Update on malaria case management policies and guidelines

A. Bosman, J. Cunningham, P. Olumese, S. Sadrudin and S. Schwarte
Prevention, Diagnostic and Treatment Unit

RBM CASE MANAGEMENT WORKING GROUP (CMWG)
10th Annual Meeting 6-8th February 2019
Global Health Campus

Global Malaria Programme
World Health Organization
Update on WHO Guidelines for the Treatment of Malaria

- Artesunate+pyronaridine, ACT in 1st trimester, *P. vivax* detecting RDTs

- Recent WHO guidance on malaria diagnostics
  - RDT procurement, uRDTs, G6PD POCT, *pfhrp2* gene deletions

- Lessons learnt on iCCM from RAcE 2015
  - Scalability, factors affecting impact and sustainability
Current WHO policy making process for malaria

Evidence Review Groups
- VCAG (with NTD)
- WHO GMP Secretariat
- WHO DG
- WHO policy recommendations

The Technical Expert Group on Malaria Chemotherapy operates as Guidelines Development Group

WHO GMP Secretariat
- Vector Control
- Surveillance monitoring evaluation
- Chemotherapy
- Drug Resistance & Containment
- The Technical Expert Group on Malaria Chemotherapy operates as Guidelines Development Group

Global Malaria Programme

World Health Organization
The WHO Guidelines for the Treatment of Malaria

- provide comprehensible, global and evidence-based guidelines for the formulation of policies and protocols for the treatment of malaria.


- is available in hard and web-based versions.

http://www.who.int/malaria/publications/atoz/9789241549127/en/
• **Target audience:**
  • Primarily policy-makers in ministries of health, who formulate national treatment guidelines.

• **Purpose and objectives:**
  • Assist policy-makers to define and refine effective national treatment policies on the basis of the best available evidence
    • *Taking into account national and local drug resistance pattern and health services capacity*
  • Promote the use of safe, effective malaria treatment
  • Protect currently effective malaria treatment against the development of resistance
Policy process map – Medicines

**Owners**
- PDPs/Mfrs
- External Review
- Cochrane

**WHO Bodies**
- GRC
- GSC
- TEG
- MPAC
- WHO-GMP

**Pipeline mgt 1-3 years**
- Present data summary, ask for input on elements of trial design

**Preparation 0.5 year**
- To be considered for policy, product must be registered with an SRA/NRA
- Publish data in peer-reviewed int'l journals

**Evidence evaluation 1.5 years**
- Systematic review
  - GRADE Table
  - Decision Table

**Guidelines dev 1 year**
- Development of draft Treatment Guidelines
- Review draft guidelines

**Finalization & dissemination 0.5 year**
- Review of draft guidelines
- Issue Guidelines
  - Technical editing
  - Printing
  - Translation
  - Distribution

**Milestones**
1. Guidelines Review Committee
2. Guidelines Steering Committee
3. Technical Expert Group
4. Malaria Policy Advisory Committee
5. Standards typically include safety, high cure rate, superiority or equivalence to existing products, ease of use, simplified regimen, cost, etc.
6. Guidelines Development Group
7. Declaration Of Interest
8. Conflict Of Interest
9. Population Intervention Comparator Outcome
10. Essential Medicines List
11. Prequalification
12. Expert Review Panel to get a one year interim recommendation

Source: BCG policy review of WHO/GMP
## ACTs prequalified by WHO (updated on 04.02.2019)

<table>
<thead>
<tr>
<th>API</th>
<th>Strength (mg) and Formulation</th>
<th>Ajanta</th>
<th>Alfasigma</th>
<th>Cipla</th>
<th>DNDi</th>
<th>Guillin</th>
<th>Ipca</th>
<th>McLeods</th>
<th>Micro Labs</th>
<th>Novartis</th>
<th>Sanofi</th>
<th>Shin Poong</th>
<th>Strides</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>20/120 dispersible tablets</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AL</td>
<td>20/120 tablets</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AL</td>
<td>40/240 tablets</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AL</td>
<td>60/360 tablets</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AL</td>
<td>80/480 tablets</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS + AQ</td>
<td>50 + 150 Co-Blister</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASAQ</td>
<td>67.5/25 Fixed-dose combination (FDC)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASAQ</td>
<td>135/50 FDC</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASAQ</td>
<td>270/100 FDC</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASMQ</td>
<td>25/50 tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASMQ</td>
<td>100/200 tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASSP</td>
<td>50 + 500/25 tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>ASSP</td>
<td>100 + 500/25 tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>ASPyr</td>
<td>20/60 granules for oral suspension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>ASPyr</td>
<td>60/180 tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>DHA/PPQ</td>
<td>20/160 tablet</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHA/PPQ</td>
<td>40/320 tablet</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

World Health Organization
Quality assured ACTs delivered and distributed

NMP data reflect the public health sector distribution; AMFm in 2010-2013, GF co-payment mechanism in 2014-2017

Source: WMR 2018.
Based on 19 household surveys conducted in sub-Saharan Africa in 2015–2017, a median of 28% of children (IQR: 18–36%) had a fever in the previous 2 weeks, with minor variation by age. 

