Update from GMP – Malaria Prevention, Diagnostics and Treatment

Interagency Pharmaceutical Coordination (IPC) Group Meeting
WHO, Geneva, Switzerland, 8-9 December 2016

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Outline

**Publications**
- WMR 2016 – release next week
- Policy brief: Testing for G6PD deficiency for safe use of primaquine in radical cure of *P. vivax* and *P. ovale* malaria

**Diagnosis**
- Rapid diagnostic tests and HRP2 deletion
- Transition from product testing to WHO PQ

**Treatment**
- New quality-assured medicines
World Malaria Report 2016

WMR 2016 will be launched on Tuesday, 13 December 2016
G6PD testing and safe administration of primaquine

Testing for G6PD deficiency for safe use of primaquine in radical cure of *P. vivax* and *P. ovale* malaria

Policy brief

Full policy brief available at

G6PD testing and safe administration of primaquine

Complete cure of *P. vivax / P. ovale* infection requires:

- antimalarial medicine to cure the blood-stage infection *plus*
- primaquine (PQ) to cure the liver-stage infection and prevent relapse

PQ is currently the *only available anti-relapse medicine* – however, its full potential is not used because it produces *dose-dependent AHA in individuals with G6PD deficiency.*

Challenge: G6PD testing often not available at the point of care, and PQ is either:

- administered without prior G6PD testing, exposing some patients to the risk of drug-induced AHA, or
- not administered, exposing patients to the risk of repeated relapses with consequent morbidity and contribution to transmission.
G6PD testing and use of PQ for radical cure of vivax malaria

Male and female patients with confirmed *P. vivax* or *P. ovale* malaria (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient)

Qualitative G6PD testing

< 30% G6PD activity

**Female and male: G6PD deficient**

Patient counselling*

8 weeks' primaquine regimen
(0.75 mg base/kg body weight once a week)
under *medical supervision*;
blood transfusion available

> 30% G6PD activity

**Female:** the individual could be G6PD normal or G6PD intermediate with potential risk for haemolysis

Patient counselling*

14 days' primaquine regimen
(0.25-0.5 mg base/kg body weight daily)

**Male:** G6PD normal

Qualitative G6PD testing unavailable

*Risk-benefit assessment**

*More information on risk-benefit assessment, patient counselling and medical supervision is provided in the text.*
In April 2016, the **WHO Prequalification** team announced expansion to G6PD tests – procedures under development.

An **Expert Review Panel for diagnostics** mechanism has been established by the Global Fund and UNITAID, coordinated by WHO.

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**BOX 4**

**PREFERRED PRODUCT CHARACTERISTICS FOR QUALITATIVE POINT-OF CARE G6PD TESTS**

- The **sensitivity** should be > 95% of that of spectrophotometry or equivalent quantitative tests for detecting G6PD enzyme activity at levels < 30% of normal.

- The **negative predictive value** should be > 95%, i.e. provide a 95% probability that the patient has > 30% normal G6PD activity when the diagnostic test indicates that he or she is not deficient.

- The product should be stable at the **temperatures** expected in tropical settings (30–40 °C).

- The test should have a **visual read-out** that clearly distinguishes between “deficient” and “normal” G6PD activity.
RDTs have increased access to malaria diagnosis

WHO African Region has had the largest increase in levels of malaria testing, from:

- 36% of suspected malaria cases tested in 2005
- to 41% in 2010 and
- 65% in 2014

Expansion of diagnostic testing attributable to malaria RDTs

Source: World Malaria Report 2015
**HRP2 deletion**

Review the currently available data, and to define the scope and scale of *pfhrp2/3*-deleted parasite populations based on published or in-press reports and recent unpublished investigations.

