FIND

Because diagnosis matters

Diagnostics for malaria in pregnancy

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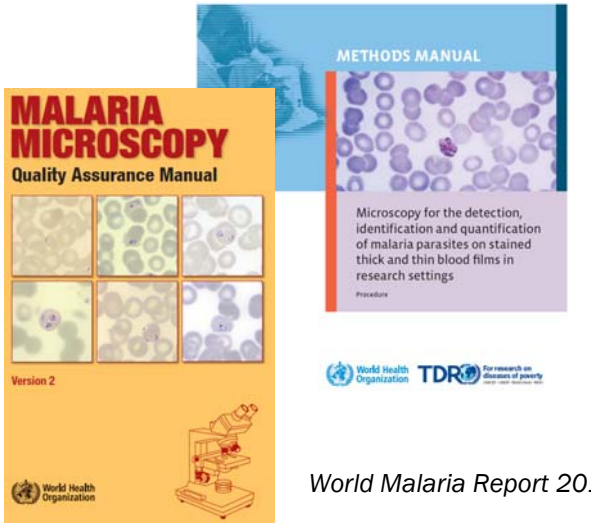
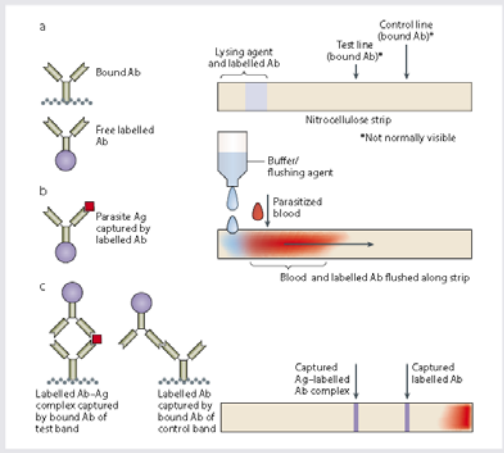
Microscopy continues to be the gold standard for malaria diagnosis

- 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



World Malaria Report 2014

More than 200 malaria rapid diagnostic tests (RDTs) are available globally



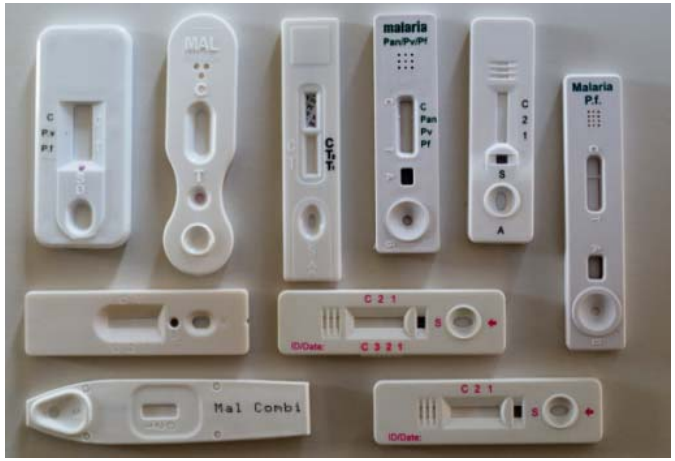


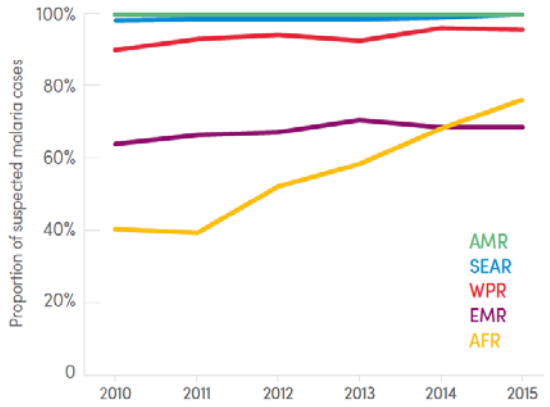
Table 3. Antigen targets of rapid diagnostic tests for malaria

Plasmodium species	HRP2	pLDH				Aldolase
		pLDH-Pf	pLDH-pan	pLDH-Pvom	pLDH-Pv	
P. falciparum	X	X	X			X
P. vivax			X	X	X	X
P. malariae			X	X		X
P. ovale			X	X		X

