

APMEN

Vivax Working Group (VxWG)

Objectives and Governance



Created: 14 – 15 February 2010, Kandy, Sri Lanka

Background

The global efforts towards the control and elimination of malaria are based upon two key strategies: early diagnosis and prompt treatment (EDT) and a reduction in transmission of infection from the mosquito host. The deployment of artemisinin combination therapy (ACT), impregnated bed nets and strengthening of healthcare infrastructure, have led to significant reductions in the burden of malaria reported in many parts of the malaria endemic world. These successes have been documented mainly for infection with *Plasmodium falciparum*. Outside of Africa, the transmission intensity of malaria is generally low, however *P. falciparum* almost invariably co-exists with *Plasmodium vivax*, the most widely transmitted of the human plasmodia. *P. vivax* threatens almost 40% of the world's population and causes more than half of all malaria cases outside of Africa with an estimated 132 - 391 million clinical episodes of vivax malaria each year. The public health importance of *P. vivax* is usually underestimated.

Effective control of falciparum malaria in vivax endemic areas usually reveals a substantial hidden burden of vivax malaria. Indeed in areas where intensive control measures have been implemented, the relative proportion of malaria due to *P. vivax* usually increases compared to that from *P. falciparum*. *Plasmodium vivax* is notoriously difficult to eliminate. Our ability to prevent and treat vivax malaria is limited by a poor understanding of the fundamental biology, pathogenesis, transmission, and management of *P. vivax*, which lags far behind that of *P. falciparum*. Under-diagnosis and ineffective treatment impede effective control and clinical management of vivax malaria. Immediate critical challenges for control of *P. vivax* are increasing resistance to chloroquine, with the emerging threat of multidrug resistance, a limited ability to provide radical cure of dormant liver stages, and a poor epidemiologic assessment measures.

At the inaugural meeting of the APMEN (APMEN I) in Brisbane in February 2009, presentations from all national malaria control programs highlighted *P. vivax* as the major challenge for malaria elimination in the region. The ultimate goal of the global elimination of malaria will not be achieved without a better understanding of the biology of this complex and resilient parasite, and new tools for its assessment, prevention and treatment. However major advances in rationalising malaria control programs are feasible through the use of existing tools, and a major collaborative approach between country programs, researchers, and policy makers.

The Aim of the Vivax Working Group (VxWG)

*Develop and coordinate operational research that will provide the evidence base for the successful control and ultimate elimination of *P. vivax* in APMEN Country Partners and the greater Asia-Pacific.*

Objectives:

- Identify knowledge gaps and operational research priorities necessary for the optimal control and elimination of vivax malaria
- Share research and operational experience between APMEN Country Partners to maximise synergistic activities and minimise unnecessary duplication
 - e.g. study design, standard operating procedure and other research methodologies.
 - A document reviewing research activities, assets, collaborators currently being undertaken in Country Partners.
- Fund catalytic research projects to address key knowledge gaps, and facilitate their implementation, analysis and feedback to the Network.
- Develop partnerships with key stakeholder involved in the regional elimination for vivax malaria (including but not limited to WHO, Malaria Atlas Project (MAP), WorldWide Antimalarial Resistance Network (WWARN), Malaria Elimination Group (MEG), Foundation for Innovative New Diagnostics (FIND), Asian Vivax Network, research institutions, funding bodies) in order to:
 - Facilitate surveillance strategies to define, monitor, and collate the burden of vivax in APMEN Country Partners.
 - Provide evidence for rational diagnostic and treatment guidelines for *P. vivax*.
- Work with APMEN Country Partners and Partner Institutions to develop a series of integrated translational research programs, apply for external funding and facilitate their implementation.
- Work through APMEN to advocate for improved funding of *P. vivax* control and research activities.
- Promote collaborative research partnerships amongst APMEN Country Partners

Impact and attributed benefits

The overall goal of this Vivax Working Group is to provide an evidence base to inform decision making about optimal vivax surveillance, prevention, and case management. Research to inform better use of existing tools will result in considerable progress on the road to ultimate elimination of malaria. Because of the burden of *P. vivax* associated morbidity in infants and pregnant women, the proposed agenda will have direct relevance towards achieving the Millennium Development Goals 4, 5 and 6. The proposed agenda is also in alignment with the Global Malaria Action Plan, which encourages support of countries pursuing elimination through collection and dissemination of best-practice approaches, research & development for new tools, and funding and technical assistance by partners.

Membership

VxWG brings together Country Partner's National Malaria Control Programs with partner research institutions, giving it significant credibility in supporting translational research. The VxWG will consist of representatives from the 10 APMEN Country Partners National Malaria Control Programs, partner research institutions, WHO and the APMEN Secretariat. Members of the VxWG participate as volunteers.

Each APMEN Country Partner will be represented within the VxWG both to contribute to the coordination of research and implementation activities, and disseminate reports and progress updates to their respective countries.

