PvA: Diagnosis of *Plasmodium vivax* malaria acute infection

Defining the next generation of *Plasmodium vivax* diagnostic tests for control and elimination: Target product profiles

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S2 Table. TPP PvA: Diagnosis of *Plasmodium vivax* malaria acute infection

Type	Characteristic	Minimal (M) / Description	Optimal (O)	Comment
Scope	Intended use	The test goal is to provide a parasitological confirmation of suspected symptomatic episodes of *P. vivax* malaria to guide the management of clinical cases. Therefore, the test needs to accurately detect biologically active erythrocytic forms of *P. vivax*.		
	Test outcome	Guide blood-stage and, if appropriate, liver-stage treatment		
	Target population	The target population is any individual suspected to suffer from a symptomatic episode of *P. vivax* malaria, including neonates, children, and pregnant women.		
	Target users	The target users include community health workers with minimal training and any health worker with a similar or superior training level.		
	Implementation level	The target implementation levels are community health facilities, health posts, and health centers [5].		
Performance	Analytical sensitivity	Limit of detection for target analyte corresponding to a peripheral parasitaemia of 25 p/μL	Limit of detection for target analyte corresponding to a peripheral parasitaemia of 5 p/μL	"M" corresponds to typical *P. vivax* pyrogenic threshold and is in line with malERA recommendation. "O" corresponds to the order of magnitude of the lowest peripheral parasitaemia at presentation for uncomplicated *P. vivax* malaria and is more stringent than WHO recommendation (25 p/μL) but same as malERA recommendation (5 p/μL) [1,4,6-8].
	Analytical specificity	Discriminate between *P. vivax* and other *Plasmodium spp*. Do not cross-react with any other pathogen infecting humans	Discriminate between *P. vivax*, *P. falciparum* and other *Plasmodium spp*. Do not cross-react with any other pathogen infecting humans	"M" enables the specific identification of *P. vivax*. "O" provides a unique test for *P. vivax* and *P. falciparum* co-endemicity areas. Cross-reactivity between *P. vivax* and *P. ovale* might be beneficial to identify both of these relapsing species.
	Diagnostic outcome	Binary	Binary	A continuous (quantitative) outcome is not required for the intended use of the test.
	Diagnostic sensitivity	> 95% as compared to standard PCR with known limit of detection of 1p/μL	≥ 99% as compared to standard PCR with known limit of detection of 1 p/μL	"M" equals existing best *P. vivax* RDTs sensitivity (95% [0.95CI: 86% to 99%]). "O" provides a distinguishing advantage over this value (≥ upper 0.95CI) [9].

Type	Characteristic	Minimal (M) / Description	Optimal (O)	Comment
	Diagnostic specificity	> 95% as compared to standard PCR with known limit of detection of 1p/µL	≥ 99% as compared to standard PCR with known limit of detection of 1p/µL	"O" is equivalent to existing best *P. vivax* RDTs specificity (99% [0.95CI: 99% to 100%]) [9].
	Repeatability (inter-operators)	*Kappa* > 0.8	*Kappa* > 0.9	Kappa statistic can be used to evaluate binary outcomes agreement. Suggested values are arbitrary.
	Reproducibility (inter-laboratories)	*Kappa* > 0.7	*Kappa* > 0.9	See *Repeatability*
Operational aspects	Assay format	End point, single-use *in vitro* diagnostic	End point single-use *in vitro* diagnostic	Suspected cases should be tested and treated as soon as possible and as such require a single determination per test.
	Assay throughput	Single assessment per test	Single assessment per test	See *assay format*
	Assay packaging	Package of single kits sharing reagents (if required) and user manual	Package of single kits with individual reagents sharing user manual	"M" and "O" reflect current packaging formats of RDTs.
	Operation conditions	5°C – 40°C Up to 90% relative humidity (RH)	5°C – 45°C Up to 90% RH	"M" and "O" reflect extreme conditions of endemic countries. RDT transportation and storage temperatures regularly exceed 30°C, rarely 40°C [10].
	Transportation and storage stability	≥ 12 months at 35°C and 70% RH with transport stress (3 days at 60 °C), no cold chain needed	≥ 12 months at 45°C and 90% RH with transport stress (3 days at 60 °C), no cold chain needed	"M" and "O" reflect typical and possible extreme transportation and storage conditions observed for RDTs [10].
	In use stability	> 1 hour for single-use test once opened	> 1 hour for single-use test once opened	Tests are likely to be used extemporaneously and as such this characteristic is unlikely to be limiting.
	Reagents reconstitution	Reconstitution of reagent acceptable if number of step is limited (≤ 5) and not requiring external equipment	All reagents provided and ready to use.	"M" is more stringent than the actual characteristic of LM (Giemsa solution preparation requires several precise steps). "O" is met by current RDTs.
	Equipment	Small (≤ 100 cm^2 footprint) and portable (≤ 5 kg)	None	

Type	Characteristic	Minimal (M) / Description	Optimal (O)	Comment
	Power requirement	Battery operated with ≥ 24 hours testing autonomy	None	
	Maintenance	≤ once per year	None	
	Sample type	Capillary blood	Capillary blood or any less invasive validated sample	Sample types less invasive than capillary blood include saliva, urine, breath or transdermal detection [11].
	Sample volume	≤ 100 µL of capillary blood	≤ 50 µL of capillary blood	Variable for other sample types
	Sample preparation	≤ 5 steps	None	"M" reflects the actual characteristic of LM (*i.e.* fix, rinse, stain, rinse, dry). "O" is met by current RDTs.
	Overall test preparation	≤ 10 steps, of which ≤ 2 are timed	≤ 3 steps, of which ≤ 1 is timed	"M" and "O" reflect actual characteristics of LM and RDT.
	Time-to-result	≤ 1 hour	≤ 30 minutes	"M" is based on WHO recommendation, "O" would allow uninterrupted management between diagnostic and treatment. "M" is less stringent than malERA recommendations [1,12].
	Internal control	Included	Included	
	External control	Available	Included	External controls, such as positive control wells for RDT, are especially important in low endemic settings (*i.e.* in area of low positivity rate)
	Assay interpretation	Unequivocal, recorded by operator	Unequivocal, recorded by operator or electronically	
	Data capture	Manual by operator	Electronic automated	
	Data transfer	Manual by operator	Automated via internet or GSM connectivity	
	Training	≤ 1 day for inexperienced health worker	≤ 0.5 days for inexperienced health worker	Include plan for quality control and proficiency monitoring

Type	Characteristic	Minimal (M) / Description	Optimal (O)	Comment
	Biosafety	Class B IVD (moderate individual and low public health risk)	Class A IVD (low individual and public health risk)	According to risk-based classification of diagnostics for WHO prequalification [13].
	Language	English, Spanish and Portuguese	Local languages	
Cost	End user price per test	≤1.0 USD	≤ 0.5 USD	"O" is more stringent than malERA recommendation [1].
	Cost of diagnosis	≤ 2.0 USD	≤ 1.0 USD	RDT and LM costs of diagnosis were reported to be between 2.0 and 1.0 USD in 2011 in Uganda [14].

Supplementary References

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