### Pfhrp2 gene deletions confirmed

<table>
<thead>
<tr>
<th>South America</th>
<th>Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peru</td>
<td>Eritrea</td>
</tr>
<tr>
<td>Brazil</td>
<td>DRC</td>
</tr>
<tr>
<td>Colombia</td>
<td>Ghana</td>
</tr>
<tr>
<td>Suriname</td>
<td>Zambia</td>
</tr>
<tr>
<td>Bolivia</td>
<td>(Mali)</td>
</tr>
<tr>
<td></td>
<td>(Senegal)</td>
</tr>
</tbody>
</table>

**Analysis based on discordant results between RDT or microscopy/PCR or WGS and no deletions identified**

- Mozambique
- Tanzania
- Western Kenya
- Uganda
2016: Serious public health threat

- **May 2016:** WHO issued an information note on causes of false negative RDTs and *pfhrp2/3* gene deletions

- **July 2016:** WHO technical consultation on *pfhrp2/3* gene deletions

- **September 2016:** Malaria Policy Advisory Committee (MPAC) review of recommendations

- Development of an Action/Response Plan
Changes to WHO criteria on RDT procurement

**Since 2009:**
WHO Malaria RDT Product Testing Programme

Malaria Rapid Diagnostic Test Performance

Results of WHO product testing of malaria RDTs: round 6 (2014–2015)

12 malaria RDTs from 4 manufacturers are WHO prequalified:
- 7 Pf-only
- 4 Pf and non-Pf
- 1 all species (but does not distinguish between them)

Products accessible at:

http://www.who.int/diagnostics_laboratory/evaluations/en/

Test name | Manufacturer | 2014 MS (in category) | 2014 MS (overall) | Prequalified date
--- | --- | --- | --- | ---
Pf Only
1. CareStartTM Malaria HRP2 (Pf) | Access Bio | 34% | 31% | 28-May-15
2. First Response® Malaria Ag P. falciparum (HRP2) Card Test | PMI | 15% | 9% | 25-Feb-15
3. ParastatTM Ver. 1.0 Rapid Test for P.falciparum Malaria Dipstick | Span/Arkay | 0% | 7-Oct-14 |
4. ParastatTM Ver. 1.0 Rapid Test for P.falciparum Malaria Dipstick | Span/Arkay | 3% | 2% | 7-Oct-14
5. SD BIOLINE Malaria Ag Pf | Alere/SD | 41% | 26% | 6-Dec-10

Pf/pan
1. Carestart pf/pv Combo | Access Bio | 12% | 4% | 28-May-15
2. SD BIOLINE Malaria Ag Pf/Pv | Alere/SD | 72% | 21% | 8-Jul-15

Pf/P
1. CareStartTM Malaria HRP2/pLDH (Pf/Pv) COMBO | Access Bio | 6% | 0% | 28-May-15
2. SD BIOLINE Malaria Ag Pf/Pv | Alere/SD | 94% | 5% | 16-Oct-15

Other
1. CareStartTM Malaria HRP2/pLDH (Pf) | Access Bio | 2% | 2% | 28-May-15
2. CareStartTM Malaria pLDH (P) | Access Bio | 0% | 0% | 28-May-15
3. SD BIOLINE Malaria Ag Pf/Pv | Alere/SD | 1% | 1% | 16-Oct-15

7%
Quality-assured antimalarial medicines  (last updated 06.12.2016)

- **Fixed-dose combinations (FDCs)**
  - **AL 20/120mg:** Ajanta, Cipla, Ipca, Macleods, Mylan, Novartis, Strides
  - **AL 20/120mg dispersibles:** Ajanta, Novartis
  - **AL 40/240mg:** Mylan
  - **AL 80/480mg:** Novartis
  - **ASAQ:** Ajanta, Cipla, Guilin, Ipca, Sanofi
  - **ASMQ:** DNDi/Cipla
  - **DHA-PPQ (20/160mg, 40/320mg):** Sigma-Tau

- **Co-Blisters (Co-B)**
  - **AS + AQ:** Cipla, Guilin, Ipca, Strides
  - **AS + SP:** Guilin