Country Partner Representatives	
Sri Lanka	Gawrie Nirdoshi Galappaththy
Bhutan	Karma Lhazeen
China	Gao Qi
ROK	Jung-Yeon Kim
DPRK	Kim Yun Chol
Philippines	Marina Dorina Bustos
Malaysia	Junaidden Mohamad Zain
Indonesia	Rita Kusriastuti
Vanuatu	George Taleo
Solomon Islands	Albino Bobogare
Partner Research Institutions	
MSHR	Nick Anstey
AMI	Dennis Shanks / Qin Cheng
QIMR / UQ	James McCarthy
Burnett	John Reeder
Ejkmann Oxford	Kevin Baird
PNGIMR	Inoni Betuela / Ivo Mueller
Karolinska Institute	Akira Kaneko
Coordinating Team	
VxWG Chair	Ric Price (chair)
Clinical Coordinator	Lorenz von Seidlein
Project Manager	Vijaya Joshi
Secretariat	
UQ	Arna Chancellor
GHG	Michelle Hsiang

Partners

The Vivax Working Group will collaborate with APMEN Partner Research Institutions and other key organisations which will ensure that knowledge generated by VxWG will be synthesised and interpreted within the wider context of regional malaria control programs and associated stakeholders.

Identified key organisations include but are not limited to:

WHO	SEARO and WPRO
The Malaria Atlas Project	MAP
Worldwide Antimalarial Resistance Network	WWARN
Foundation for Innovative New Diagnostics	FIND
Asian Vivax Network	
Medicines for Malaria Venture	MMV
Walter Reid Army Institute of Research	WRAIR

Coordinating Team

VxWG will be coordinated through the Menzies School of Health Research (MSHR) in Darwin, identified at APMEN I as an Australian institute with expertise in vivax research and commitment to APMEN.

Funding has been made available to maintain a support group of full time / part time equivalent staff.

This was deemed necessary to:

- Develop a coordinated agenda within the group
- Ensure activities executed in timely manner
- Manage research grants
- Ensure quality of work
- Provide liaison between the VxWG and APMEN participants

Vivax Working group Coordinating Team will include:

- A full time clinical coordinator
- Full or part time research officer(s)
- Administrative officer

Communication Strategy

The VxWG will endeavour to maintain close communication and dialogue between its partners, the Coordinating Team, the APMEN Country partners and partner research institutions and the APMEN Advisory board. To minimize travel expenses this communication will mainly be through telecommunications (email, video and telecon) and news bulletins, although face to face meetings will be held at least once per year. The APMEN Secretariat will also be kept informed of news items and updates and will communicate these to the Network via the APMEN website.

Communication activities will include:

- Annual meeting timed to coincide with the APMEN annual technical meeting.
- Six monthly bulletins to: VxWG partners, Partner Countries and the APMEN Board and key partners and stakeholders. These will consist of updates on activities of the group, funding of projects and any final reports from funded projects.
- Opportunistic meetings at major international conferences. Travel budget permitting the VxWG will endeavor to bring key stakeholders to these meetings who wouldn't otherwise be attending.
- The APMEN website will be updated regularly with VxWG activities for view by APMEN partners, colleagues in endemic countries, research community, media and general public.
- Online provision of reports, publications, and resources (e.g. open access SOPs)

Governance

The VxWG annual report and proposed yearly work plan will be presented to the APMEN Network for review and approval. Any complaints about the due process will be referred from the Secretariat to the APMEN Advisory Board for resolution.

The coordinating institution will submit 6 monthly financial reports and 12 monthly progress reports to APMEN and financing partners (including AusAID) through the APMEN Secretariat UQ.

An evaluation of the governance and coordination process and activities will be reviewed by the Network eighteen months after inception.

Research Priorities

At the Vivax Working Group round table discussions in Colombo, Sri Lanka (14-15th February 2010), five themes of research were identified for 2010 (see Appendix I). These were endorsed by the APMEN Country Partners in the Business meeting:

- i) Optimizing the treatment of blood stage
- ii) Understanding relapse and achieving radical cure
- iii) G6PD deficiency - Risks, prevalence and diagnostics
- iv) Diagnostics for case management and population surveillance
- v) Public Health, Monitoring and Evaluation

These priorities represent the key issues that need to be addressed for the optimal control of vivax malaria from the perspective of the National Malaria Control Programs. This list of priorities sets the scope of the research activities that will be undertaken and coordinated through the VxWG. The list will be reviewed and revised at each annual meeting.

Funding / Review Process

The VxWG has an annual indicative budget of AUS \$300,000 to support small to midsize operational catalytic research projects. Proposals will come from the 10 APMEN Country Partners (Bhutan, China, Democratic People's Republic of Korea, Indonesia, Malaysia, Philippines, Republic of Korea, Sri Lanka, the Solomon Islands and Vanuatu) and be endorsed by the National Malaria Control Program. They should address one of the five research priorities listed above and also in *Appendix I*.

