Target Product Profile:

Point-of-Care Malaria *Plasmodium falciparum* Highly Sensitive Rapid Diagnostic Test

For rapid detection of low-density, malaria infections

Updated November 2015

PATH
A catalyst for global health

Context

Defining the need for a highly sensitive point-of-care test for the rapid detection of low-density, malaria infections

Malaria control efforts have yielded significant progress toward reducing the burden of malaria. Between 2001 and 2013, there have been an estimated 670 million cases and 4.3 million malaria-related deaths averted [1]. However, the emergence of multiple forms of resistance by both the parasite to drugs and the vector to insecticides, the cost of sustained control efforts, and a long history of malaria resurgence [2] following near elimination have fuelled recent policy, guidance [3], and funding dedicated to achieving elimination and eradication goals.

In high-prevalence regions, low-mortality and low-morbidity goals can be achieved with optimal application of existing control measures along with malaria diagnostic tools used to passively detect malaria cases. However, the challenge of interrupting transmission in low-prevalence settings requires actively finding low density infections with suitably sensitive assays.

As national malaria control programs contemplate their options for shifting tactics and tools to support malaria elimination [4], it is imperative that the malaria community reassess diagnostic priorities in low-prevalence settings. The epidemiology of malaria changes significantly as regions transition from control to pre-elimination prevalence levels [5]. Infections tend to become less uniform in the population and more focal by defined geographic areas, are frequently imported from higher transmission regions, and become increasingly dependent on behavioral risks. In low-prevalence regions, a larger proportion of ongoing transmission is attributed to low density infections that cannot be readily detected by currently available rapid diagnostic tests (RDTs) or microscopy [6,7,8].

Accordingly, passive case detection strategies that drive diagnostic use in control programs need to be augmented by active infection detection (ID) tactics and more accurate diagnostic tools in an elimination context. Currently available microscopy and RDTs have insufficient analytical sensitivity required to identify the subclinical cases targeted by active ID tactics. Modeling suggests that new RDTs should have an LOD at least 10 times lower than current commercially available RDTs to enable transmission interruption using test-and-treat tactics [9].

The proposed Rapid Diagnostic Test (RDT) is intended for qualitative detection of *Plasmodium falciparum* (*P. falciparum*; *Pf*) infections. Specifically, the test is intended for use in active ID interventions aimed at identifying and treating low parasite density infected individuals and populations that serve as reservoirs of parasite biomass. The proposed will use human blood from a finger-stick sample on a lateral-flow immunochromatographic (RDT) assay format and include HRP2 at a minimum as a target antigen to ensure the strongest correlation with transmission risk.

Executive Summary Table

Variable	Minimal requirement	Optimal Requirement
1. Product Use Summary/Differentiation Strategy		
1.1 Intended use(s)	Active infection detection (ID) and treatment interventions aimed at low-density and subclinical infection detection.	Same.
1.2 Proposed target population	Individuals and populations at risk of *Plasmodium falciparum* (*Pf*) infection, whether or not they have apparent symptoms of infection.	Same.
1.3 Lowest infrastructure level	The test will be performed under zero-infrastructure conditions including community health centers, households, and outdoor conditions.	Same.
1.4 Lowest level user	The test will be performed by community health workers, trained lay persons, and community volunteers.	Same except no to bare minimum training required of lay persons.
2. Design		
2.1 Format	Lateral-flow immunochromatographic strip in cassette format with battery powered, portable reader if necessary to achieve minimal limit of detection [LOD] requirements.	No instrument required.
2.2 Target analyte	*Pf* HRP2.	*Pf* HRP2.
2.3 Sample type/collection	Peripheral whole blood from finger stick (heel prick for infants).	Same.
2.4 Sample volume	1–50 µl.	1-10 µl
2.5 Detection	High-contrast, clear results for naked-eye, indoor and outdoor reading. Battery powered, portable reader if necessary to achieve minimal limit of detection [LOD] requirements.	High-contrast, clear results for naked-eye, indoor and outdoor reading.
2.6 Quality control	1. Endogenous positive control. 2. Exogenous process control line.	1 Endogenous positive control. 2. Exogenous process control line. 3. Colorimetric indicator to identify excessive heat exposure.
2.7 Supplies needed	All reagents and supplies are included in self-contained kit.	All reagents and supplies are included in self-contained kit.
2.8 Lancet	Included in kit. Auto-retracting style. Adequate to achieve specified blood volumes.	Same.
2.9 Blood collection and transfer device	Included in kit. Adequate to collect and transfer specified blood volumes.	No device necessary; specimen transfer directly from finger stick.
2.10 Portability	Highly portable.	Same.