- **Injectables**
  - **AS (30/60/120mg) powder for inj:** Guilin

- **SP + AQ (76.5+25012.5mg, 153+500/250mg):** Guilin
- **Primaquine (7.5mg, 15mg):** Remedica, Sanofi
- **Chloroquine:** Alliance Pharma, Remedica, Sanofi
- **SP (500/25mg):** Guilin
### List of Malaria Pharmaceutical Products

**classified according to the Global Fund Quality Assurance Policy**

**Edition: Version 83 - 07th December 2016**

**List of ERP (Expert Review Panel) Reviewed Products which are permitted for time limited procurement:**

If there is no or only one A or B product available (supply of the product cannot be done within 90 days after the receipt of the Purchase Order by the manufacturer), grant funds may be used to procure a ERP reviewed product eligible for procurement for limited time (12 months) period. The PR must send the “notification form” (available at http://www.theglobalfund.org/en/procurement/quality/?lang=en) to the Global Fund and upon receiving the “No Objection” letter from the Global Fund, the procurement can proceed. Please note that the QC test of the selected ERP product will be performed by the Global Fund.

<table>
<thead>
<tr>
<th>Ref.No</th>
<th>International Non-proprietary name</th>
<th>Strength / Dose</th>
<th>Dosage form</th>
<th>Supplier / Manufacturer(s)</th>
<th>Global Fund QA Standard</th>
<th>Period Validity for ERP Review</th>
<th>Manufacturing Site</th>
<th>Country</th>
<th>Material</th>
<th>Pack</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amodiaquine (as Hydrochloride) + Sulfadoxine / Pyrimethamine</td>
<td>75mg + 250mg / 12.5mg</td>
<td>Co-blistered Disp tablet</td>
<td>Guilin Pharmaceuticals</td>
<td>ERP reviewed</td>
<td>2/7/2017</td>
<td>Guilin Pharmaceuticals Co. Ltd, No. 43 Quilian road, Gulin</td>
<td>China</td>
<td>Alu / PVC Blister</td>
<td>50x (3+1)</td>
</tr>
<tr>
<td>2</td>
<td>Amodiaquine (as Hydrochloride) + Sulfadoxine / Pyrimethamine</td>
<td>150mg + 500mg / 25mg</td>
<td>Co-blistered Disp tablet</td>
<td>Guilin Pharmaceuticals</td>
<td>ERP reviewed</td>
<td>2/7/2017</td>
<td>Guilin Pharmaceuticals Co. Ltd, No. 43 Quilian road, Gulin</td>
<td>China</td>
<td>Alu / PVC Blister</td>
<td>50x (3+1)</td>
</tr>
<tr>
<td>3</td>
<td>Amodiaquine (as Hydrochloride) + (Sulfadoxine / Pyrimethamine)</td>
<td>75mg + (250mg / 12.5mg)</td>
<td>Co-Blistered tablet</td>
<td>Guilin Pharmaceuticals</td>
<td>ERP reviewed</td>
<td>10/17/2017</td>
<td>Guilin Pharmaceuticals Co. Ltd, No. 43 Quilian road, Gulin</td>
<td>China</td>
<td>Alu / PVC Blister</td>
<td>50x (3+1)</td>
</tr>
<tr>
<td>4</td>
<td>Amodiaquine (as Hydrochloride) + (Sulfadoxine / Pyrimethamine)</td>
<td>150mg + (500mg / 25mg)</td>
<td>Co-Blistered tablet</td>
<td>Guilin Pharmaceuticals</td>
<td>ERP reviewed</td>
<td>10/17/2017</td>
<td>Guilin Pharmaceuticals Co. Ltd, No. 43 Quilian road, Gulin</td>
<td>China</td>
<td>Blister</td>
<td>50x(3+1)25x(3+1)</td>
</tr>
<tr>
<td>5</td>
<td>Artesunate + (Sulfadoxine / Pyrimethamine)</td>
<td>50mg + (500mg / 25mg)</td>
<td>Tablet Co-blister</td>
<td>Guilin Pharmaceuticals</td>
<td>ERP reviewed</td>
<td>2/24/2017</td>
<td>Guilin, Guangxi</td>
<td>China</td>
<td>PVC / Al u Blister</td>
<td>(3+1), (6+2)</td>
</tr>
<tr>
<td>6</td>
<td>Artesunate + (Sulfadoxine / Pyrimethamine)</td>
<td>100mg + (500mg / 25mg)</td>
<td>Tablet Co-blister</td>
<td>Guilin Pharmaceuticals</td>
<td>ERP reviewed</td>
<td>2/24/2017</td>
<td>Guilin, Guangxi</td>
<td>China</td>
<td>PVC / Al u Blister</td>
<td>(3+1), (6+3)</td>
</tr>
<tr>
<td>7</td>
<td>Sulfadoxine + Pyrimethamine</td>
<td>500mg + 25mg</td>
<td>Tablet FDC</td>
<td>Guilin Pharmaceuticals</td>
<td>ERP reviewed</td>
<td>10/17/2017</td>
<td>Guilin Pharmaceuticals Co. Ltd, No. 43 Quilian road, Gulin</td>
<td>China</td>
<td>HDPE bottle; Blister</td>
<td>1000's 3'</td>
</tr>
<tr>
<td>8</td>
<td>Artesunate</td>
<td>100mg</td>
<td>Suppository</td>
<td>Cipla Limited</td>
<td>ERP reviewed</td>
<td>12/3/2017</td>
<td>Cipla Limited, Dr, MIDC Industrial area, Karkumb, Dist Pune 413002 MP</td>
<td>India</td>
<td>Alu / Alu Blister</td>
<td>2'</td>
</tr>
</tbody>
</table>

