Global **Malaria** Programme

Recommended selection criteria for procurement of malaria rapid diagnostic tests

EFFECTIVE DECEMBER 2018

INFORMATION NOTE

The aims of this WHO information note[1] are to list the criteria recommended for selecting tests, to provide a list of products meeting those criteria as well as to provide an overview of additional considerations in the procurement of malaria RDTs.

WHO POLICY ON MALARIA DIAGNOSIS

WHO recommends parasitological confirmation of malaria in all settings by quality-assured diagnosis before treatment is started.[2] Treatment solely on the basis of clinical suspicion should be considered only when a parasitological diagnosis is not available within two hours of presentation of a patient for treatment. A diagnosis of malaria can be confirmed rapidly by good-quality microscopy or with a good-quality malaria antigen-detecting RDT for *Plasmodium falciparum* and non-falciparum infections. In most countries, both diagnostic methods are required, as microscopy and RDTs often play different roles, depending on the clinical situation or the setting.[3]

PRODUCT EVALUATIONS

The heterogeneous diagnostic performance of malaria RDTs currently available on the market can undermine the confidence of health professionals in the accuracy of these tests. Over the past decade, the WHO malaria RDT product testing programme, coordinated by the Global Malaria Programme and the Foundation for Innovative New Diagnostics (FIND) and executed in collaboration with the United States Centers for Disease Control and Prevention, has provided comparative data on the performance of the RDTs available on the market to guide procurement. Since 2008, 327 products have been fully evaluated in eight rounds of product testing, comprising 227 unique products and 61 product resubmissions. Each round

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of product testing has begun with an invitation to all companies that manufacture products under ISO-13485 (Medical devices–Quality management systems–Requirements for regulatory process) to submit RDTs for evaluation. The submitted RDTs are evaluated against panels of low- and high- parasite density including 20 culture-derived of *P. falciparum* samples, 100 of patient-derived *P. falciparum* samples, about 35 *P. vivax* parasite samples and a panel of 100 parasite-negative cultures. In round 8, a panel of 40 culture and patient-derived *pfhrp2/3* negative *P. falciparum* samples was included. This included both single (*pfhrp2-/pfhrp3+*) and double-deleted (*pfhrp2-/pfhrp3-*) parasites.

The main measure of performance against the parasite containing panels described above, is the panel detection score,[4] which is measured separately for each RDT evaluated at both the lower and the higher parasite density. The thermal stability of the products and their ease of use are also evaluated.[5]

Round 8 (https://www.who.int/malaria/publications/atoz/9789241514965/en/) is the last distinct 'round' of product evaluations coordinated by WHO/GMP and FIND. Product evaluations will now be performed continuously or in small batches, under the coordination of the WHO Prequalification of in vitro diagnostics (IVD) programme. All inquiries concerning product evaluations should be directed to: diagnostics@who.int and for details of the prequalification process: https://www.who.int/diagnostics_laboratory/evaluations/en/.

Product resubmissions and anomalies

Since round 5, there has been a requirement for re-submission of products for re-evaluation within 5 years of their original testing. Products that are not re-tested within this time are removed from the summary documents of tested products found here: https://www.who.int/malaria/publications/atoz/9789241514965/en/. However, henceforth, there will be no requirement for product resubmission and monitoring will be via WHO prequalification of IVD procedures.

Since round 5, anomalies observed during RDT product testing were recorded.

Instructions for use and product labelling

In round 7 of WHO malaria RDT product testing, for the first time, adherence to a list of recommendations on instructions for use and product labelling was assessed. Overall, products scored well in this assessment for labelling of the main device and labelling of the device packaging and of the primary product box, with some exceptions, especially in warnings and precautions. The scores for adherence to recommendations on labelling of buffer bottles and other accessories were lower. The instructions for use were highly variable, with some important omissions, particularly on laboratory safety, product performance and interpretation.

It is expected with the availability of guidance[6] that compliance will improve over time, and this will be monitored through the WHO Prequalification process.

