Target product profiles for the next generation of *Plasmodium vivax* diagnostic tests

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The need for better *P. vivax* diagnostic tools was ranked as top priorities at the APMEN VxWG meeting in 2015

<table>
<thead>
<tr>
<th>Topic</th>
<th>Priority</th>
<th>Research partners</th>
<th>NMCP representatives</th>
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<tbody>
<tr>
<td>Improved RDT for <em>P. vivax</em></td>
<td>1</td>
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<td>Improved available G6PD diagnostics</td>
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<td>RDT for <em>P. knowlesi</em></td>
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<tr>
<td>Standardized methods for <em>P. vivax</em> PCR and quality control</td>
<td>2</td>
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<td>Establish LAMP as a field robust diagnostic for reactive case detection</td>
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<td>Pragmatic considerations for RDTs (buffer, cheaper bivalent RDTs)</td>
<td>2</td>
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Limitations of RDTs for the diagnosis of *P. vivax*

- pLDH RDTs are less heat-stable than HRP2 RDTs (Chiodini *et al.* 2007)
- Pv-pLDH RDT display specificity issues (Maltha *et al.* 2010)
- Out of 12 WHO prequalified malaria RDTs, two only have a Pv-pLDH test line.
Better diagnostic tools for *P. vivax* are needed

Symptomatic infections

Asymptomatic infections

Pv-pLDH RDTs
- limited sensitivity
- limited specificity
- stability issues

Microscopy
- limited sensitivity
- user dependent

Microscopy misses between 10% and 68% of all *P. vivax* infections, mostly asymptomatic (Cheng *et al.* 2015)
Target Product Profiles

Current diagnostic tests + Target Product Profiles $\rightarrow$ Understand the adequacy of current test

Technology landscape + Target Product Profiles $\rightarrow$ Evaluate the potential of new tests and guide decision-making process

Make TPPs publicly available to inform the malaria R&D community, test developers and guide product development
**Development of *P. vivax* Dx TPPs**

- **Nov. 2015**
  - Expert meeting at ASTMH
    - Review of current Dx practices for *P. vivax*
    - Discussion of draft TPPs: intended uses and draft characteristics

- **Oct. 2016**
  - 5 rounds of revisions and discussions with group of experts
  - Survey for final decisions
  - Manuscript ready for submission
Three TPPs to address specific needs

TPP PvA
- Intended use: For parasitological confirmation of symptomatic suspected cases of *P. vivax*
- Test outcome: Guide individual treatment in passive case detection

TPP PvB1
- Intended use: For detection of all *P. vivax* infections (symptomatic and asymptomatic)
- Test outcome: Guide individual treatment in active case detection

TPP PvB2
- Intended use: For detection of present or recent *P. vivax* infection for surveillance activities
- Test outcome: Inform epidemiological surveys, guide population interventions
1. Scope
- Intended use
- Test outcome
- Target population
- Target users
- Implementation level

2. Performance
- Analytical sensitivity
- Analytical specificity
- Outcome measure
- Diagnostic sensitivity
- Diagnostic specificity
- Repeatability
- Reproducibility

3. Operational aspects
- Assay format
- Assay throughput
- Packaging
- Operation conditions
- Transport and storage conditions
- In use stability
- Reagents reconstitution
- Equipment
- Power requirement
- Maintenance
- Sample type
- Sample volume
- Sample preparation
- Test preparation
- Time to results
- Internal control
- External control
- ...

4. Cost
- End user price
- Cost of diagnosis
**Key assumptions and rational**

**P. vivax**

**Low parasitemia**
- *P. vivax* pyrogenic threshold is typically in the range of 200 p/µL (5-10 times lower than *P. falciparum*).
- *P. vivax* peripheral parasitemia at presentation is typically in the range of 4’000 p/µL (3-4 times lower than that of *P. falciparum*).
- Peak parasitemia rarely exceeds 100’000 p/µL

**Early appearance gametocyte**

**Hypnozoites**

- TPPs have been defined to be as generic as possible.
- For each TPP characteristic, **minimal** and **optimal** values have been defined.
- Minimal values were set to provide a distinguishing advantage over existing diagnostic solution for *P. vivax*.
- Optimal values were set to provide the highest possible diagnostic value.
- Defining quantitative values is challenging for most characteristics.
A minimal \textbf{PvA test} for passive case detection detects specifically \textit{P. vivax} parasites at 25 p/µL with 95% diagnostic specificity and sensitivity using less than 100 microL of capillary blood with results in less than hour.

\textbf{A minimal \textbf{PvB1 test} for active case detection} is very similar to a \textit{PvA} test but requires the option to test batches of up to 100 samples easily.

\textbf{A minimal \textbf{PvB2 test} for surveillance} detects recent past infection or parasitemia as low as 0.1 p/µL in a 96-well format, can be relatively complex and does not need to produce results before one month after sample collection.

- Improved \textit{Pv}-PLDH RDT?
- Improved or automated microscopy?
- New \textit{P. vivax} antigens for RDT?
- High-sensitivity RDT?
- Loop-mediated isothermal amplification (LAMP)?
- New technologies?
- High-throughput high-sensitivity PCR?
- Serology-based assay?
Summary

Most RDTs for *P. vivax* are not as effective as those for *P. falciparum*

Improved diagnostics for *P. vivax* are needed

- For the passive detection of symptomatic cases
- For the active detection of asymptomatic cases

Defining target product profile is an essential first step to better understand the specific needs associated with *P. vivax* diagnosis and guide the development and adoption of new diagnostic solutions.

In collaboration with a large group of experts, FIND has established an initial set of three TPPs:

- PvA: confirmation of suspected symptomatic cases
- PvB1: detection of all *P. vivax* infection regardless of symptoms
- PvB2: detection of all *P. vivax* infection for surveillance purposes
Thank you for your attention.

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