Plasmodium vivax Control & Elimination:
Development of Global Strategy and Investment Case

September 2012

1. Background

While Plasmodium falciparum is responsible for the vast majority of cases and deaths from malaria worldwide, P. vivax, the most geographically widespread species, is responsible for a large number of cases; it is increasingly recognized as a cause of severe malaria and even death. There are an estimated 2.6 billion people at risk of P. vivax; and the World Malaria Report 2011 estimated 19.4 million P. vivax cases (range 13.4 to 24.6 million) in 2010, with the greatest number in Asia and Latin America. A number of countries have exclusively P. vivax transmission.

There are abundant data showing that transmission of P. falciparum is actually more responsive to malaria control measures. As a result, in areas where the two species co-exist, the scale up of integrated malaria control measures generally results in a shift in the balance between the two species such that P. vivax becomes the dominant species. This phenomenon can be attributed in part to a number of factors, including: 1) that P. vivax has a dormant liver stage (hypnozoite) that is not killed by any currently used antimalarial other than primaquine; 2) the earlier appearance of gametocytes during infection (even prior to the appearance of clinical symptoms); 3) the tolerance of its sporogonic cycle to lower temperatures; and 4) the vectors of P. vivax are exophilic and/or exophagic in some areas. Therefore, transmission control measures such as LLIN and IRS that were successfully implemented for P. falciparum may have less impact on reducing the P. vivax burden. Therefore more robust efforts are required for reduction and elimination of P. vivax transmission.

There are numerous strains of P. vivax that are broadly grouped into temperate and tropical strains. P. vivax is increasingly becoming resistant to chloroquine, the primary drug used for treatment. To date, P. vivax has often been considered benign, with country and global policy and programming priority given to the prevention and control of P. falciparum, especially in Africa.

The prevention of P. vivax, especially in settings where vectors are exophilic and/or exophagic, has received inadequate attention. Although control strategies such as mass treatment with primaquine have been used successfully in some settings in Central Europe and Asia, inadequate documentation of safety and efficacy has prevented the wider uptake of such interventions. Parasitological diagnosis of P. vivax has been hampered by late development and slow roll out of highly sensitive and specific bivalent Rapid Diagnostic Tests (RDTs). WHO recommends standard treatment regimens for P. vivax based on available evidence, but radical
treatment of confirmed *P. vivax* infection with primaquine is not a policy recommendation in some transmission areas; where it is a policy, it is sometimes not prescribed by health workers due to fears of primaquine-induced haemolytic anaemia among patients with G6PD deficiency, for which reliable field tests are still not available. Where primaquine is recommended, there is often confusion and disagreement over dosages and duration of treatment as well as approaches for ensuring full compliance -- which is required for complete cure (thereby preventing relapses). Overall, the long treatment duration is a barrier to uptake of primaquine.

There have been many technical guidance documents on malaria control in recent years, including updated guidelines for the Treatment of Malaria (WHO 2010), the operational manual on Universal Access to Diagnostic Testing (WHO 2011); Community-based Reduction of Malaria Transmission (WHO 2012); and an updated version of the Handbook for the Management of Severe Malaria (WHO 2012, in development). In addition, a global strategy -- the Global Malaria Action Plan -- was developed by the Roll Back Malaria partnership in order to harmonize partner efforts with regard to malaria control and elimination (RBM 2008). While each of these technical and strategy documents makes reference to *P. vivax*, there has never been a global strategy developed that articulates how to approach the problem of *P. vivax* at a global, regional and country levels, and that proposes time-bound objectives for these efforts.

Researchers and academics continue to call for more support for basic and operational research in diagnostic testing and treatment. There are on-going research consortia focused on *P. vivax*, including the i-VAX research Consortium, and PregVax- *Plasmodium vivax* Malaria in Pregnancy Project, both of which are coordinated by the Barcelona Centre for International Health Research (CRESIB). There is focus on *P. vivax* elimination by the Asia Pacific Elimination Network. The evidence and experience generated from these groups will support the development of a global strategy for prevention and control of *P. vivax* in the short to medium term, and the identification of research gaps.

