Single Low Dose Primaquine to Interrupt P. falciparum Transmission in Africa: A Roadmap Update

MEETING SUMMARY

The Global Health Group at the University of California, San Francisco and the Malaria Centre at the London School of Hygiene & Tropical Medicine hosted a primaquine roadmap update meeting in London, England on March 29th and 30th, 2016. The summary below includes highlights from presentations and discussions but are not entirely comprehensive.

Session 1. Welcome and overview
Session chair: Roly Gosling (University of California, San Francisco) and Chris Drakeley (London School of Hygiene and Tropical Medicine)

The goals of this meeting are to review progress using the low-dose primaquine roadmap, last updated in 2014:

1) To update the single low-dose primaquine (SLD PQ) roadmap progress
2) To discuss appropriate scenarios of SLD PQ use beyond clinical case management
3) To determine the next steps for the single low-dose primaquine group.

Session 2. In-country perspectives for primaquine use
Session Objectives:
1) How are various countries using or planning to use SLD PQ?
2) What are the perceived benefits to SLD PQ use?
3) Are these countries facing barriers to SLD PQ implementation?
Session chair: Dennis Shanks (Australian Army Malaria Institute)

Common issues across different countries included procurement and formulation (see Table 1):

- Suggested procurement solution: to organize larger shipments to central organizations such as regional offices of WHO and distribute smaller quantities of PQ doses to countries with procurement problems;
- PQ formulation: Current crushing-and-dissolving method is for clinical trial use; difficulties with this method are expected in daily practice. Scoring is difficult, as pills are small. Sanofi is preparing an uncoated breakable pill.
Table 1. Barriers to single low dose primaquine rollout

<table>
<thead>
<tr>
<th>Barriers to rollout</th>
<th>Countries with SLD PQ written into national treatment guidelines</th>
<th>SLD PQ not written into policy</th>
<th>SLD PQ written into some policies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Botswana Namibia Senegal Swaziland Zanzibar South Africa WHO East Mediterranean Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country-level data needed</td>
<td>CYP2D6 variants X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>G6PD deficiency</td>
<td></td>
<td>X X</td>
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<tr>
<td>Regulatory affairs and supplies</td>
<td>Registration X X</td>
<td></td>
<td>X X</td>
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<td></td>
<td>Procurement X X X</td>
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<td>X X</td>
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<tr>
<td></td>
<td>Pediatric formulation X</td>
<td></td>
<td>X X</td>
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<tr>
<td>Programmatic needs</td>
<td>Training X X X X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Pharmacovigilance X</td>
<td></td>
<td>X X</td>
</tr>
</tbody>
</table>

Session 3. Research: Therapeutic Dose Range

**Session Objectives:**
1) Have we established a therapeutic dose range to facilitate the implementation of SLD PQ?  
2) Is additional evidence needed to enable further implementation of SLD PQ?

**Session chair:** Alice Chi Eziefula (London School of Hygiene and Tropical Medicine)

Table 2. Summary of SLD PQ efficacy studies since 2014 meeting

<table>
<thead>
<tr>
<th>Countries</th>
<th>PQ doses (in mg/kg)</th>
<th>Partner drug</th>
<th>Sample size</th>
<th>Gametocyte status</th>
<th>Membrane feeding</th>
<th>Results (lowest efficacious dose, in mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkina Faso</td>
<td>0.25 / 0.40</td>
<td>AL</td>
<td>360</td>
<td>Positive</td>
<td>Yes</td>
<td>0.25</td>
</tr>
<tr>
<td>Mali</td>
<td>0.0625 / 0.125 / 0.25 / 0.50</td>
<td>DP</td>
<td>81</td>
<td>Positive</td>
<td>Yes</td>
<td>0.125 - 0.25</td>
</tr>
<tr>
<td>Senegal</td>
<td>0.25</td>
<td>AL / DP / AS + AQ</td>
<td>300</td>
<td>Positive</td>
<td>No</td>
<td>Not yet Available</td>
</tr>
<tr>
<td>Gambia</td>
<td>0.20 / 0.40 / 0.75</td>
<td>DP</td>
<td>1200</td>
<td>Positive</td>
<td>No</td>
<td>Not yet Available</td>
</tr>
<tr>
<td>Tanzania</td>
<td>0.25</td>
<td>AL</td>
<td>206</td>
<td>Positive</td>
<td>No</td>
<td>Not yet Available*</td>
</tr>
<tr>
<td>Kenya</td>
<td>0.25</td>
<td>DP</td>
<td>120</td>
<td>Positive</td>
<td>Yes</td>
<td>Not yet Available</td>
</tr>
<tr>
<td>Cambodia</td>
<td>0.25</td>
<td>AS / AS + AQ</td>
<td>205</td>
<td>Positive</td>
<td>No</td>
<td>Not yet Available**</td>
</tr>
</tbody>
</table>
Table 3. Summary of SLD PQ safety studies since 2014 meeting

