission settings diagnostic tests are used in passive case detection, i.e. febrile patients presenting in a clinical setting. In such a setting the parasite densities tend to be high and it is important to accurately recognise the species causing the infection, i.e. sensitivity of the test can be less of an issue than specificity. In contrast in a low elimination setting diagnostics may be used to detect asymptomatic, low density infections, trends of infection, impact of interventions and the introduction of new strains.

**Detecting Plasmodium vivax**

Work in Temotu, Solomon Islands illustrates that the large majority of the remaining infections in such a low transmission setting tend to be sub-microbial. This finding is of particular importance for *P. vivax* elimination which tends to have lower densities than falciparum infections.

- **PCR** diagnosis appears much more accurate in low transmission settings than microscopy. PCR is however more expensive and time consuming than microscopy. The major challenges for *Plasmodium* detection methods in low transmission settings include sensitivity, cost effectiveness, and field deployability. Using microscopy in low transmission settings requires continuous quality assurance as screening of large numbers of negative slides are likely to have a negative influence on slide reading accuracy. Ultimately the question will be when to switch from microscopy to more accurate and reliable methods.

- The quality of **rapid diagnostic tests**, also known as point of care diagnostics has been steadily improving. Essential features for such tests include quality control, heat stability, good sensitivity and specificity, species detection, positive control wells, sustainable quality assurance program in country, and low cost. New urgently needed requirements for RDTs include the detection to detect gametocytes and ideally hypnozoites. RDTs have been systematically evaluated by FIND/WHO.

- Newer diagnostic approaches include Loop-Mediated Isothermal Amplification (LAMP). This methodology has a similar sensitivity as PCR, but doesn’t require DNA extraction, a PCR machine, and best of all the products are visible to the unarmed eye. This promising, novel technology will require further field evaluation prior to wide deployment.

- **Serology** is a promising diagnostic tool in the context of malaria elimination. It can identify asymptomatic infections and foci of recent transmission (hot spots), monitor impact of intervention and demonstrate the absence of malaria over a given period in a geographically defined space. Urgently needed improvements of serology which could make this methodology...

---

8 Malaria Rapid Diagnostic Test Performance- Results of WHO product testing of malaria RDTs: Round 2 (2009); http://apps.who.int/tdr/svc/publications/tdr-research-publications/rdt_round2
more widely deployable include the availability of more antigens as exposure indicators for *P. vivax*, a stable supply of antigens, and improved sensitivity.

**Diagnosing G6PD deficiency**

Screening to detect G6PD deficiency was discussed. Currently the only radical cure of vivax infections is primaquine, a drug with the distinct disadvantage to cause haemolysis in G6PD deficient patients. Old detection methods of G6PD deficiency include brilliant cresyl blue decolourization test and methaemoglobin reduction test. These methods are being replaced by NADPH fluorescent spot tests which require UV lamps. Other promising diagnostic essays such as the Binax tests come with additional requirements such as two pipettors, stopwatch and ambient temperature requirements which currently limit their fieldability.

In summary:

- There is currently no diagnostic test suited for in-field mass-screening of G6PD deficiency.
- However more promising approaches such as the WST8/1-methoxy PMS method⁹ are under evaluation.
- Current key issues are the precise relationship between phenotype (actual level of enzyme activity) and propensity to PQ-induced haemolysis and secondly is there a safe dose/dose regimen of PQ that can be administered at a given G6PD level?

---

⁹ Kuwahata et al. Malaria J 2010
2) **Knowledge gaps in surveillance and community based public health interventions**  
(Prof Gao Qi, Jiangsu Institute of Parasitic Diseases; Michelle Hsiang, UCSF Global Health Group)

- Prof. Gao Qi reviewed the current malaria survey methods employed in China. With a shift from malaria control to malaria elimination the surveillance strategy has to shift from passive surveillance to active detection of each infection.
  - Malaria control can treat clinical cases without laboratory diagnosis. In contrast during malaria elimination laboratory evaluation of each malaria case is required.
  - **PCR** is a potentially useful tool for malaria diagnosis in the elimination phase but has little or no role in malaria diagnosis while transmission is high.
  - With decreasing malaria transmission there is an increasing need for **case investigations**.
    - In China **active surveillance and door to door investigations** are performed within a week after a case report is received. In the presence of a single case, blood samples are collected from all villagers with fever in the past 2 weeks. In sites with more than 1 case blood samples are collected from family members and other potentially exposed individuals.
    - **Vector surveys** are conducted if the case occurs during the transmission season and recent vector data are not available.
    - Other activities in case sites include health educations, treatment of infected individuals and indoor residual spraying if indicated.
    - Prof. Gao briefly elaborated on the practice of “spring treatment”: Individuals who have been diagnosed of malaria during the preceding season receive treatment just before the next malaria season starts.