There is now a growing need and demand for a comprehensive global strategy and plan with operational guidance to support containment and elimination of *P. vivax* and acceleration of research and development of new tools. This global strategy would be based on: 1) a review of the most recent evidence on programmatic effectiveness of different prevention, control and surveillance interventions of vivax malaria; 2) a review of the current policy and practice on *P. vivax* service delivery at country and regional level; 3) a review of *P. vivax*-specific recommendations that are dispersed across various WHO guidance documents and 4) an analysis of on-going research with regard to *P. vivax*, and how results emerging from such work are likely to influence control and elimination strategies over the next decade, and what research gaps remain; and 5) an economic analysis of the requirements for *P. vivax* control and elimination.
2. Goal

To develop a global strategy and investment case for *P. vivax* control and elimination

3. Specific Objectives

1) Conduct country case studies and document regional overviews
2) Review the current global epidemiology of *P. vivax*
3) Review the diagnostic techniques for *P. vivax*
4) Review the drugs and treatment regimens for radical cure of *P. vivax*
5) Review the mass treatment and chemoprophylaxis options for the control of *P. vivax*
6) Review the malaria vector control interventions that are cost-effective to reduce *P. vivax* transmission
7) Review the cost of *P. vivax* control and the potential economic benefits of control in affected countries
8) identify gaps between expert opinion/treatment recommendation and knowledge/attitudes and behavior of prescribers and develop strategies to close these gaps
9) Identify the evidence gaps and define research priorities and programs on *P. vivax*
10) Prepare a Global Strategy and investment case for *P. vivax* Control and Elimination

4. Method of work

1) Establish a small steering committee to develop a more detailed plan of work and identify topics and countries for the reviews
2) Establish an evidence review group (ERG) reporting to the Malaria Policy Advisory Committee (MPAC)
3) Recruit consultant to WHO secretariat in preparatory work for the ERG
4) Support WHO regions and countries to prepare country case studies and regional overviews
5) Provide APWs for the conduct reviews in different thematic areas for *P. vivax* control & elimination
6) Conduct a wider stakeholder and partner consultation to get input on the Strategy and Investment Case
7) Present Strategy, Investment Case to the Malaria Policy Advisory Committee (MPAC) for review and endorsement
8) Design and implement knowledge management and launch strategies for the above-mentioned documents

5. Outputs/ Products

1) Regional overviews with Country case studies on *P. vivax*
2) Thematic peer reviews of key areas of *P. vivax* management and containment
3) Global Strategy for *P. vivax* Control and Elimination
4) Costed business plan / investment case for the control and elimination of *P. vivax*
5) Provide specific recommendations on the target audience, key contents, core interventions which will lead to the later development of a WHO Operational manual on the control and elimination of *P. vivax*.

**Other**

Chapter on *P. vivax* in World Malaria Report 2013
Web page on the WHO site http://www.who.int/malaria/en/

6. **Collaborating alliance on *P. vivax* control and elimination**

- **Proposed Key regions and countries (final list subject to confirmation):** PAHO: Brazil, Peru, Guatemala, Venezuela; SEARO: India, Indonesia, DPRK, Sri Lanka and Myanmar; EURO: Azerbaijan and Tajikistan; EMRO: Afghanistan and Pakistan; AFRO Ethiopia and Eritrea; WPRO: China and Papua New Guinea.

- **Proposed Steering Group:** Barcelona Centre for International Health Research-Spain; Medicines for Malaria Venture (MMV); Centres for Disease Control and Prevention (CDC-USA); Eijkman-Oxford Clinical Research Unit –Jakarta

- **Other Key Technical Partners:** National Institute for Research and Indian Council for Medical Research - India; Martinowsky Institute - Russia; Centres for Disease Control (CDC) - Shanghai; Eijkman-Oxford Clinical Research Unit –Jakarta; Mahidol-Oxford University - Thailand; Tropical Medicine Foundation of Amazonas – Brazil; University of Cali

- **Key Development Partners:** AusAID; China; DFID; Gates Foundation; Global Fund; Russian Federation; USAID; and others.

- **Key Private Sector Partners:** (SANOFI, IPCA, GSK and others)

7. **Time line 2012 and 2013 and estimated budget**

**Vivax strategy development: Time lines 2012 and 2013 and estimated budget**

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*Possible countries include: Brazil, Venezuela, Guatemala, Peru, India, Indonesia, DPRK, Myanmar, Sri Lanka, Azerbaijan, Tajikistan, Afghanistan, Pakistan, Ethiopia, Eritrea, China, PNG
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