Product variation

As manufacturers may modify their product between rounds of WHO product testing and as the results of product testing may be applied only to a specifically defined, labelled, unique product, manufacturers have been requested to inform the product testing programme of variations in products.

Since round 8 and henceforth, a submission to the WHO Prequalification of in vitro diagnostic (IVD) programme is a prerequisite for product evaluation and therefore all manufacturers should now follow WHO PQ procedures to report changes to a product(http://www.who.int/diagnostics_laboratory/evaluations/141203_changes_guidance_final.pdf). Notification of changes to WHO prequalified products will be described in product specific public reports: http://www.who.int/diagnostics_laboratory/evaluations/pq-list/malaria/public_report/en/.

WHO SELECTION CRITERIA FOR PROCUREMENT OF RDTS AND CHANGES IN 2019

Experts convened at the inaugural meeting of the Malaria Policy Advisory Committee, held in Geneva in early 2012, updated the WHO recommendations for procurement of RDTs.[7] Products should be selected according to the following criteria, after assessment in the malaria RDT product testing programme:[8]

- For the detection of *P. falciparum* in all transmission settings, the panel detection score against *P. falciparum* samples should be at least 75% at 200 parasites/µL.
- For the detection of *P. vivax* in all transmission settings, the panel detection score against *P. vivax* samples should be at least 75% at 200 parasites/µL.
- The false-positive rate[9] should be less than 10%.
- The invalid rate should be less than 5%.

In December 2017, the WHO prequalification of IVD programme and the Global Malaria Programme announced that all malaria rapid diagnostic tests that diagnose *P. falciparum*-only through detection of histidine rich protein 2 (HRP2) will be required to be prequalified for WHO procurement starting 1 January 2018.

The requirement for prequalification will be extended to include all HRP2, pan-LDH and/or pv-LDH combination RDTs as of January 2019.

Both the WHO prequalification of IVD programme and the Global Malaria Programme are closely monitoring the pipeline to ensure this plan is compatible with malaria endemic country needs and that it will not endanger supply security.

The WHO prequalification of IVDs programme will continue to accept new applications for all types of antigen-detecting malaria RDTs.

RDT procurers and national malaria control programmes are encouraged to review their policies for future malaria RDT procurements and to align them with these revised recommendations. Use of current malaria RDT stocks and existing contractual agreements need not be interrupted to meet these new requirements.

RDTs for areas with high prevalence of *pfhrp2/3* gene deletions

Due to the lack or limited number of WHO prequalified RDTs that can be used in areas with a high prevalence of *pfhrp2/3* deletions, the requirements for WHO procurement of pan-LDH-only RDTs and combination RDTs containing non-HRP2, *P. falciparum* specific targets will remain the same – valid ISO

13485:2003, application for WHO prequalification submitted, and acceptable performance indicators against both HRP2 expressing and HRP2 non-expressing (*pfhrp2/3* single or double deletions) based on the most recent WHO laboratory assessment. Data on performance against non-HRP2 expressing parasite panels is currently limited and varies depending on single or double deletions of *pfhrp2* and *pfhrp3* due to the cross reactivity of HRP3 with HRP2 test lines. Therefore, using these results to inform procurement and predict RDT performance in the field requires a detailed understanding of the local epidemiology and should be done in consultation with experts.

Generally, for areas with high prevalence of *pfhrp2/3* deletions, and where there is no need to distinguish between *P. falciparum* and non falciparum infections, pan-LDH only RDTs are the best option.

At present, no Pf-LDH based combination RDTs that aims to detect and distinguish between Pf and non-Pf infections meet WHO *P. falciparum* recommended panel detection score criteria on both low density (200 p/µL) HRP2 expressing and non-HRP2 expressing (mixed *pfhrp2-/pfhrp3+* and *pfhrp2-/pfhrp3-*) *P. falciparum* panels. At higher parasite densities i.e. 2000 p/µL, all RDTs perform well (PDS >82%) against the panel of deleted *pfhrp2/3* parasites. These tests can be used as a survey tool to identify suspected pf*hrp2/3* deleted parasites but are not recommended for use in case management as they may lead to false negative results amongst low density (<2000p/µL), *pfhrp2 +/- 3 P. falciparum* infections.