Source: WMR 2018.
Ongoing review of WHO recommendations

- Recommendation on the use of **artesunate-pyronaridine**
  - The WHO Advisory Committee on Safety of Medicinal Products commissioned a safety review with focus on hepatotoxicity (15th ACSoMP meeting, April 2018): expected completion in April 2019
  - Publication of Cochrane Systematic Review on «Pyronaridine-artesunate for treating uncomplicated *P. falciparum* malaria», basis for deliberations of WHO Technical Expert Group on Malaria Chemotherapy (Dec 2017), concludes:
    - Pyronaridine-artesunate was efficacious against uncomplicated *P. falciparum* malaria, achieved a PCR-adjusted treatment failure rate of less than 5% at days 28 and 42, and may be at least as good as, or better than other marketed ACTs.
    - Pyronaridine-artesunate increases the risk of episodes of raised ALT > 5 x ULN. This meets criteria for mild drug-induced liver injury. On one instance this was linked to raised bilirubin, indicating moderate drug-induced liver injury. No episodes of severe drug-induced liver injury were reported. The findings of this review cannot fully inform a risk-benefit assessment for an unselected population. Readers should remain aware of this uncertainty when considering use of pyronaridine-artesunate in patients with known or suspected pre-existing liver dysfunction, and when co-administering with other medications which may cause liver dysfunction. 
      
• The WHO Technical Expert Group on malaria Chemotherapy in December 2017, as Guidelines Development Group generated the following recommendation: “Artemisinin combination treatments should be used to treat malaria in pregnant women in the first trimester of pregnancy except where the partner drug is contraindicated as with AS+SP.” The recommendation was endorsed by MPAC in July 2018 and the release of these new recommendations is pending internal agreement with WHO LEG and PUB on the disclaimer to be added to the all WHO guidelines and publications which recommend “off-label use” of medicines.
Stillbirth and exposure to quinine and artemisinins during the 1st trimester of pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Exposed Group #Stillbirth/ #Total</th>
<th>Comparison Group #Stillbirth/ #Total</th>
<th>Crude Hazard Ratio (95% CI)</th>
<th>% Weight</th>
<th>P-value</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemisinin vs Unexposed to Antimalarials, 1st Trimester</td>
<td>IPD Africa à 10/ 534 165/ 6027</td>
<td>SMRU Thailand 0/ 120 179/ 17799</td>
<td>0.67 (0.35, 1.27) 0.67 (0.35, 1.27)</td>
<td>100.00 0.00</td>
<td>0.220 0.220</td>
<td>0.65 (0.34, 1.23) 0.65 (0.34, 1.23)</td>
<td>0.184 0.184</td>
</tr>
<tr>
<td>Artemisinin vs Unexposed to Antimalarials, Embryo-sensitive period</td>
<td>IPD Africa à 0/ 331 165/ 6027</td>
<td>SMRU Thailand 0/ 40 179/ 17799</td>
<td>0.76 (0.37, 1.56) 0.76 (0.37, 1.56)</td>
<td>100.00 100.00</td>
<td>0.458 0.458</td>
<td>0.75 (0.37, 1.54) 0.75 (0.37, 1.54)</td>
<td>0.440 0.440</td>
</tr>
<tr>
<td>Quinine vs Unexposed to Antimalarials, 1st Trimester</td>
<td>IPD Africa à 5/ 105 165/ 6027</td>
<td>SMRU Thailand 6/ 510 179/ 17799</td>
<td>1.85 (0.74, 4.63) 1.16 (0.51, 2.60)</td>
<td>44.16 55.84</td>
<td>0.744 0.730</td>
<td>1.83 (0.73, 4.59) 0.94 (0.35, 2.56)</td>
<td>0.197 0.905</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.445)</td>
<td>1.42 (0.77, 2.61)</td>
<td>100.00 0.259</td>
<td>1.35 (0.69, 2.65)</td>
<td>0.398</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine vs Unexposed to Antimalarials, Embryo-sensitive period</td>
<td>IPD Africa à 3/ 53 165/ 6027</td>
<td>SMRU Thailand 2/ 401 179/ 17799</td>
<td>2.22 (0.68, 7.22) 0.40 (0.12, 1.35)</td>
<td>53.31 48.80</td>
<td>0.185 0.322</td>
<td>2.20 (0.68, 7.19)</td>
<td>0.191</td>
</tr>
<tr>
<td>Subtotal (I-squared = 61.6%, p = 0.106)</td>
<td>1.10 (0.26, 4.68)</td>
<td>100.00 0.903</td>
<td>2.20 (0.68, 7.19)</td>
<td>0.191</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artemisinin vs Quinine, 1st Trimester</td>
<td>IPD Africa à 10/ 534 5/ 105</td>
<td>SMRU Thailand 6/ 510 6/ 510</td>
<td>0.30 (0.06, 1.05) 0.30 (0.06, 1.05)</td>
<td>100.00 100.00</td>
<td>0.060 0.060</td>
<td>0.29 (0.08, 1.02) 0.29 (0.08, 1.02)</td>
<td>0.053 0.053</td>
</tr>
<tr>
<td>Artemisinin vs Quinine, Embryo-sensitive period</td>
<td>IPD Africa à 8/ 331 3/ 53</td>
<td>SMRU Thailand 2/ 401 2/ 401</td>
<td>0.76 (0.27, 2.12) 0.76 (0.27, 2.12)</td>
<td>100.00 100.00</td>
<td>0.600 0.600</td>
<td>0.73 (0.26, 2.06) 0.73 (0.26, 2.06)</td>
<td>0.551 0.551</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Control group
Higher risk of stillbirth in comparison group
Higher risk of stillbirth in exposed group
Exposed group