In 2010, there will be three funding bands for the Vivax Working Group research grants:

- Grants up to AUD\$10,000 (to be completed within 6 months)
- Grants between AUD\$10,001 – AUD\$49,999 (to be completed within 18 months)
- Grants for greater than AUD\$50,000 (to be completed within 2 years)

The funding process, review and grant allocation will adhere to the APMEN directives as laid out in the **APMEN Research Grants Guidelines** document.

A 3-step review process is envisioned:

1. Soliciting pre-proposals

APMEN countries will be requested to submit a brief (4 page) outline of proposals to be conducted in the coming 48 months. The pre-proposals form is in a standard format and needs to address the following:

1. Title
2. Theme the project will address
3. Institution/Collaborative Partners
4. Contact person (email)
5. Outline of the proposal (400 words)
6. Proposed Budget with justification

Pre-proposals should be sent to the VxWG Working Group Coordinator apmenvivax@menzies.edu.au. The Coordinating Team will assure that as many research priorities as possible will be addressed and that as many of the partner countries as possible can participate.

2. Requesting further development of proposals

Initial **Feedback** on each proposal will be provided by the VxWG Coordinating Team within one month of receiving the pre proposals

The VxWG Coordinating Team will recommend and assist in the further development of priority proposals.

The format for the **full proposal** will follow the approved APMEN Research Grants format, (maximum 6 A4 pages, budget, and budget justification). A template will be provided by the Coordinating Team via the APMEN website.

3. Approval process

Reviewers

Proposals will be reviewed by members of the APMEN Vivax Working Group. Selection of reviewers will be called from within the VxWG. Proposals will be reviewed by two reviewers: one from an APMEN country partner, and the other from a partner research institution or a member of the coordinating team. The allocation of reviewers to proposals will be coordinated so as to match the most suitable reviewers with proposals while avoiding conflicts of interests.

The proposals will be reviewed differently for the three funding bands:

- Grants up to AUD\$10,000 can be approved directly by the 3 members of the VxWG Coordinating Team
- Grants between AUD\$10,001 – AUD\$49,999 will be reviewed by 2 internal WG members (one Country Partner and one Partner Institution)
- Grants for greater than AUD\$50,000 will be reviewed 2 internal VxWG reviewers (one Country Partner and one Partner Institution) and at least one external content specialist who may be a non APMEN participant.

Applications will be graded 1-5 by the Vivax Working Group reviewers based on the below criterion. The composite score from the reviewers will be used by the research review panel to prioritise funding.

Once the review process is complete the recommendations will be forwarded to the Research review panel which consists of Menzies- Vivax working Group Chair (Ric Price,) APMEN Project Co coordinator-Director (Maxine Whittaker) Vivax Working Group Clinical Coordinator (Lorenz von Seidlein).

This panel will review the reviewer's recommendations in light of available funds, distribution of research grants within the network and make the final decisions. The review panel will endeavour to fund all themes that fulfil the criteria funding permitting. Where this is not possible because the budget is not sufficient the VxWG Coordinating team will work with applicants /countries to develop proposals for external funding.

If there is lack of consensus amongst the research review panel, the Advisory Board may be consulted for advice and dispute resolution.

Applicants will be informed of the outcome of their application by the Vivax Co-coordinating Team.

The following criteria will act as guidelines for prioritising the funding of research projects:

- Policy Relevance
- Significance
- Capacity Building
- Research design and Methods
- Research team
- Communication and Engagement
- Budget

The Coordinating Team will endeavour to fund all themes that fulfil these criteria funding permitting. Where this is not possible because the budget is not sufficient the VxWG will work with countries to develop proposals for external funding.

Ethical Issues

Project must adhere to the ethics guidelines established for APMEN research grants. Internal review board approval must be obtained in the country where the project will take places, as well as from collaborating research institutions according to the institutional guidelines.

Arbitration

Any issues with due process or complaints will be referred by the APMEN Secretariat to the APMEN Advisory Board for resolution according to the Board terms of reference and processes.

Year 1 Deliverables

1. Consensus on the VxWG Terms of Reference, structure and governance will be expressed through acceptance of the final version of this document.
2. Drafting of a manuscript which summarises the discussions of the working group: "Operational Research Priorities for Elimination of *P. vivax* in the Asia Pacific Region". The manuscript will be submitted for publication in a peer reviewed journal, e.g. malaria journal.
3. Review and documentation of current status of research activities, collaborators and partners in APMEN Country Partners. The VxWG will review data from several sources, regarding research activities, partners, assets and collaborators in each Country Partner. This will include a systematic review of the published literature as well as grey, unpublished literature, country reports etc.
4. Commission/grant and begin work on 5-10 catalytic operational research projects.
5. End of year report of VxWG activities.