A full list of products evaluated between rounds 5-8 and their performance against HRP2 and non HRP2 expressing Pf panels at low and high density, *P. vivax* panels at low density and malaria negative samples is available in Annex 1.

Web-based interactive guide for the selection of malaria RDTs

For several years, FIND has maintained an interactive web-based guide designed to short-list rdts according to programme needs and recommended selection criteria. The guide is based on the performance of the tests in rounds 5-8 of the product testing programme and can be found at: http://www.rdt-interactive-guide.org/. The interactive guide allows selection of rdts on the basis of: the target malaria species, the panel detection score for *P. falciparum* at 200 and 2000 parasites/µl, the panel detection score for *P. vivax* at 200 and 2000 parasites/µl, false-positive rate, invalid rate, test format, heat stability, who prequalification status and procedural characteristics to enable rapid selection of products with the same: blood volume requirement, number of buffer drops and time until result.

ADDITIONAL CONSIDERATIONS IN PROCUREMENT OF MALARIA RDTS

Stability requirements at temperatures of intended storage, transport and use

In rounds 1-8, RDTs submitted to WHO for testing were evaluated against a single cultured *P. falciparum* isolate at 200 parasites/µL at baseline and after 60 days of incubation at room temperature, 35 °C and 45 °C. For the first time in round 6, heat stability of pan and *P. vivax* detecting products was assessed against a wild-type *P. vivax* sample. In the future, an independent heat stability assessment will not be included as part of the WHO prequalification coordinated laboratory evaluation.

It is recommended that RDTs with high thermal stability be selected for use in areas with very high ambient temperatures.

Ease of use, anomalies and training requirements for health workers

In rounds 1–8, RDTs submitted to WHO for testing were also evaluated for blood safety, the quality of the instructions, the number of steps, the time to results, the blood transfer device, the format and kit completeness. Cassettes are easier to use than dipsticks. For reasons of blood safety, kits that include lancets and alcohol swabs are preferred to kits that do not contain these items. The report of round 6 of product testing of malaria RDTs gives guidance on assessing ease of use in the field.[10] Occasionally unexpected features, referred to as anomalies appear while performing RDTs; these include red background, incomplete clearing, ghost lines and patchy lines among others. Anomalies may be attributed to defects in the manufacturing process, damage that has occurred to the RDTs during storage, or as a consequence of end user error. Since round 7, reports include the product-specific frequency of anomalies found in the two lots submitted for testing. Overall rates are low. Since anomalies may interfere with correct interpretation of results, manufacturers are encouraged to reduce or eliminate anomalies where possible, and end-users should be aware of those that occur commonly and the appropriate action to take in response.

Price

After consideration of all the above factors, good procurement practice requires that the price be taken into account.

Programme requirements[11]

The diagnostic performance of RDTs in the field depends on all the parameters listed above as well as on the effectiveness of training and supervision and the functioning of the supply management system. Plans to replace RDTs should be devised carefully, taking into consideration the training and supervision necessary to support the introduction of new RDTs and the production capacity and expected time for deliveries from the suppliers of the new RDTs. As protocol differences between RDTs can pose a challenge when new RDT brands are procured, categorization of products according to the same procedural characteristics was included in product testing reports (Annex 1) since round 6 and the interactive online guide has filter options, to help end users identify products with the same protocol. If similar products replace the previous ones, this may help reduce end user error, and the need for retraining.

For a comprehensive guide to procurement of malaria RDTs, beyond selection criteria, see the WHO manual on Good practices for selecting and procuring rapid diagnostic tests for malaria.[12] The manual contains practical advice on quantification, budgeting, technical specifications for tenders, management of tenders and contracts, supply management up to the arrival of goods at the port of entry, monitoring of supplier performance and managing product variations.