https://doi.org/10.1371/journal.pmed.1002290

Global Malaria Programme
World Health Organization
## Miscarriage and exposure to quinine and artemisinins during the 1st trimester of pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Exposed group</th>
<th>Comparison group</th>
<th>Crude Hazard Ratio (95% CI)</th>
<th>% Weight</th>
<th>P-value</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Artemisinin vs Unexposed to Antimalarials, 1st Trimester</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPD Africa^a</td>
<td>14/ 488</td>
<td>123'464</td>
<td>1.02 (0.58, 1.79)</td>
<td>35.22</td>
<td>0.934</td>
<td>1.00 (0.57, 1.76)</td>
<td>0.999</td>
</tr>
<tr>
<td>SMRU Thailand</td>
<td>23/ 183</td>
<td>1963/ 22927</td>
<td>1.43 (0.94, 2.15)</td>
<td>64.76</td>
<td>0.091</td>
<td>1.28 (0.8, 2.04)</td>
<td>0.305</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.348)</td>
<td></td>
<td></td>
<td>1.27 (0.91, 1.77)</td>
<td>100.00</td>
<td>0.168</td>
<td>1.16 (0.81, 1.66)</td>
<td>0.426</td>
</tr>
<tr>
<td><strong>Artemisinin vs Unexposed to Antimalarials, Embryo-sensitive period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPD Africa^a</td>
<td>10/ 340</td>
<td>123'464</td>
<td>1.09 (0.56, 2.00)</td>
<td>40.03</td>
<td>0.611</td>
<td>1.08 (0.56, 2.09)</td>
<td>0.000</td>
</tr>
<tr>
<td>SMRU Thailand</td>
<td>12/ 76</td>
<td>1495/ 20534</td>
<td>2.48 (1.40, 4.37)</td>
<td>51.97</td>
<td>0.002</td>
<td>2.66 (1.46, 4.82)</td>
<td>0.001</td>
</tr>
<tr>
<td>Subtotal (I-squared = 71.5%, p = 0.061)</td>
<td></td>
<td></td>
<td>1.67 (0.74, 3.75)</td>
<td>100.00</td>
<td>0.218</td>
<td>1.71 (0.71, 4.15)</td>
<td>0.232</td>
</tr>
<tr>
<td><strong>Quinine vs Unexposed to Antimalarials, 1st Trimester</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPD Africa^a</td>
<td>4/ 103</td>
<td>123'464</td>
<td>2.07 (0.74, 5.77)</td>
<td>3.95</td>
<td>0.166</td>
<td>2.12 (0.76, 5.94)</td>
<td>0.153</td>
</tr>
<tr>
<td>SMRU Thailand</td>
<td>92/ 842</td>
<td>1963/ 22927</td>
<td>1.48 (1.20, 1.82)</td>
<td>96.05</td>
<td>&lt;0.001</td>
<td>1.45 (1.15, 1.84)</td>
<td>0.002</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.532)</td>
<td></td>
<td></td>
<td>1.50 (1.22, 1.84)</td>
<td>100.00</td>
<td>&lt;0.001</td>
<td>1.48 (1.18, 1.88)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Quinine vs Unexposed to Antimalarials, Embryo-sensitive period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPD Africa^a</td>
<td>1/ 52</td>
<td>123'464</td>
<td>1.03 (0.14, 7.56)</td>
<td>1.73</td>
<td>0.978</td>
<td>1.04 (0.14, 7.65)</td>
<td>0.971</td>
</tr>
<tr>
<td>SMRU Thailand</td>
<td>57/ 642</td>
<td>1495/ 20534</td>
<td>1.38 (1.06, 1.80)</td>
<td>98.27</td>
<td>0.017</td>
<td>1.37 (1.02, 1.84)</td>
<td>0.037</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.775)</td>
<td></td>
<td></td>
<td>1.37 (1.06, 1.80)</td>
<td>100.00</td>
<td>0.018</td>
<td>1.36 (1.02, 1.82)</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>Artemisinin vs Quinine, 1st Trimester</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPD Africa^a</td>
<td>14/ 488</td>
<td>123'464</td>
<td>0.51 (0.14, 1.81)</td>
<td>11.55</td>
<td>0.296</td>
<td>0.52 (0.14, 1.87)</td>
<td>0.316</td>
</tr>
<tr>
<td>SMRU Thailand</td>
<td>23/ 183</td>
<td>1963/ 22927</td>
<td>0.97 (0.61, 1.53)</td>
<td>88.45</td>
<td>0.861</td>
<td>0.78 (0.45, 1.34)</td>
<td>0.365</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.348)</td>
<td></td>
<td></td>
<td>0.96 (0.56, 1.69)</td>
<td>100.00</td>
<td>0.033</td>
<td>0.73 (0.44, 1.21)</td>
<td>0.228</td>
</tr>
<tr>
<td><strong>Artemisinin vs Quinine, Embryo-sensitive period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPD Africa^a</td>
<td>10/ 340</td>
<td>1/ 52</td>
<td>0.84 (0.33, 2.16)</td>
<td>38.77</td>
<td>0.715</td>
<td>0.93 (0.36, 2.43)</td>
<td>0.882</td>
</tr>
<tr>
<td>SMRU Thailand</td>
<td>12/ 75</td>
<td>57/ 542</td>
<td>1.80 (0.96, 3.35)</td>
<td>61.23</td>
<td>0.065</td>
<td>1.15 (0.46, 2.87)</td>
<td>0.760</td>
</tr>
<tr>
<td>Subtotal (I-squared = 42.7%, p = 0.187)</td>
<td></td>
<td></td>
<td>1.34 (0.65, 2.78)</td>
<td>100.00</td>
<td>0.433</td>
<td>1.04 (0.54, 2.01)</td>
<td>0.910</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Control group Higher risk of miscarriage in comparison group Exposed group