YEAR 1

Activities	Date
Establish Identity and Work Agenda	
Convene first meeting of Vivax Working Group and report to Network, and prepare written document	Feb 2010
Produce a consensus document laying out the VxWG Terms of reference , structure and governance	Feb/March 2010
Establish Coordinating Team /administrative core	Feb / March 2010
Identify knowledge gaps in the optimal diagnosis, management, and surveillance of <i>P. vivax</i> and define operational research priorities	Feb 2010
Establish mechanism to fund and support catalytic operational research projects.	Feb -March2010
First Round of Funding	
Develop a transparent and equitable funding process agreeable to all APMEN Country Partner and initiate first call for pre-proposals	March-April 2010
Deadline for first round Pre Proposals submissions	31st May 2010
Receive and review initial Letters of Intent (LOI) for grant submission.	April-May
Review proposals, give feedback and assist in developing full applications	June-July
Deadline for submission of full proposal	1st August 2010
Review Process of Applications	August
Funding decision on first round applications	1 st September

Research Activities	
Review current vivax research programs and activities in APMEN Country Partners.	March/April/May 2010
Begin synthesis and retrospective projects.	April 2010
Begin funded prospective projects.	September 2010
Reporting Activities	
Short report and flyer on Operational Research Priorities for Elimination of P. vivax in the Asia Pacific Region	Feb/March 2010
Coordinating Team keeps APMEN informed of external funding possibilities	Ongoing
Monthly telecom with APMEN Secretariat	
Provide updates on project progress	
Annual progress report and financial report submitted to APMEN Secretariat UQ per calendar year	1 November 2010
Six monthly financial report submitted to APMEN Secretariat UQ	1 November 2010 1 May 2011

Appendix I Research Priorities

These research priorities were identified by the Vivax Working Group panel at round table discussions at a meeting in Colombo, Sri Lanka on the 14-15th February 2010.

Those line items shaded in grey were recognised as being the top priorities for funding and coordination within the APMEN VxWG.

Theme	Notes
Theme 1. Optimizing the treatment of blood stage	
In vivo efficacy studies of first line treatment	E.g. opportunistic testing like Day7 CQ levels, support efficacy studies (CQ, ACT) that are already funded such as with GF funding
In vitro efficacy studies	funded through other sources
Seed funds to develop larger clinical trials	E.g. support comparative studies that are funded through other sources like GF grants
Chemoprophylaxis in high risk groups	Seed funds to support prelim data for ITPi ITPp proposals
Theme 2. Understanding relapse and achieving radical cure	
Defining relapse patterns in each country	Special populations returning to non/low endemic areas
Genotyping to determine relapse from new infection	
Primaquine safety & tolerability	In all risk groups, for use of high doses/short course or low dose/long course in MDA settings
Seed funds to develop PQ efficacy and effectiveness studies	Seek external funding
Mass primaquine administration	
Theme 3. G6PD deficiency - Risks, prevalence and diagnostics	
Review pros/cons of available rapid G6PD deficiency tests	
Compare G6PD deficiency test results -rapid, phenotypic assays, and genotyping	
Define G6PD deficiency prevalence	School or Household surveys

Theme	Notes
Theme 4. Other Diagnostics	
Case management	
Review the performance of different RDTs	
Evaluate sensitivity and specificity of high potential RDTs using microscopy and PCR (prospective studies in different settings)	3 available in Round 1, 2 available in Round 2 (only is Pv only), can be in health facility or in cross sectional surveys, liaise closely with companies to improve RDTs for field/ elimination settings
Population Surveillance	
Use of high throughput PCR to identify infective asymptomatic carriers	E.g. in prevalence surveys, mass screening and treatment of high risk populations, case investigations around reported cases
Genotyping to look at allele diversity	Population structure and dynamics, distinguish new vs. recrudescence vs. relapse, imported vs. local
Role of serology to inform transmission intensity and asymptomatic carriers	Prevalence surveys to show progress toward elimination, identify transmission foci and sites for clinical trials
Theme 5. Public Health, Monitoring and Evaluation	
Monitoring and Evaluation	
Mapping Pv transmission at country level and among APMEN Country Partners	Facilitate prevalence surveys, also mapping of relapse patterns, G6PD def / MAP
Standardising protocols for demographic and prevalence surveys	Community/household/school surveys, age stratification, sampling
Mathematical models for assessing interventions and predicting optimal elimination strategies	Perhaps more role of research community, MalERA, but can provide links to countries. Pf and Pv dynamics
Burden of disease, disease severity	
Pv economic burden	Burden of disease, costing and cost effectiveness of Pv elimination; leave more for greater APMEN, MEG
Characterize Pv disease severity	Case definitions, and hospital surveillance