Diagnostics for malaria in pregnancy

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Microscopy continues to be the gold standard for malaria diagnosis

- First diagnostic tool in *P. vivax* endemic settings:
  - In the African Region increased from 33 million in 2010 to 50 million in 2014
  - More than 120 million microscopy tests were undertaken in India in 2014
  - India is one of the three countries that report more than 80% of global *P. vivax* malaria cases (with Ethiopia and Pakistan)

- Allows speciation, stage differentiation, and parasite quantification (>20 parasites/ul of blood)

- Requires competent microscopist, equipment and supplies maintenance, continuous training, and regular quality assessments
More than 200 malaria rapid diagnostic tests (RDTs) are available globally

![Image of RDTs]

### Table 3. Antigen targets of rapid diagnostic tests for malaria

<table>
<thead>
<tr>
<th>Plasmodium species</th>
<th>HRP2</th>
<th>pLDH-Pf</th>
<th>pLDH-pan</th>
<th>pLDH-Pvom</th>
<th>pLDH-Pv</th>
<th>Aldolase</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. falciparum</em></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><em>P. vivax</em></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><em>P. malariae</em></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><em>P. ovale</em></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

HRP2 – histidine-rich protein 2  
pLDH – *Plasmodium* lactate dehydrogenase  
Pf – *P. falciparum*  
pan – all *Plasmodium* species  
Pvom – *P. vivax*, *ovale* and *malariae*  
Pv – *P. vivax*
The use of RDTs has significantly increased in the last decade.

Improved access to malaria diagnosis mainly in Africa due to increased use of RDTs (165 million in 2014 to 179 million in 2015 of RDTs distributed by NMCPs).

Figure 4.3 Proportion of suspected malaria cases attending public health facilities who receive a diagnostic test, by WHO region, 2010–2015. Source: National malaria control programme reports.

Figure 2.8 Number of RDTs sold by manufacturers and distributed by NMCPs, 2010–2015. Sources: NMCP reports and data from manufacturers eligible for the WHO Foundation for Innovative New Diagnostics/US Centers for Disease Control and Prevention Malaria Rapid Diagnostic Test Product Testing Program.

World Malaria Report 2016
The WHO-FIND global RDT evaluation programme is guiding procurement practices

- 202 unique RDTs products have been evaluated since 2008
- Performance of tested RDTs has improved since programme implementation
- Part of the laboratory evaluation for WHO pre-qualification
- Basis for the WHO and Global Fund procurement recommendations

J. Cunningham, WHO/GMP
However, better RDTs are still needed

**hrp2/hrp3 deleted *P. falciparum* parasites are present in several countries**

An important proportion of Pan and *P. vivax* RDTs are not stable at tropical conditions

**pLDH-based RDTs could be missing an important proportion of clinical infections**

Limited data show poor performance of RDTs with *P. ovale* and *P. malariae*
A new highly sensitive HRP2 RDT for screening-and-treatment is currently in field evaluation.

Current field studies target different potential scenarios:

- Identification of transmission foci for targeted interventions
- Reactive case detection after index case
- Population at risk – pregnant women:
  - Ongoing studies in Colombia and Benin
Combination HS-RDTs to improve detection of all forms of malaria are in development