Global Malaria Programme

https://doi.org/10.1371/journal.pmed.1002290
Treatment with quinine + clindamycin

7 days of quinine (10 mg salt/kg bw, three times a day)  
plus clindamycin (10mg/kg, two times a day)

- With quinine sulfate 300 mg tablets and clindamycin 300mg capsules, a pregnant women of 60 kg bw needs to take 2 tablets of quinine three times a day for seven days (=42 tablets) plus two capsules of clindamycin twice a day for seven days (=28 capsules) at different times of the day.
- This regimen and the side effects of quinine explain the poor adherence to treatment and, for this reason, pregnant women do not receive an effective treatment for malaria.
- In reality, clindamycin is often not available and the different formulations and strengths of quinine tablets on the market, make even more difficult to adhere to the above recommendations for malaria treatment in pregnancy.

Global Malaria Programme
MIP in low and unstable transmission areas

Pregnant women are a high risk group

Acquired Immunity = Low

Clinical Illness

Severe Disease

Risk to Mother
- Death following severe malaria

Risk to Fetus
- Prematurity
- Miscarriage
- Stillbirth

- All pregnancies at risk
- Up to 60% fetal loss and 10% maternal deaths
- 50% maternal mortality with severe disease

Global Malaria Programme

World Health Organization
Recommendation on the use of RDT to diagnose vivax malaria

- Current text (page 30 of WHO Guidelines for the Treatment of Malaria):
  - “Where *P. vivax* malaria is common and microscopy is not available, it is recommended that a combination RDT be used that allows detection of *P. vivax* (pLDH antigen of *P. vivax*) or pan-malarial antigens (Pan-pLDH or aldolase).”

- The WHO Technical Expert Group on malaria Chemotherapy in December 2017, as Guidelines Development Group recommended to revise the text as follows:
  - “Where *P. vivax* is common, either microscopy or a Rapid Diagnostics Test that allow detection of *P. vivax* pLDH antigen may be used for *P. vivax* diagnosis.”
Product testing Rd 5-8: *P. vivax* results

Figure S2: Malaria RDT performance in phase 2 of rounds 5-8 against wild-type (clinical) samples containing *P. vivax* at low (200) and high (2000 or 5000) parasite densities (parasites/μL) and clean-negative samples. 
PDS ≥ 75%
Relapses and transmission of P. vivax

Battle KE et al., Adv Parasitol 2012; 80:1-111
Primaquine for radical cure

Preventing relapse in *P. vivax* or *P. ovale* malaria

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.