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

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

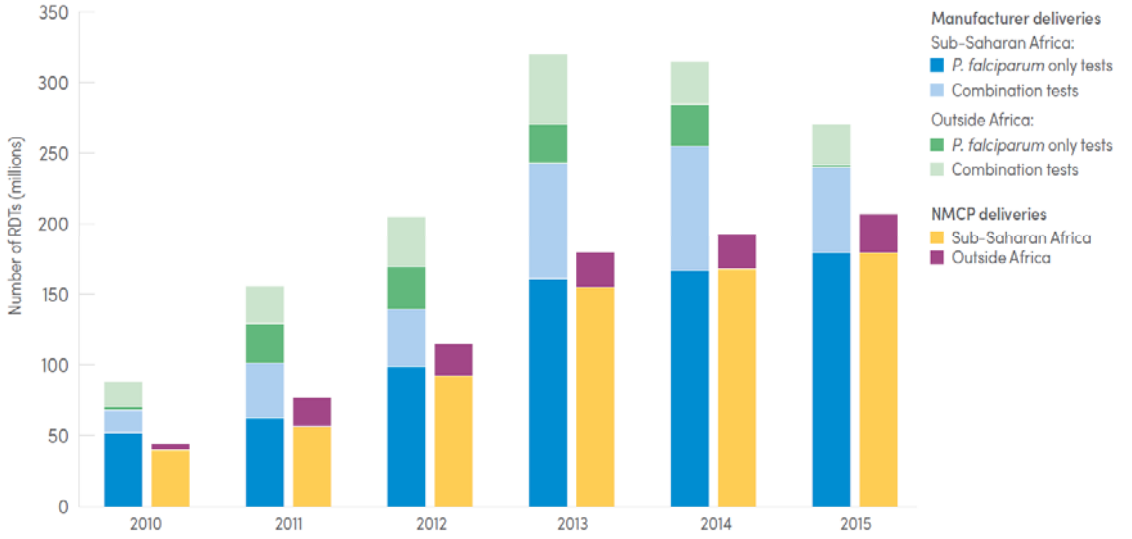


AFR, WHO African Region; AMR, WHO Region of the Americas; EMR, WHO Eastern Mediterranean Region; SEAR, WHO South-East Asia Region; WPR, WHO Western Pacific Region

World Malaria Report 2016

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

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

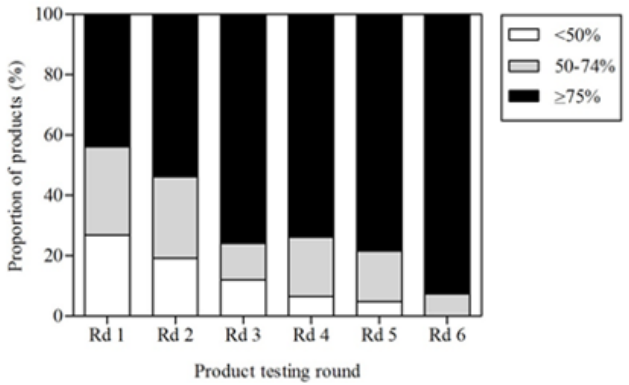


NMCP, national malaria control programme; RDT, rapid diagnostic test

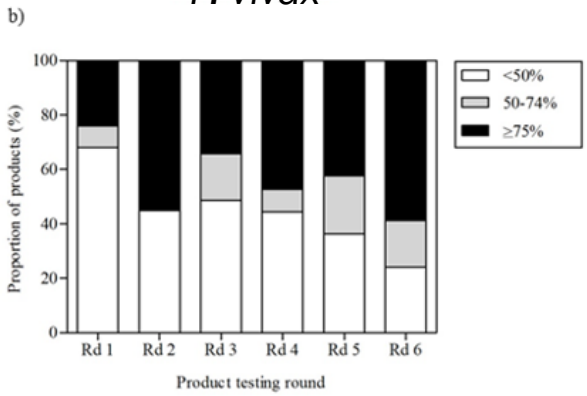
The WHO-FIND global RDT evaluation programme is guiding procurement practices