Summary of discussions with MoHs and other key stakeholders

<table>
<thead>
<tr>
<th>Test type</th>
<th>Treatment</th>
<th>Pros</th>
<th>Cons</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan/Pf</td>
<td>Pan(+) / Pf(-) → ACT</td>
<td>Detects all species</td>
<td>Undetect: Pan(+) / Pf(+) could be a mixed infection requiring PQ. Pan(+) / Pf(-) would not receive PQ if Pf not confirmed.</td>
<td>• Helpful for surveillance in drug resistant areas because differentiates Pf • 25% of current RDT volume market • Common, familiar format</td>
</tr>
<tr>
<td></td>
<td>Pan(+) / Pf(-) → CQ+PQ</td>
<td>Differentiates Pf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pf/Pv</td>
<td>Pf(+)/Pv (+) → ACT+PQ</td>
<td>Differentiates Pf</td>
<td>Does not detect Pm/Po/Pk</td>
<td>• Helpful for surveillance in drug resistant areas because differentiates Pf • 6% of current RDT volume market • Preference for case management</td>
</tr>
<tr>
<td></td>
<td>Pf(+)/Pv(-) → ACT</td>
<td>Allows targeted Pv radical cure</td>
<td>Undertreat: Does not target Po radical cure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pf(-)/Pv(+ → CQ+PQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pf/Pvom</td>
<td>Pf(+)/Pvom(+ → ACT+PQ</td>
<td>Differentiates Pf</td>
<td>Over-treatment of Pm with PQ</td>
<td>• Helpful for surveillance in drug resistant areas because differentiates Pf • Commercial product available</td>
</tr>
<tr>
<td></td>
<td>Pf(+)/Pvom(-) → ACT</td>
<td>Allows targeted Pv and Po radical cure</td>
<td>Does not detect Pk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pf(-)/Pvom(+ → CQ+PQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pan/Pvo</td>
<td>Pan(+)/Pvo(+ → ACT+PQ</td>
<td>Detects all species</td>
<td>Does not differentiate Pf</td>
<td>• Shift from CQ to ACT for Pv and Po • Speciation at reference lab required (PCR) for surveillance purposes</td>
</tr>
<tr>
<td></td>
<td>Pan(+)/Pvo(-) → ACT</td>
<td>Allows targeted Pv and Po radical cure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pan only</td>
<td>Pan(+) → ACT + PQ</td>
<td>Detects all species</td>
<td>Over-treatment of Pf/Pm/Pk with PQ</td>
<td>• Speciation at reference lab required (PCR) for surveillance purposes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Does not differentiate Pf</td>
<td></td>
</tr>
<tr>
<td>Pan/Pf/Pv</td>
<td>Pan(+)/Pf(+)/Pv(+) → ACT+PQ</td>
<td>Detects all species</td>
<td>Does not target Po radical cure</td>
<td>• Helpful for surveillance in drug resistant areas because differentiates Pf • Strong program interest • Difficult interpretation by end user • Technically challenging</td>
</tr>
<tr>
<td></td>
<td>Pan(+)/Pf(-)/Pv(+) → ACT</td>
<td>Differentiates Pf</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pan(+)/Pf(-)/Pv(-) → CQ+PQ</td>
<td>Allows targeted Pv radical cure</td>
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</table>

PQ refers to radical cure with PQ or TQ (when available) and assuming testing for G6PD deficiency is available and done when required.
Molecular methods are currently the most sensitive assays for sub-microscopic infections.

Nucleic acid amplification techniques (NAATs) for malaria:

- Qualitative and/or quantitative parasite detection
- Determination of species and multiplicity of infection
- Genotyping to distinguish recrudescence from re-infections
- Detection of mutations related to drug resistance

**PCR**
- Detection of <0.02 parasites/ul blood (high-volume PCR)
- Requires cold chain and special equipment
- Results in >2 hours

**LAMP**
- Detection of >1 parasite/ul of blood
- Commercial kit stable at ambient temperature
- Easy to perform with standard equipment
- Results in 1 hour
- Performance equivalent to PCR
- CE-mark Pan/Pf kit available in the market

Several NAATs with different performance characteristics are currently available for malaria.
LAMP is equivalent to PCR for the detection of sub-microscopic malaria infections

- CE-marked Pan/Pf LAMP kit commercially available
- Global distribution in place
- *P. vivax* specific kit currently in clinical evaluation
- Impact and cost-effectiveness studies are ongoing
An EQA scheme to demonstrate performance and comparability of NAATs has started.

Detection rates at 9 different laboratories were variable mainly at low parasite densities.

1.25 to 5 p/ul

A WHO external quality assurance scheme for malaria nucleic acid amplification testing.
8-9 June 2015, London, United Kingdom Meeting report.
Evidence to demonstrate usefulness of highly sensitive diagnostics is needed

• Meeting of Experts:
  November 5th, 2017 – Baltimore (ASTMH meeting)

• Objectives:
  - To review existing evidence and research gaps on the effect of sub-microscopic infections in pregnant women and new-borns.
  - To discuss potential usefulness of new highly sensitive diagnostic test and required improvements for screening and treatment of malaria during pregnancy.

• Expected outcomes:
  - Draft target product profiles for ideal diagnostic tests for malaria screening and treatment during pregnancy.
  - Draft roadmap for clinical studies required to demonstrate usefulness and impact of highly sensitive diagnostics for malaria during pregnancy.
Acknowledgments

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Thank you

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ww.finddx.org/malaria/