**Good practice statement**

To prevent relapse, treat *P. vivax* or *P. ovale* malaria in children and adults (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, and people with G6PD deficiency) with a 14-day course (0.25–0.5 mg/kg bw daily) of primaquine in all transmission settings.

**Strong recommendation, high-quality evidence**

In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg/kg bw once a week for 8 weeks, with close medical supervision for potential primaquine-induced haemolysis.

**Conditional recommendation, very low-quality evidence**

When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine.

**Good practice statement**

**Pregnant and breastfeeding women**

In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse.

**Conditional recommendation, moderate-quality evidence**
Available qualitative G6PD POCT RDT

http://www.who.int/malaria/publications/atoz/g6pd-testing-pq-radical-cure-vivax/en/
Available G6PD point-of-care RDT

Qualitative point-of-care RDTs

- No laboratory skills
- No laboratory equipment
- No cold chain
- Ambient temperature use
- Low cost

Quantitative POCT

SD Biosensor
STANDARD G6PD Test

AccessBio
CareStart G6PD Biosensor

Global Malaria Programme

World Health Organization
Since 2008 WHO-FIND coordinate an international quality assurance scheme for malaria RDTs comprised of independent pre- and post-purchase RDT performance assessments (product testing and lot testing, respectively), guidance on procurement, transport and storage, operational manuals, and multiple training resources to support large-scale implementation.

Since 2008, 327 RDT products have been evaluated in 8 rounds of product testing, comprising 227 unique products.

Since 2018, WHO procurement criteria require prequalification for P. falciparum-only HRP2-detecting RDTs. As of January 2019 the requirement for prequalification has been extended to include all HRP2, pan-LDH and/or pv-LDH combination RDTs.
<table>
<thead>
<tr>
<th>Cible</th>
<th>Nom du produit</th>
<th>No catalogue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pf/Pv</td>
<td>Meriscreen Malaria Pf/Pv Ag</td>
<td>MFLRPD-02</td>
</tr>
<tr>
<td>Pf</td>
<td>ParaHIT F Ver. 1.0 Rapid Test for Pf</td>
<td>55IC104-50</td>
</tr>
<tr>
<td>Pf</td>
<td>SD Bioline Malaria Ag Pf (HRP2/pLDH)</td>
<td>05FK90</td>
</tr>
<tr>
<td>Pf</td>
<td>SD Bioline Malaria Ag Pf</td>
<td>05FK50</td>
</tr>
<tr>
<td>Pf/Pv</td>
<td>SD Bioline Malaria Ag Pf/P.v</td>
<td>05FK80</td>
</tr>
<tr>
<td>Pf/Pan</td>
<td>SD Bioline Malaria Ag Pf/Pan</td>
<td>05FK60</td>
</tr>
<tr>
<td>Pan</td>
<td>CareStart™ Malaria PAN (pLDH) Ag RDT</td>
<td>RMNM-02571</td>
</tr>
<tr>
<td>Pf</td>
<td>CareStart Malaria Pf (HRP2/pLDH)</td>
<td>RMPM-02571</td>
</tr>
<tr>
<td>Pf/Pv</td>
<td>CareStart™ Malaria Pf/Pv (HRP2/pLDH) Ag Combo</td>
<td>RMVM-02571</td>
</tr>
<tr>
<td>Pf</td>
<td>CareStart Malaria Pf (HRP2) Ag</td>
<td>RMOM-02571</td>
</tr>
<tr>
<td>Pf</td>
<td>First Response Malaria AB Pf (HRP2)</td>
<td>I13FRC25</td>
</tr>
<tr>
<td>Pf/Pan</td>
<td>CareStart™ Malaria Pf/PAN (HRP2/pLDH) Ag Combo RDT</td>
<td>RMRM-02571</td>
</tr>
<tr>
<td>Pf/Pv</td>
<td>SD BIOLINE Malaria Ag P.f/P.f/P.v</td>
<td>05FK120</td>
</tr>
<tr>
<td>Pf/Pv</td>
<td>First Response® Malaria Ag. P.f./P.v. Card test</td>
<td>PI19FRC25</td>
</tr>
<tr>
<td>Pf/Pan</td>
<td>First Response® Malaria Ag. pLDH/HRP2 Combo Card Test</td>
<td>PI16FRC</td>
</tr>
<tr>
<td>Pf</td>
<td>First Response® Malaria Ag P. falciparum (HRP2) Card Test</td>
<td>PI13FRC</td>
</tr>
</tbody>
</table>

As of today WHO has prequalified 16 RDTs, including:
- 5 targeting HRP2 only,
- 5 " HRP2-PvpLDH,
- 3 " HRP2-PanpLDH
- 2 " HRP2-PfpLDH
- 1 " PanpLDH

There is a need for more prequalified sources of RDTs targeting PanpLDH et PfpLDH, to detect parasites with pfhrp2 gene deletions.