<table>
<thead>
<tr>
<th>Countries</th>
<th>PQ doses (in mg/kg)</th>
<th>Partner drug</th>
<th>Sample size</th>
<th>G6PD normal</th>
<th>G6PD deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkina Faso</td>
<td>0.25 / 0.40</td>
<td>AL</td>
<td>40</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mali</td>
<td>0.40 (adaptive)</td>
<td>-</td>
<td>28</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Senegal</td>
<td>0.25</td>
<td>AL / DP / AS + AQ</td>
<td>300</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tanzania</td>
<td>0.25</td>
<td>AL</td>
<td>220</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tanzania</td>
<td>0.75</td>
<td>SP / AS</td>
<td>204</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Uganda</td>
<td>0.10 / 0.40 / 0.75</td>
<td>AL</td>
<td>468</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- The lowest efficacious dose of SLD PQ is between 0.125 and 0.25 mg/kg, according to membrane feeding studies conducted in Mali (Table 2). The highest safe dose of SLD PQ is up to 0.50 mg/kg in west African G6PD-deficient men in Mali (Table 3). WHO representatives noted that WHO guidance states the SLD PQ therapeutic dose range to be between 0.15mg/kg and 0.375mg/kg and findings presented in the meeting support this range.

- WWARN is preparing a pooled analysis using data from SLD PQ trials and programs, to establish the therapeutic dose range. This, taken together with dose modelling, can facilitate the implementation of the WHO recommendation by translating a weight-based recommendation (0.25 mg/kg of SLD PQ) to age-based doses. Preliminary dose modelling studies using a therapeutic dose range of 0.125 – 0.4 mg/kg show that using 3.75 mg PQ tablets can allow for a 96% dose accuracy in Africa across all age groups, while 99% dose accuracy can be achieved using 2.5 mg PQ tablets.

- There are two tools available to promote the safe implementation of SLD PQ in program settings:
  1) A risk management manual for the use of SLD PQ in programs under development.
  2) The Primaquine Rollout Monitoring Pharmacovigilance Tool (PROMPT) is available as a pharmacovigilance and risk management tool consisting of three parts: a standardized form designed to support passive or active surveillance, a patient information card with instructions to return to the provider if signs of haemolysis are suspected, and a database compiling recorded information.

- Two important questions remain: what is the effect of PQ on G6PD deficient, *P. falciparum* positive, anaemic individuals? And what is the optimal partner drug to be used with PQ?
Session 4. Relevant research development

Session Objective: Are new tools or research findings available to provide further insights on SLD PQ safety and efficacy?

Session Chair: David Wesche (Bill & Melinda Gates Foundation)

- Risk assessment of SLD PQ use faces multiple complexities; suggested research directions include a focus on quantifying potential harm within the most vulnerable groups to SLD PQ. This may entail identification of the most vulnerable groups through detailed population-level surveys that assess G6PD activity levels in both males and females, as well as genotypic characterization of individuals with low enzyme activity. The risk of SLD PQ should be weighed against the transmission-reducing benefit offered by SLD PQ.

- Cytochrome P450 2D6 (CYP2D6) liver enzymes are responsible for producing the active PQ metabolite against both *P. vivax* hypnozoites and *P. falciparum* gametocytes. For gametocytocidal efficacy, intermediate (IMs) and poor metabolizers (PMs) of CYP 2D6 might clear gametocytes less efficiently after SLD PQ than ultrarapid and extensive metabolizers. The population-level implications for efficacy are at this point unclear; as a next step, mathematical models might help to investigate the potential impact of CYP2D6 IMs and PMs on overall transmission blocking activity on a population level.

- PQ metabolism is necessary for both efficacy and toxicity. Several hydroxylated metabolites have been identified including: 5-HPQ (highly unstable and reactive, depleting GSH in G6PD deficient red blood cells), 2-HPQ, 3-HPQ, 4-HPQ (these three metabolites are relatively stable and do not appear to be active or toxic *in vitro or in vivo*) and 8-NHPQ (a reactive species).

- Prof Walker’s group at the Cancer Institute of the University of Mississippi Medical Center are highly specialized in research into the efficacy and hematological toxicity of PQ. They are actively seeking samples for pharmacokinetic analysis on clinical samples to measure standard plasma levels of primaquine and carboxyprimaquine, low-level metabolites and primaquine enantiomers. These studies may provide insights into basic research and mechanisms of action, which could inform the development of future transmission-blocking drugs. Contact lwalker@olemiss.edu.

Session 5. Regulatory affairs and supply

Session Objectives:
1) Are there regulatory hurdles that delay or prevent implementation of SLD PQ, and if so, how these be overcome?
2) Is the current supply of PQ sufficient for its use as a falciparum malaria transmission blocker and if not, is there anything we can do about this?