- 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

P. falciparum



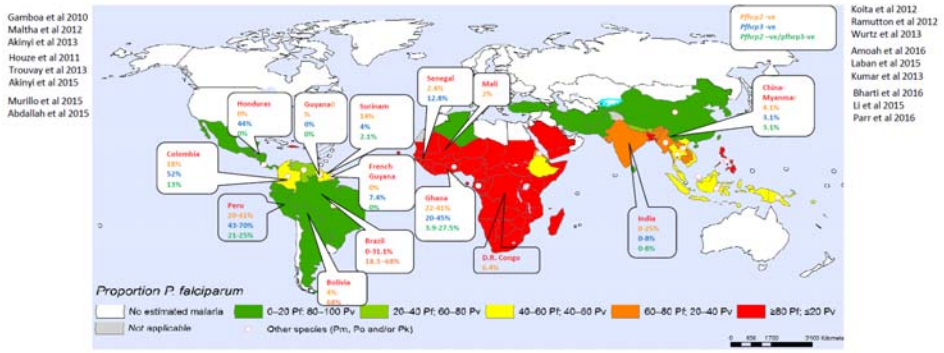
P. vivax



J. Cunningham, WHO/GMP

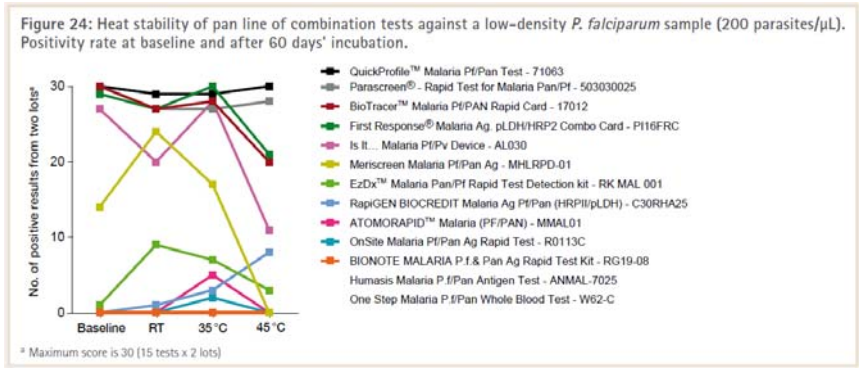
However, better RDTs are still needed

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



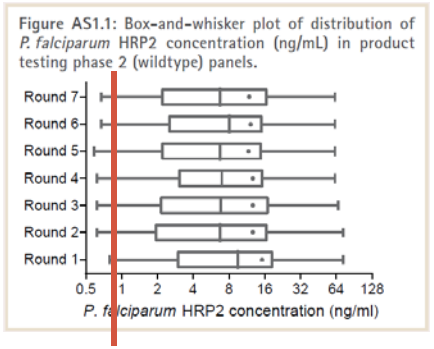
Cheng Q. AMMI

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

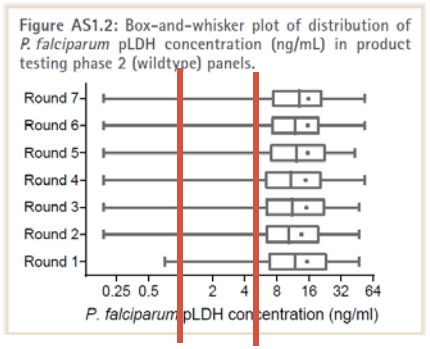


RDT report 2017

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*

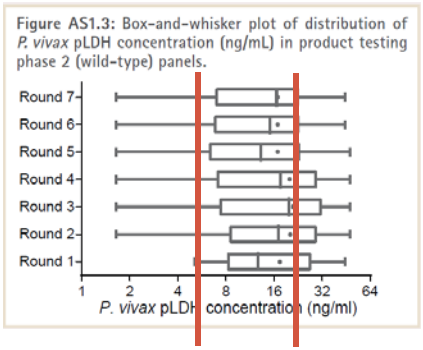


LOD HRP2 RDTs (0.8 ng/ml)



LOD Pf-LDH RDTs (1 ng/ml)

LOD Pan-LDH RDTs (5 ng/ml)



LOD Pan-LDH RDTs (5 ng/ml)

LOD Pv-LDH RDTs (25 ng/ml)

Jiménez et al. 2017

A new highly sensitive HRP2 RDT for screening-and-treatment is currently in field evaluation

Current RDT
Limit-of-detection:
[HRP2] = **800-1000** pg/ml
50-200 parasites/ µℓ

HS-RDT
Limit-of-detection:
[HRP2] = **40-80** pg/ml
In order of 2 parasites/ µℓ

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: Analysis of band combination for next generation malaria RDTs

This table assumes that the difference among case management and ACD relies only on the limit of detection of the test (better LOD for ACD test to detect sub-microscopic infections) and that treatment would be the same in both scenarios. All bands in a single test would have the same limit of detection.