(as of 29.1.2019)
Between 2007-2017
• Between 1 and 5 lots failed every year
• Between 1 and 10 lots failed stability tests every year **
• Most of the tests are requested pre-shipment

Demand for lot testing of malaria RDTs *

Equivalent to > 200 M of RDTs

At present only the Research Institute of Tropical Medicine in the Philippines provides lot testing for malaria RDTs for all countries.

India: 11-41 lots/year for MOH
Nigeria: 25 lots in 2017; 50 lots Evaluated after distribution to health facilities

* Without including lots tested in India and Nigeria
RDTs anomalies identified in lot testing

- Red background
- Incomplete clearing/streaking
- Failure to flow
- Faint lines
- Ghost lines
- Patchy broken lines
- Diffuse lines

Graph showing percentage of products with different anomalies.
WHO GMP convened a technical consultation in June 2018 to identify the evidence required to develop recommendations on the use of highly-sensitive point-of-care tests

• Conclusions presented and endorsed at MPAC in October 2018

• Principles of evidence assessment for diagnostics
  1. Technical evaluation: lab studies using reference samples of known parasite and antigen concentrations
  2. Accuracy studies: systematic review of field-based accuracy studies across transmission settings.
  3. Impact studies: evaluating the effect on patient and/or community outcomes, diagnosis and treatment, and cost-effectiveness. As impact studies may not be feasible in many settings, modelling-based studies may provide insight on potential impact

• Priority research to assess potential impact of HSPOCT in accelerating elimination (i.e., “rapid” reduction in transmission of indigenous cases), surveillance for elimination, SSTp in 1st trimester

• Importance of studies of natural history of infections and longitudinal infection dynamics

• Other applications for HSPOCTs considered of lower priority include border screening clinical case management, and ISTp (including in HIV co-infections).
**Pfhrp2 gene deletions – update**

- HRP2 is a malaria protein specific to *P. falciparum*; found on surface of Pf-infected erythrocytes, in plasma and culture media.
- Functions of HRP2 (and HRP3) are still undefined but not essential for parasites growth.
- Deletions of *pfhrp2* gene cause false negative results with HRP2-detecting RDTs.
- In 2017, 66% of global RDT sales (276 Mio) were Pf only tests delivered to Africa.
- Non-HRP2 based RDTs (either alone or in combination with HRP2) are very limited.

**Switching to non-HRP2 based tests will pose serious supply security issues and affect diagnostic performance (lower sens and heat stability).**
PfHRP2 deletions....first in South America

A Large Proportion of P. falciparum Isolates in the Amazon Region of Peru Lack pfhrp2 and pfhrp3: Implications for Malaria Rapid Diagnostic Tests

Dionicia Gamboa1,2, Mei-Fong Ho3,4, Jorge Bendezu1, Katherine Torres1, Peter L. Chiodini5, John W. Barnwell5, Sandra Incardona6, Mark Perkins6, David Bell6,7, James McCarthy3,6, Qin Cheng5,10,*

- Recommendations against use of HRP2 based RDTs
- Urgent need for investigation of the abundance and geographic distribution of these parasites in Peru and neighboring countries.
- 2011-2013: surveys conducted in Bolivia, Colombia, Guyana, Peru, Suriname, Brazil, Honduras

41% (61/148) isolates lacked pfhrp2; 21% lacked both pfhrp2 and pfhrp3.
Situation in Eritrea in 2015

Ghindae Hospital (n=25)
- Pfhrp2 negative: 81%
- Pfhrp3 negative: 92%

Massawa Hospital (n=26)
- Pfhrp2 negative: 42%
- Pfhrp3 negative: 71%

Source: Araia Berhane et al Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 24, No. 3, March 2018
Suspected false-negative RDT results should be investigated when:

- Pf-\textit{hrp2/hrp3} gene deletions should be suspected and the NMCP and WHO informed when:

- on an \textit{individual basis}, a patient sample tests negative on the HRP2 test line of at least two quality-assured malaria RDTs \textbf{and either} positive on the \textit{pan-} or \textit{pf-pLDH} test line of a combination RDT \textbf{or} the sample is confirmed by microscopy to be positive for \textit{P. falciparum} by qualified microscopist;

- on a \textit{programmatic basis}, the rates of discordance between RDT and microscopy results are \textbf{systematically} $\geq 10\text{-}15\%$, with higher positivity rates with microscopy, where routine quality control is done by cross-checking or both are performed on the same individuals (e.g. during surveys) and/or \textbf{when the NMCP receives multiple reports of RDTs returning false negative results for} \textit{P. falciparum}. 