WHO lot testing programme

As the performance of individual products is likely to vary between lots over time, WHO recommends that all RDT production lots be checked, either before or, ideally, after shipment, and in response to concerns/complaints post-deployment, at a lot-testing centre that collaborates with the WHO, as part of good procurement practice. In 2019, this service will remain free of charge at the Research Institute for Tropical Medicine (Philippines).[13] Full information on WHO-recommended procedures for RDT lot testing are available at: http://www.who.int/malaria/areas/diagnosis/rapid-diagnostic-tests/evaluation-lot-testing/en/ and for compiled results of lots evaluated

go to: https://www.finddx.org/wp-content/uploads/2017/08/Malaria-lot-testing-results-2007-endJune-2017_30AUG17.pdf.

WHO has commissioned annual independent, external quality laboratory assessments of the National Institute of Malaria Research (NIMR), New Delhi, India and the ANDI Centre of Excellence for Malaria Diagnosis, University of Lagos, Nigeria and these laboratories are compliant with WHO malaria RDT lot testing standard operating procedures. These laboratories will be conducting lot verification for RDT batches imported into their respective countries. Contact: India: anvikar@gmail.com; shbira@gmail.com; Nigeria: andimalariacentre@unilag.edu.ng

Role of recombinant antigen panels in lot testing

In 2018, the WHO-FIND RDT Evaluation Programme Steering Committee concluded that the HRP2 or pLDH recombinant antigen panels (manufactured by Microcoat: https://www.microcoat.de/Products/recombinant-panels-for-malaria-diagnostic-tests/) should not be used for malaria RDT lot testing purposes as some critical knowledge gaps on the panel characteristics remain. Also, data analysis showed that the lot testing procedure based on recombinant panels is not fully equivalent to the current one based on clinical samples.

Notes

1. This information note on recommended selection criteria for procurement of malaria rapid diagnostic tests replaces earlier versions released between 2009, 2016, 2017 and 2018 (January).
2. WHO guidelines for the treatment of malaria. Third edition. Geneva: World Health Organization; 2015 (http://who.int/malaria/publications/atoz/9789241549127/en/).
3. Universal access to malaria diagnostic testing – an operational manual. Geneva: World Health Organization; 2013 (http://www.who.int/malaria/publications/atoz/9789241502092/en/).
4. The percentage of malaria samples in the panel that give a positive result in two RDTs per lot at the lower parasite density or in a single RDT per lot at the higher parasite density. As each sample is tested with RDTs from two lots, for a sample to be positive at the lower parasite density, the RDT must show a positive result in four tests (two RDTs per lot for two lots); at the higher parasite density, it must show a positive result in two tests (one RDT per lot for two lots). Thus, the panel detection score is a combined measure of positivity rate, incorporating inter-test and inter-lot consistency. Consequently, it is not the same as the clinical sensitivity of an RDT, which is a measure of the proportion of people known to have the disease who test positive for it.
5. Assessed after 2 months of storage at room temperature, or 35 °C or 45 °C with 75% humidity.
6. Malaria rapid diagnostic test products: Suggested use of terms, requirements and preferences for labelling and instructions for use. Geneva: World Health Organization; 2017 (http://who.int/malaria/publications/atoz/rdt-labelling-instructions-for-use/en/).
7. WHO Malaria Policy Advisory Committee and Secretariat. Inaugural meeting of the Malaria Policy Advisory Committee to the WHO: conclusions and recommendations. Malar J 2012;11:137 (http://www.malariajournal.com/content/11/1/137).
8. The full report of round 6 of the WHO malaria RDT product testing programme is available at http://www.who.int/malaria/publications/atoz/9789241510035/en/
9. Proportion of tests deemed invalid, i.e. with no visible control band.
10. Malaria rapid diagnostic test performance. Results of WHO product testing of malaria RDTS: round 7 (2015-2016). Geneva: World Health Organization–FIND; 2015 (http://who.int/malaria/publications/atoz/978924151268/en/).
11. This section is based on advice from the WHO Global Malaria Programme secretariat and not on recommendations by experts convened for a WHO technical consultation.
12. Good practices for selecting and procuring rapid diagnostic tests for malaria. Geneva: World Health Organization; 2011 (http://who.int/malaria/publications/atoz/9789241501125/en/).
13. Research Institute for Tropical Medicine, Muntinlupa City, Philippines, and Institut Pasteur in Cambodia in Phnom Penh.