Session Chair: Anja Terlouw (Liverpool School of Tropical Medicine)

- The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) is the largest funder of antimalarials and has a clear policy on quality assurance of pharmaceutical products. Globally, only two manufacturers fit the GFATM quality assurance policy: Sanofi (15 mg tablet) and Remedica (7.5 mg tablet). Currently, there are no concerns with the Sanofi production capacity for SLD PQ although forecasting would be helpful to plan for higher levels of implementation of the WHO recommendation.
Sanofi is currently developing scored tablets and pediatric formulations of primaquine. PQ may need to be registered for repurposing, as a gametocytocide. To achieve this, cooperation between the WHO, National Malaria Control Programs, and scientists will be necessary. Sanofi will produce a list of needed information to support their efforts in registration and share it with the PQ Roll Out Group.

SLD PQ can potentially be approved for off-label use, to block \textit{P. falciparum} transmission. For example, the WHO, local authorities, and other agencies/authorities have “approved” the off-label use of ivermectin and albendazole for certain indications. Sanofi and MMV continue to offer their leadership for the regulatory process for SLD PQ.

A barrier to SLD PQ procurement is in-country registration. Do we need a centralized supply management or a regional supply management?

**Session 6. Implementation and Policy**

**Session Objectives**
1) Are there additional ways that SLD PQ should be used?
2) What additional questions do we need to answer with regard to SLD PQ use in community applications?

**Session Chair:** Michelle Chang (Centers for Disease Control and Prevention)

- SLD PQ may be particularly useful if targeted towards highly mobile populations, for example, refugees transiting an international border, internally displaced persons, or high risk occupational groups (e.g. miners in Brazil). Targeting these populations may be very challenging, particularly as individuals are not symptomatic, do not want to be delayed in transit, and furthermore it may not be feasible for health workers to follow mobile populations.
- SLD PQ can be used in Mass Drug Administration (MDA) campaigns, however adequate pharmacovigilance is recommended, with care to only attribute PQ-related adverse events to PQ. Furthermore, models suggest that the use of SLD PQ in MDA only offer a small transmission reducing benefit, but that SLD PQ has a greater impact on transmission when coverage reaches 80% or higher, and also when partner drug does has no gametocytocidal activity, and/or treatment for clinical cases is delayed. Furthermore, most models have evaluated the addition of SLD PQ in the context of low transmission settings. It is also important to investigate the benefits of SLD PQ use in outbreak settings, post-elimination settings (e.g. resurgence), and highly focal transmission settings.
- The effectiveness of MDA requires high coverage, for which community participation and engagement are key. Reaching new individuals in every MDA round might also increase the likelihood of success, although the exclusion of certain groups (e.g. pregnant women) is inevitable. Also, while MDA reduces prevalence and incidence of malaria in the short term, if transmission is not interrupted or malaria importation is not prevented, transmission will return to the original level, unless the vectorial capacity is also reduced. Standardized metrics to assess MDA success are necessary. Is the goal to reduce transmission or to reach elimination?
- The WHO now recommends MDA for \textit{P. falciparum} elimination in areas approaching interruption of transmission, including in the Greater Mekong subregion (GMS) due to
spread of artemisinin resistance, as well as for epidemic control and in complex emergencies, when the health system is overwhelmed.

**Sessions 7 and 8. Discussion and activity/Synthesis and next steps**

**Session Objectives:** To identify and prioritize gaps in the roadmap

1. **Registration**
   - Conduct landscaping study for different regulatory pathways
   - Explore the possibility for pooled registration in some regions of Africa
   - In countries without *P. vivax* malaria, drug companies could work with global platform for Global Good, led by WHO (e.g. this process was used for African trypanosomiasis)

2. **Procurement**
   - Encourage the WHO to support a centralized or regional supply chain

3. **Pharmacovigilance**
   - Need to train healthcare workers at all levels, establish a multi-dimension risk management plan with pharmaceutical compan(ies), and establish a common platform to collect information, potentially the World Malaria Report
   - Data collection recommendations:
     - Baseline (prior to PQ implementation) information on haemolysis
     - Population-level surveys on G6PD deficiency, including specific mutations
     - Information on partner drugs, to establish if there are potential drug-drug interactions
   - Strategic recommendations:
     - Start pharmacovigilance on small scale and expand if successful, keeping note of barriers to conducting pharmacovigilance in country
     - Establish how to conduct pharmacovigilance in the private sector
     - Conduct active pharmacovigilance for vulnerable groups

4. **Use in MDA:**
   - Conduct a cost-benefit analysis of adding SLD PQ, including opportunity costs
   - Establish standardized metrics to determine PQ efficacy in MDA
   - Establish the best drug combination for PQ use
   - Provide clear guidelines to national malaria control programs for MDA
     - WHO is preparing a manual of operations for MDA (not restricted to PQ)
   - Use haemoglobin testing as a safety measure
   - Establish how to encourage people to take PQ for community-level benefit, not individual-level benefit

5. **Next Steps:**
   - Consider evolving into a consortium focused upon drug-based strategies for malaria elimination
     - Focus on transmission-blocking drugs
     - Collaborate with ivermectin consortium
     - Consider other tools to stop transmission (e.g. vaccines)
     - Include how to target approaches and tailor use to specific settings
   - Establish a platform to enhance information flow between national programs, researchers and other stakeholders