Global Malaria Programme
**WHO Guidance**

**False-negative RDT results and implications of new reports of *P. falciparum* histidine-rich protein 2/3 gene deletions**

**Objectives**
- Provide guidance on the implications of reports of *P. falciparum* histidine-rich protein 2 (PfHRP2)/histidine-rich protein 2 (PfHRP3) gene deletions in Plasmodium falciparum parasites for case management and to outline procedures for investigating suspected false-negative RDT results.

**Causes of false negative RDTs**
- Product design or quality
- Operator errors
- Host parasite density
- Transport and storage
- Parasite factors – *pfhrp2* deletion

**Initial evidence to suspect *pfhrp2* deletion: patient and programme level**
- Two negative HRP2 RDTs and either positive by QA microscopy or RDT anti pf-pLDH or pan-pLDH
- SPR by microscopy >10-15% RDT positivity rate
- Multiple complaints or anecdotal reports of inaccurate RDT results

**Where to conduct surveys & alternative RDT options**
- Any report of *pfhrp2* deletions should be followed by survey in the affected country and neighbouring country to establish prevalence
- Alternative RDT options are limited

---

**World Health Organization**

---

**Global Malaria Programme**
Survey protocol for *pfhrp2/3* gene deletions & Lab network

Network of reference laboratories to support molecular analysis requirements of surveys to ensure reliable, comparable and rapid results.

WHO can link countries with reference labs

Once deletions have been confirmed to exceed a specific threshold, continuous surveillance and mapping of distribution is probably no longer needed.

Prevalence of false-negative HRP2 RDT results due pfhrp2 gene deletions among symptomatic patients attending public health facilities with *P. falciparum* infection detected by microscopy or a pf-pLDH RDT.
Review of 94 unique eligible studies comparing RDTs with microscopy:

- For HRP-2, the meta-analytical average sensitivity and specificity (95% CI) were 95.0% (93.5% to 96.2%) and 95.2% (93.4% to 99.4%), respectively.

- For pLDH, the meta-analytical average sensitivity and specificity (95% CI) were 93.2% (88.0% to 96.2%) and 98.5% (96.7% to 99.4%), respectively.

RDTs for areas with high prevalence of *pfhrp2/3* gene deletions

- Until there will be an adequate number of suppliers of prequalified RDTs for use in areas with high prevalence of *pfhrp2/3* deletions, the requirements for WHO procurement of pan-LDH-only RDTs and combination RDTs targeting Pf-pLDH will remain:
  - valid ISO 13485:2003,
  - application for WHO prequalification submitted, and acceptable
  - performance indicators against both HRP2 expressing and HRP2 non-expressing

- Using the laboratory results to inform procurement and predict RDT performance in the field requires a detailed understanding of the local epidemiology and should be done in consultation with experts.

- Generally, for areas with high prevalence of *pfhrp2/3* deletions, and where there is no need to distinguish between *P. falciparum* and non-falciparum infections, **pan-LDH only RDTs are the best option.**

- At present, no Pf-LDH based combination RDTs that aims to detect and distinguish between Pf and non-Pf infections meet WHO *P. falciparum* recommended panel detection score criteria on both low density (200 p/µL) HRP2 expressing and non-HRP2 expressing (mixed *pfhrp2-/pfhrp3+* and *pfhrp2-/pfhrp3-*) *P. falciparum* panels.

- At higher parasite densities i.e. 2000 p/µL, all RDTs perform well (PDS >82%) against the panel of deleted *pfhrp2/3* parasites. These tests can be used as a survey tool to identify suspected *pfhrp2/3* deleted parasites but are not recommended for use in case management as they may lead to false negative results amongst low density (<2000p/µL), *pfhrp2 +/− 3 P. falciparum* infections.
Conclusions on \textit{pfhrp2} deletions

- The full extent of the threat posed by \textit{pfhrp2} deletions is not yet known and the alternative RDT options i.e. \textit{pf-pLDH} RDTs are extremely limited and have inferior performance to HRP2 RDTs for \textit{P. falciparum} detection
- Information on prevalence in much of the world is spotty
- Must balance risk of missed cases of falciparum malaria due to \textit{pfhrp2/3} deleted strains against the equally real risk of missing cases by changing to a less sensitive RDT and the longer term risk of eroding confidence in antigen-based confirmatory testing for malaria
Global Affairs Canada awarded WHO-Global Malaria Programme CAD 75 million to support the RAcE Programme from 2012 to June 2018, to:

1. Contribute to the reduction of child mortality by increasing access to treatment for common childhood illnesses in five African countries; and

2. Stimulate policy updates and catalyze scale-up of iCCM.
• **Country selection criteria:**
  - high disease burden
  - enabling policy
  - potential for scale-up