ANNEX 1. PERFORMANCE OF MALARIA RDTS IN ROUNDS 5–8 OF WHO MALARIA RDT PRODUCT TESTING

The table below is based on Table S2 in the summary results of rounds 1–8 of WHO product testing of malaria RDTs (https://apps.who.int/iris/bitstream/handle/10665/276193/9789241514958-eng.pdf), with the tested products in alphabetical order by product name, catalogue number and manufacturer. The WHO-recommended selection criteria for RDT procurement were applied to this list. With the results of rounds 5-8 of the RDT product testing programme as the basis, a green box indicates that the recommended criterion has been met, whereas a white box indicates that the criterion has not been met, two columns indicate if all WHO procurement criteria have been met against HRP2 expressing and non-expressing *P. falciparum* panels, as per the selection criteria described on page 3. If requirements for compulsory submission were not met, products were delisted and are not eligible for WHO procurement.

Disclaimer

Reference to any company or product in this information note does not constitute an endorsement, certification or warranty of fitness by WHO of the company or product for any purpose and does not imply any preference over companies or products of a similar nature that are not mentioned. Furthermore, WHO does not warrant that the lists are complete or error-free or that any products listed are of acceptable quality or have obtained regulatory approval in any country or that their use is otherwise in accordance with the national laws and regulations of any country, including but not limited to patent laws. Inclusion of the names of any products in this information note, particularly in any of the lists on pages 9–16, does not imply approval by WHO of these products (which is the sole prerogative of national authorities).

The results of the WHO malaria RDT product testing programme are used by the WHO programme of prequalification of diagnostics and medical devices as the laboratory evaluation component of prequalification of malaria RDTs. A regularly updated list of WHO-prequalified diagnostics, including malaria RDTs, is available at http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/.

The lists of malaria RDTs included in this information note are not exhaustive. They include those products that were submitted for evaluation in rounds 5-8 of the WHO malaria RDT product testing programme and indicate the extent to which these products, as manufactured by the listed companies, were found at the time of their evaluation to meet the above-mentioned set of minimum performance criteria. The evaluation results indicated in the figures and tables apply only to the specific product listed with its unique product code or catalogue number, as manufactured by the listed company.

Improper storage, transport and handling of malaria RDTs may affect their performance.

Products that are not included in the lists in this information note have not or not yet been submitted for evaluation by WHO, or their evaluation has not yet been completed and published. This list and the WHO PQ assessement pipeline[1] are updated regularly.

Although updated evaluation results and public reports[2] are published by WHO, WHO cannot represent that products included in the lists will continue to meet the

procurement criteria in the same manner as indicated. WHO recommends, therefore, that before deploying malaria RDTs to the field, each lot of that product be tested at the Research Institute for Tropical Medicine, Philippines.[3]

WHO disclaims any and all liability and responsibility whatsoever for any injury, death, loss, damage or other prejudice of any kind that may arise as a result of or in connection with the procurement, distribution and use of any product listed on pages 9–16 of this information note.

This information note may not be used by manufacturers or suppliers for commercial or promotional purposes.

Notes

1. http://www.who.int/diagnostics_laboratory/pq_status/en/
2. http://www.who.int/diagnostics_laboratory/evaluations/pq-list/malaria/public_report/en/
3. https://www.who.int/malaria/areas/diagnosis/rapid-diagnostic-tests/evaluation-lot-testing/en/