Variable	Minimal requirement	Optimal Requirement
2.11 Safety	Auto-retracting lancet. No mixing well needed. Strip contained within a cassette. No buffer-mixture leakage from cassette. Normal use does not create additional hazards to the operator when Universal Blood Safety precautions are observed.	No blood transfer required.
3. Performance		
3.1 Species differentiation	*Pf* only.	Same.
3.2 Analytic sensitivity/ limit of detection	Limit of detection for HRP2 is 10x LOD of commercially available tests. LOD is 80pg PfHRP2/ml whole blood.	Limit of detection for HRP2 is 50x LOD of commercially available tests. LOD is 8pgHRP2/ml whole blood.
3.3 Diagnostic/Clinical sensitivity	95% (LL95%CI) in a 10-30% prevalence population against a composite qPCR and HRP2 ELISA reference.	98% (LL98%CI) in a 10-30% prevalence population against a composite qPCR and HRP2 ELISA reference.
3.4 Diagnostic/Clinical specificity	97% (LL90%CI) in qRT-PCR negative specimens from donors who have not had malaria within the last 28 days.	99% (LL95%CI) in qRT-PCR negative specimens from donors who have not had malaria within the last 28 days.
3.5 Time to results	Less than 20 minutes.	Less than 5 minutes.
3.6 Throughput	Seven tests per hour; at least 70% of the throughput of existing RDTs.	More than 10 tests per hour; better than throughput of existing RDTs.
3.7 Target shelf life/ stability	24 months at temperatures between 2°C and 40°C; stable for 2 weeks at 40°C.	36 months at temperatures between 2°C and 40°C; stable for 2 weeks at 50°C; time-temperature monitors included on each kit.
3.8 Ease of use	One or no timed steps; ten or less user steps, instructions should include diagram of method and results interpretation.	No timed steps; ten or less user steps, instructions should include diagram of method and results interpretation.
3.9 Ease of results interpretation	Clear positive/negative readout in indoor and outdoor lighting conditions. Reader.	Clear positive/negative readout in indoor and outdoor lighting conditions.
3.10 Operating temperature	20°C to 40°C.	15°C to 40°C.
4. Validation/Configuration/Format/Other		
4.1 Comparator methods	80 pg/ml as confirmed with dilution panels and qPCR with LOD of less than 0.1 parasites/ml	Same.
4.2 Shipping conditions	Conformance to applicable requirements of ASTM D4169-05 and ISO 11607-1: 2006.	Same.
4.3 Training requirements	Less than one day for any level of provider. Language-appropriate training materials, results guide, and job aid should be made available via the Internet.	One hour or less for health care workers familiar with RDTs and half day or less for lay person.
4.4 Instrumentation requirements	No instrumentation required unless a reader is necessary to achieve performance specifications.	No instrumentation required.

Variable	Minimal requirement	Optimal Requirement
4.5 If instrumentation is required (a) Instrumentation size	75cm^3	No instrumentation required.
4.6 If instrumentation is required (a) Instrumentation weight	0.23kg	No instrumentation required.
4.7 Calibration	A single calibration card for reader.	None required.
4.8 Service and support	None required.	None required.
4.9 Waste disposal	Includes only materials that can be disposed of in the normal laboratory waste streams.	Includes only material that can be disposed of in the normal laboratory waste streams and the material is biodegradable.
4.10 Precision/ concordance	Individual test lines should be 95% concordant with a validated ELISA test (for the same target antigen) that has been validated at or below the same LOD as the IDT.	Individual test lines should be 99% concordant with a validated ELISA test (for the same target antigen) that has been validated at or below the same LOD as the IDT.
4.11 Power requirements	Self-contained kit operates independent of mains power.	Same.
4.12 Water requirements	Self-contained kit operates independent of any external water source.	Same.
4.13 Labelling	Conformance with WHO PQ labelling guidance and recommendations from the Enhanced Malaria RDT Harmonization Procurement & Supply Chain Management Working Group where appropriate.	Same.
5. Product Costs and Channels to Market		
5.1 Target pricing per test	Less than US$1.00.	Less than US$1.00 (at volumes of 10 M) or identical to current RDT?
5.2 Capital cost	None, unless a reader is required to achieve performance specifications. Any reader should be optimistically less than 50 dollars, minimally less than 200 dollars.	Zero capital cost.
5.3 Target launch countries	Priority elimination countries for the Bill and Melinda Gates Foundation.	Additional countries contemplating elimination of *Pf* and other species.
5.4 Product registration path	• CE mark • Country-level regulatory requirements may apply for target launch countries. • World Health Organization Prequalification (PQ)	• Clinical Laboratory Improvement Amendments (CLIA) waivable. • Country-level regulatory requirements may apply for target launch countries. • World Health Organization prequalification (PQ)
5.5 Channels to market	Donor/research driven market for first three years.	Shares same distribution channels as clinical-use RDTs.
5.6 Supply, service, and support mechanisms	TBD	TBD

1. Change Management

Version	Key changes from previous version
EXAMPLE DD-MM-YYYY	UPDATE
V2.0 18th November 2015	Update of TPP in context of current understanding of demand and technical feasibility

[1] World Health Organization (WHO). *World Malaria Report 2013*. Geneva: WHO; 2014.

[2] Cohen JM, Smith DL, Cotter C, et al. Malaria resurgence: a systematic review and assessment of its causes. *Malaria Journal.* 2012;11(122):1–17.

[3] WHO. *Malaria Elimination: A Field Manual for Low and Moderate Endemic Countries.* Geneva: WHO; 2007.

[4] The malERA Consultative Group on Diagnoses and Diagnostics. A research agenda for malaria eradication: diagnoses and diagnostics. *PLoS Medicine*. 2011;8(1):1–10.

[5] Cotter C, Sturrock HJ, Hsiang MS, et al. The changing epidemiology of malaria elimination: new strategies for new challenges. *Lancet.* 2013;382(9895):900–911.

[6] Bottius E, Guanzirolli A, Trape JF, Rogier C, Konate L, Druilhe P. Malaria: even more chronic in nature than previously thought; evidence for subpatent parasitaemia detectable by the polymerase chain reaction. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* 1996;90(1):15–19.

[7] Laishram DD, Sutton PL, Nanda N, et al. The complexities of malaria disease manifestations with a focus on asymptomatic malaria. *Malaria Journal*. 2012;11(29):1–15.

[8] Policy brief on malaria diagnostics in low-transmission settings, WHO, 2013

[9] Slater et al 2015: How sensitive do next-generation rapid diagnostic tests need to be to for use in *Plasmodium falciparum* malaria elimination?