Test type	Treatment	Pros	Cons	Remarks
Pan/Pf	• Pan(+)/Pf(+) → ACT • Pan(+)/Pf(-) → CQ+PQ	Detects all species Differentiates Pf	Undertreat: Pan(+)/Pf(+) could be a mixed infection requiring PQ Pan(+)/Pf(-) would not receive PQ if Pv not confirmed	• Helpful for surveillance in drug resistant areas because differentiates Pf • 29% of current RDT volume market • Common, familiar format
Pf/Pv	• Pf(+)/Pv(+) → ACT+PQ • Pf(+)/Pv(-) → ACT • Pf(-)/Pv(+) → CQ+PQ	Differentiates Pf Allows targeted Pv radical cure	Does not detect Pm/Po/Pk Undertreat: Does not target Po radical cure	• Helpful for surveillance in drug resistant areas because differentiates Pf • 6% of current RDT volume market • **Preference for case management**
Pf/Pvom	• Pf(+)/Pvom(+) → ACT+PQ • Pf(+)/Pvom(-) → ACT • Pf(-)/Pvom(+)→ CQ+PQ	Differentiates Pf Allows targeted Pv and Po radical cure	Over-treament of Pm with PQ Does not detect Pk	• Helpful for surveillance in drug resistant areas because differentiates Pf • Commercial product available
Pan/Pvo	• Pan(+)/Pvo(+) → ACT+PQ • Pan(+)/Pvo(-) → ACT	Detects all species Allows targeted Pv and Po radical cure	Does not differentiate Pf	• Shift from CQ to ACT for Pv and Po • Speciation at reference lab required (PCR) for surveillance purposes
Pan only	• Pan(+) → ACT + PQ	Detects all species	Over-treatment of Pf/Pm/Pk with PQ Does not differentiate Pf	• Speciation at reference lab required (PCR) for surveillance purposes
Pan/Pf/Pv	• Pan(+)/Pf(+)/Pv(+) → ACT+PQ • Pan(+)/Pf(+)/Pv(-) → ACT • Pan(+)/Pf(-)/Pv(+) → CQ+PQ • Pan(+)/Pf(-)/Pv(-) → CQ	Detects all species Differentiates Pf Allows targeted Pv radical cure	Does not target Po radical cure	• Helpful for surveillance in drug resistant areas because differentiates Pf • **Strong program interest** • Difficult interpretation by end user • Technically challenging

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

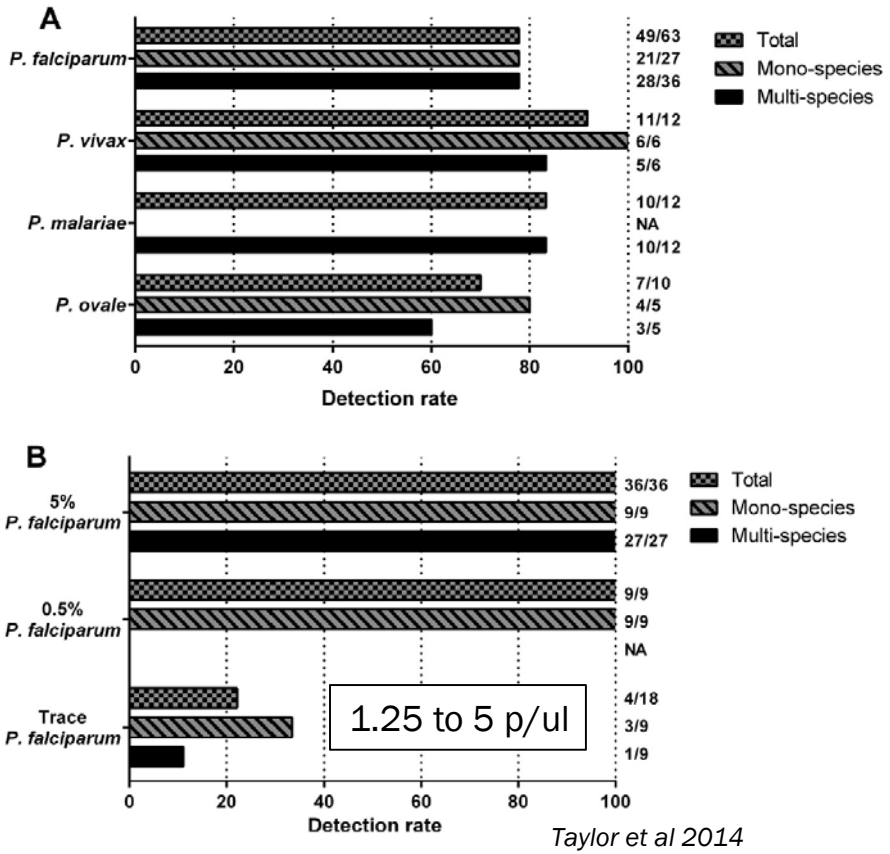
Several NAATs with different performance characteristics are currently available for malaria

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



Taylor et al 2014

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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