**Rectal artesunate – first product ERP approved**
Severe malaria

- Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular **artesunate** for at least **24 hours** and until they can tolerate oral medication.

- Once a patient has received at least 24 hours of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of **ACT** (add single dose **primaquine** in areas of low transmission).

**Parenteral alternatives where artesunate is not available.**

If artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.
Where complete treatment of severe malaria is **not** possible but injections are available, give adults and children a **single** intramuscular dose of **artesunate**, and **refer** to an appropriate facility for further care.

Where intramuscular artesunate is not available use intramuscular artemether or, if that is not available, use intramuscular quinine.

Where intramuscular injection of artesunate is **not** available, treat **children < 6 years** with a **single rectal dose (10mg/kg bw)** of **artesunate**, and **refer** immediately to an appropriate facility for further care.

Do not use rectal artesunate in older children and adults.
WHO information note to be published soon, highlighting the crucial importance of:

- Correct deployment of rectal artesunate (RAS) in remote settings (monotherapy and risk of resistance)
- Not use RAS in older children and adults
- Essential referral to higher level facilities, where complete treatment with injectable AS and oral ACT can be provided
Thank you very much for your attention
Performance evaluation of malaria RDTs: Round 6 report published – WHO selection criteria updated

Since 2009:
WHO Malaria RDT Product Testing Programme

Recommended selection criteria for procurement of malaria rapid diagnostic tests

MARCH 2016

INFORMATION NOTE

There is increasing demand for countries to improve malaria diagnosis in view of wide-scale introduction of expensive antimalarial medicines and the deceasing malaria trends in many countries. Therefore, guidance is required for selecting rapid diagnostic tests (RDTs) for malaria that meet quality standards. The aims of this WHO information note are to list the criteria recommended for selecting tests and to provide an overview of additional considerations in the procurement of malaria RDTs.

WHO POLICY ON MALARIA DIAGNOSIS

WHO recommends parasitological confirmation of malaria in all settings by quality-assured diagnosis before treatment is started. Treatment solely on the basis of clinical suspicion should be considered only when a parasitological diagnosis is not available within two hours of presentation of a patient for treatment. A diagnosis of malaria can be confirmed rapidly by good-quality microscopy or with a good-quality malaria antigen-detecting RDT for Plasmodium falciparum and non-falciparum infections. In most countries, both diagnostic methods are required, as microscopy and RDTs often play different roles, depending on the clinical situation or the setting.