- Michelle Hsiang spoke about surveillance and responses during the malaria elimination phase, emphasising the importance of diagnosis, surveillance and response.
  - The objective of surveillance and response during the elimination phase is to **track progress**, identify transmission **hot spots** and detect **asymptomatic carriers** with the ultimate aim to interrupt transmission.
  - **Challenges** include diminishing skills with decreasing case load.
  - **Pooled PCR** may be a promising diagnostic approach when approaching malaria elimination.\(^\text{10}\) PCR can also be used for the quality control of microscopists, an approach recently employed in Hainan, China.
  - With the decrease in malaria incidence the importance of active surveillance increases, which can take the form of large scale surveys such as malaria index surveys (MIS) or targeted small surveys around index cases. A recent MIS in Swaziland tested 4327 subjects with RDTs 3 of who were found positive – all three appear to be false positives by PCR testing. **Pooled PCR** testing found 2 positives in

---

182 PCR reactions suggesting large potential savings through the pooled PCR approach.

- **Serology** becomes increasingly interesting with decreasing malaria incidence as it detects past exposure. Recent used of serology in Swaziland was able to identify clusters of cases which can be targeted for interventions. While promising for *P. falciparum* more recent work in Vanuatu suggested that more work is needed the use of serology to detect exposure to *P. vivax*\(^\text{11}\).

- Finally our incomplete knowledge of **case investigations** was highlighted. Case investigations are employed in at least 6 of the APMEN countries and their efficacy is suggested by experience. Specifically mass drug administrations and mass screening and treatment (MSAT) have been historically widely used while evidence based data remains sparse. Examples provided include mass primaquine use in Jiangsu province, China and MSAT in Pailin, Cambodia.

---

3) **Knowledge gaps in vivax treatment**

*(Prof. Ric Price - Menzies School of Health Research)*

Prof. Price described the differences in knowledge between *P. falciparum* and *P. vivax* treatment.

- While *P. falciparum* transmission is decreasing globally *P. vivax* appears to be less susceptible to control efforts compared to *P. falciparum*.
- Secondly there was a 30 year gap between the emergence of chloroquine resistant *P. falciparum* and *P. vivax*.
- **Chloroquine resistance** varies considerable across the region from >60% in Papua, Indonesia and PNG to <5% in Afghanistan.
- The presence of hypnozoites confounds the interpretation of recurrent parasitaemia in *P. vivax* far more difficult than in *P. falciparum*. Not only can a recurrence of *P. vivax* be caused by a reinfection or a recrudescence infection, late relapses caused by hypnozoites are an additional source of infections and can’t yet be differentiated by genotyping.
- **ACTs** have been highly efficacious when evaluated to treat *P. vivax* and bring the added advantage of treating *P. falciparum* in co-infections. Apart from Sulfadoxine-pyrimethamine and amodiaquine, most new ACTs show good efficacy against drug resistant *P. vivax*. The major difference between regimens reflects their post treatment prophylaxis, and ability to delay the first relapse. In some regions (Thailand and Indonesia) very high rates of *P. vivax* parasitaemia (over 50%) occur within 42 days of both primary infections of *P. vivax* or *P. falciparum*.
- While there is evidence for the optimal therapy of sexual stages of *P. vivax* infections, the optimal treatment for relapses remains challenging. Recent unpublished data suggests that unsupervised administration of primaquine in Papua Indonesia had no beneficial effect in preventing relapse – this is a likely due to patients’ non adherence to complete course of therapy. **Supervised treatment** for 7 to 14 days at relatively high doses (30mg/day) appears beneficial. However the risk of haemolysis and poor adherence due to poor tolerability remain major handicaps of widespread use of primaquine.
- **Prof. Price concluded that efficacy and effectiveness antirelapse studies** should have the highest priority in any operational vivax research agenda.