• **NGO selection and review:**
  - independent Project Review Panel

• **Target under 5 population:**
  - 1.5 million children

• **Community health workers trained and deployed:**
  - almost 8500

<table>
<thead>
<tr>
<th>Country</th>
<th>Geographic scope</th>
<th>CHWs trained</th>
<th>Children covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Democratic Republic of the Congo</td>
<td>Tanganyika Province</td>
<td>1732</td>
<td>150 000</td>
</tr>
<tr>
<td>Malawi</td>
<td>8 Districts</td>
<td>1192</td>
<td>386 802</td>
</tr>
<tr>
<td>Mozambique</td>
<td>4 Provinces</td>
<td>1470</td>
<td>319 250</td>
</tr>
<tr>
<td>Niger</td>
<td>4 Districts</td>
<td>1426</td>
<td>230 833</td>
</tr>
<tr>
<td>Nigeria – Abia State</td>
<td>15 LGAs</td>
<td>1351</td>
<td>407 057</td>
</tr>
<tr>
<td>Nigeria – Niger State</td>
<td>6 LGAs</td>
<td>1320</td>
<td></td>
</tr>
</tbody>
</table>
RAcE: Roles and Responsibilities

**Ministry of Health**
- Overall leadership and establishment of iCCM programme standards
- Operations management and quality assurance

**WHO**
- Overall grant management
- Quality control: On-site supervision; review of reporting; convening RAcE programme Project Review Panel and International Steering Group; technical support for development of curriculum/implementation guidelines and operations research
- Oversight and support to monitoring and evaluation agency (ICF)
- Facilitating programme learning

**Implementing Partners (NGOs)**
- Support for training, supervision, supply chain, M&E and community mobilization
- Performance Measurement Framework (PMF) reporting and support for routine data collection
- Conducting baseline and end line surveys
- Conducting operations research and quality of care assessments
Children treated by RAcE-supported CHWs: over 8.2 million

Global Malaria Programme

World Health Organization
Malaria RDT positivity rates in RAcE sites

The graph shows the positivity rates of Malaria RDT tests in RAcE sites over the assessment periods from July 2015 to September 2016. The rates are depicted for Abia State, Malawi, Mozambique, and DRC. The positivity rates fluctuate slightly across the assessment periods, with some periods showing higher rates than others.
Results

1. Household survey - care seeking and treatment coverage
2. Evaluation of contribution of RAce on decreasing child mortality using Lives Save Tool (LiST) modelling
Care seeking and malaria, pneumonia and diarrhea treatment
### Estimated lives saved by iCCM scale-up: 4938 (LiST analysis)

<table>
<thead>
<tr>
<th>RAcE Sites</th>
<th>Under-five mortality rate (deaths per 1,000 live births) 2013 and 2016</th>
<th>% change between 2013 and 2016</th>
<th>Lives saved through increases in intervention coverage</th>
<th>Estimated lives saved by CHW-provided treatment</th>
<th>% Lives saved by CHW treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRC</td>
<td>121 to 103</td>
<td>18%</td>
<td>2182</td>
<td>1728</td>
<td>79%</td>
</tr>
<tr>
<td>Malawi</td>
<td>124 to 118</td>
<td>5%</td>
<td>4181</td>
<td>216</td>
<td>5%</td>
</tr>
<tr>
<td>Mozambique</td>
<td>94 to 94</td>
<td>0%</td>
<td>2811</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Niger</td>
<td>137 to 120</td>
<td>14%</td>
<td>2290</td>
<td>965</td>
<td>38%</td>
</tr>
<tr>
<td>Nigeria Abia</td>
<td>131 to 115</td>
<td>14%</td>
<td>1815</td>
<td>967</td>
<td>53%</td>
</tr>
<tr>
<td>Nigeria Niger</td>
<td>100 to 86</td>
<td>17%</td>
<td>1649</td>
<td>1062</td>
<td>64%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>4938</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Baseline data entered for 2013 and endline data for 2016 | Interpolated linearly from 2013 to 2016.
- Lives saved by malaria, pneumonia and diarrhoea treatments were adjusted proportionally to the percentage of cases treated by CHWs.
- Accounting for cases treated by the mature programmes in 2017, the figure should increase by 30% or **over 6000 lives saved**.
Key Lessons

- RAcE has provided evidence that iCCM is an effective strategy to save lives
- RAcE facilitated major policy changes on iCCM in the 5 countries
- iCCM extends **universal health coverage** by ensuring vulnerable people have **access to life-saving and quality** interventions to treat the **major causes of death** in children under five
  - The strength of the intervention lies in the availability of a trained, supplied, supervised CHW in the village when a child falls ill
  - Community engagement is key for quality implementation
  - Effective iCCM requires that quality commodities be supplied to CHWs reliably, promptly and in sufficient quantities
  - Supervision is essential to delivering quality iCCM services
- **iCCM has to be an integral part of the national primary health care system, and a prioritized intervention at the community level.**
Many thanks for your kind attention