

What is the precision of rapid diagnostic tests for malaria?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What is the precision of rapid diagnostic tests for malaria?*

The WHO Pocketbook of Hospital Care for Children recommends preparation of blood smears for parasites as the investigation in suspected malaria. No mention of the Rapid diagnostic testing (RDT) is made in the current edition.

INTRODUCTION

Rapid immunochromogenic tests, in simple kit form, can provide results based on fingerprick or venous blood within minutes. They can be used by village health workers after as little as an hour of training¹. Assays are based on the capture of parasite antigen by monoclonal antibodies incorporated into a test strip. Three types of antigens are targeted; parasite lactate dehydrogenase (pLDH), histidine rich protein 2 (HRP-2, found in *P. falciparum* only) and aldolase (pan-malarial antigen, found in all malarial species). HRP-2 or *P. falciparum*-specific pLDH assays are often combined with pan-specific pLDH or aldolase antigen assays in tests that can differentiate *falciparum* malaria (if the HRP-2 and pan-specific bands are positive) from non-*falciparum* malaria (if the pan-specific band only is positive). Some tests include pLDH antibodies for *P. vivax*-specific pLDH. A list of about 20 manufacturers of commercially available rapid tests with evidence of good manufacturing practice is available at the Western Pacific Regional Office website².

METHODOLOGY

For this review, 145 studies were identified from the following sources:

- PubMed (NLM/NIH) using the search strategy (rapid malaria) AND (specificityTitle/Abstract,) based on the work of Haynes et al³
- A WHO database of published reviews and trials of malaria rapid diagnostic tests (WPRO http://www.wpro.who.int/sites/rdt/reviews_trials/)
- Reviews of malarial rapid diagnostic tests^{4,5,6,7}

RESULTS

How sensitive and specific are malaria rapid diagnostic tests?

Studies of rapid diagnostic tests have demonstrated widely varying sensitivity, ranging from poor to 100%. Specificity has generally been good in most studies. It is difficult to compare studies due to different test manufacturers, possible batch-to-batch variation⁸ possible geographic variation in malarial antigens⁷ varying environmental conditions⁹, varying proportions of pre-treated patients, differing gold standards (PCR or microscopy), differing parasite densities, malarial species in disparate populations, and inadequacies in study design and reporting.

In general, field studies in endemic countries have reported lower sensitivity, possibly related to assay degradation in hot and humid conditions or batch variability⁸ and differing parasite densities in endemic populations compared to non-immune, traveller populations. Unpublished evidence suggests that HRP-2-based assays are more stable than pLDH or aldolase-based assays⁷, although newer pLDH-based tests may have improved stability⁹. Sensitivity was also lower in low-level parasitaemia (<500-1000/ μ L)^{10,11,12,13} pregnancy (with lower parasitaemia related to placental sequestration)¹⁴, non-*falciparum* malaria^{8,15}, pre-treated patients (particularly with the pLDH assay which closely correlates with parasitaemia)^{16,17} and the use of PCR (compared with microscopy) as the gold standard¹⁸.

What are the differences between the tests?

Generally, HRP2-based assays appear to be more sensitive than *falciparum*-specific pLDH RDT^{8,12,13,18,19,20,21,22,23,24,25}. This is supported by a systematic review of rapid tests in returned travelers⁵. Published data also indicates that the pLDH-based OptiMAL assay appears to be more sensitive than the aldolase antibodies used in the aldolase-based assays^{8,13,26}. However, persistence of HRP-2 antigen is prolonged compared to pLDH and thus cannot be used to predict post-treatment parasitaemia^{27,28,29,30}. pLDH and aldolase closely correlates with parasitaemia; some studies suggest that they may be used for monitoring response to treatment if microscopy is not available^{17,31,32}.

Although studies laboratory settings have demonstrated good sensitivity and specificity, several studies have reported poor sensitivity in field evaluations. Some reports assessed pLDH assays having sensitivities as low as 32-43%^{8,14}. Other studies have demonstrated poor sensitivity of HRP-2 assays (as low as 5% for *P. falciparum* only)³³, and aldolase assays as low as 3-23%^{8,28}. Given this heterogeneity, it is suggested that candidate test kits be evaluated under local field conditions prior to widespread adoption.

What are the characteristics of rapid diagnostic tests in children?

Few studies were conducted in children specifically^{24,34,35,36,37}. At least one study has demonstrated increased sensitivity of a HRP2 assay in children compared to adults, attributed to lower immunity and possibly less interference by antibodies³⁸. Despite this, there is concern that the benefits of parasitological confirmation in children under 5 years may be outweighed by the risks of not treating children with false negative tests⁷. No published studies were identified that specifically address this issue.

Are malaria rapid diagnostic tests cost-effective?

Few studies evaluated cost effectiveness and results are unlikely to be generalizable due to variations in context. Rapid tests may be cost effective in settings where microscopy is unavailable and treatment would be provided to all febrile patients³⁷ but field microscopy may be more cost effective in some situations^{39,40}, particularly where case-load is high. In areas where the prevalence of malaria is high, clinical diagnosis based on fever and/or anaemia may be even more cost effective than microscopy or rapid diagnostic testing^{24,41}. A decision on whether to adopt rapid diagnostic testing should take into account the current alternatives in a region (such as quality microscopy services), the availability of skilled personnel and resources, the baseline prevalence of malaria (including intercurrent epidemics), the predominant malarial species and the cost of acquisition and deployment (including storage and transportation) and the capacity for training and supervision

SUMMARY

- RDT storage and distribution should include a quality assurance system including monitoring of sensitivity, a cool chain where possible, appropriate instructions and training, and supervision (level 5).
- The cost-effectiveness of rapid tests should be evaluated locally prior to widespread adoption. (level 5)
- Test performance, under field conditions, should be evaluated prior to adoption, and if possible, each batch should be evaluated in a reference laboratory (level 5). Assays may be susceptible to heat and humidity.
- If cost-effective, HRP-2-based assays are recommended if *P. falciparum* is the predominant species (either alone or as a mixed infection) (such as sub-Saharan Africa and lowland Papua New Guinea) (level 5)
- If cost-effective and adequately stable, combination HRP-2 or pLDH based assays should be used in regions where multiple malarial species are present. (level 5)
- HRP-2 tests should not be used for detection of parasitaemia following treatment (level 3b). Limited data suggests that aldolase and pLDH assays may be used to monitor the response to treatment (level 3b).

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