WHO MALARIA RDT PRODUCT TESTING PROGRAMME

Product evaluation

The heterogeneous diagnostic performance of the more than 200 malaria RDTs currently available on the market can undermine the confidence of health professionals in the accuracy of these tests. The WHO malaria RDT product testing programme, coordinated by the Global Malaria
## WHO prequalified malaria RDTs

<table>
<thead>
<tr>
<th>Test name</th>
<th>Manufacturer</th>
<th>2014 MS (w/in category)</th>
<th>2014 MS (overall)</th>
<th>Prequalified date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pf Only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 CareStartTM Malaria HRP2 (Pf)</td>
<td>Access Bio</td>
<td>34%</td>
<td>21%</td>
<td>28-May-15</td>
</tr>
<tr>
<td>2 First Response® Malaria Ag P. falciparum (HRP2) Card Test</td>
<td>PMC</td>
<td>15%</td>
<td>9%</td>
<td>25-Feb-15</td>
</tr>
<tr>
<td>3 ParaHit f Ver. 1.0 Rapid Test for P.falciparum Malaria Dipstick</td>
<td>Span/Arkay</td>
<td>0%</td>
<td></td>
<td>7-Oct-14</td>
</tr>
<tr>
<td>4 ParaHit f Ver. 1.0 Rapid Test for P.falciparum Malaria Device</td>
<td>Span/Arkay</td>
<td>3%</td>
<td>2%</td>
<td>7-Oct-14</td>
</tr>
<tr>
<td>5 SD BIOLINE Malaria Ag P.f</td>
<td>Alere/SD</td>
<td>41%</td>
<td>26%</td>
<td>6-Dec-10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>93% 58%</td>
</tr>
<tr>
<td><strong>Pf/pan</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Carestart pf/pan Combo</td>
<td>Access Bio</td>
<td>12%</td>
<td>4%</td>
<td>28-May-15</td>
</tr>
<tr>
<td>2 SD BIOLINE Malaria Ag P.f/Pan</td>
<td>Alere/SD</td>
<td>72%</td>
<td>21%</td>
<td>8-Jul-13</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>84% 24%</td>
</tr>
<tr>
<td><strong>Pf/pv</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 CareStartTM Malaria HRP2/pLDH (Pf/Pv) COMBO</td>
<td>Access Bio</td>
<td>6%</td>
<td>0%</td>
<td>28-May-15</td>
</tr>
<tr>
<td>2 SD BIOLINE Malaria Ag P.f/P.v</td>
<td>Alere/SD</td>
<td>94%</td>
<td>5%</td>
<td>16-Oct-15</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>100% 6%</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 CareStartTM Malaria HRP2/pLDH (Pf)</td>
<td>Access Bio</td>
<td>2%</td>
<td></td>
<td>28-May-15</td>
</tr>
<tr>
<td>2 CareStartTM Malaria pLDH (PAN)</td>
<td>Access Bio</td>
<td>0%</td>
<td></td>
<td>28-May-15</td>
</tr>
<tr>
<td>3 SD BIOLINE Malaria Ag P.f (HRP2/pLDH)</td>
<td>Alere/SD</td>
<td>1%</td>
<td></td>
<td>16-Oct-15</td>
</tr>
<tr>
<td>4 SD BIOLINE Malaria Ag P.f (HRP1/pLDH)</td>
<td>Alere/SD</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Global Malaria Programme
Timelines

- **For products that are currently eligible** for WHO procurement, manufacturers must submit a **WHO PQ pre-submission form** to WHO PQT by **31 July 2016**.

- **For products that are new** to WHO processes or for products that are due for **compulsory resubmission** to Product Testing, manufacturers must submit to the revised EOI for Round 8, in **quarter 4 of 2016**.

- Manufacturers are expected to have submitted a **complete dossier** for each product to WHO PQT by **31 December 2016**.

- Manufacturers are expected to complete full prequalification by **31 December 2017**. Beyond this date only prequalified products will be recommended and eligible for WHO procurement.