JAMA Clinical Evidence Synopsis

Rapid Diagnostic Testing for *Plasmodium vivax* and Nonfalciparum Malaria in Endemic Areas

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CLINICAL QUESTION How sensitive and specific are rapid diagnostic tests (RDTs) for diagnosing *Plasmodium vivax* and nonfalciparum malaria in endemic areas?

BOTTOM LINE Vivax-specific RDTs were highly sensitive and specific when compared with microscopy (the gold standard) for detecting *P vivax* malaria. RDTs that can only distinguish *Plasmodium falciparum* from nonfalciparum malaria were less sensitive.

Approximately 40% of the world's population is at risk for *Plasmodium vivax* malaria.[1] Resistance to chloroquine and other antimalarials is more likely for *Plasmodium falciparum* than other *Plasmodium* species, and species identification is important to select appropriate treatment. The gold standard for diagnosing malaria is microscopic examination of thick and thin blood films. However, timely, high-quality microscopy may be unavailable in resource-poor settings. Immunochromatographic rapid diagnostic tests (RDTs) are alternatives to microscopic diagnosis. Pan-specific RDTs distinguish *P falciparum* (or mixed) infections from infections with only nonfalciparum species; differentiation between nonfalciparum species (*P vivax* from *Plasmodium ovale* and *Plasmodium malariae*) is not possible. More recently developed, vivax-specific RDTs can detect *P vivax* monoinfection or co-infection. This JAMA Clinical Evidence Synopsis summarizes a Cochrane review[2] assessing the accuracy of RDTs for detecting *P vivax* and nonfalciparum malaria in endemic countries.

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Summary of Findings

In 8 studies of vivax-specific RDTs, involving 3682 participants of whom 531 had vivax malaria, sensitivities ranged from 66% to 100% and specificities ranged from 98% to 100%. In pooled analyses, compared with microscopy, vivax-specific RDTs had a sensitivity of 95% (95% CI, 86%-99%) and specificity of 99% (95% CI, 99%-100%) (**Table**). For pan-specific RDTs, the sensitivities from individual studies varied from 25% to 100% and had wide 95% CIs. Specificities varied between 89% and 100% and had narrow CIs. Where there were sufficient data, we compared the accuracy of commercial brands within each type of pan-specific RDT, and there was no association of commercial brand with superior sensitivity or specificity. The variability and uncertainty in sensitivity estimates are probably due to the small number of malaria cases in some studies. The mean specificity of each of the 3 types of pan-specific RDTs was high (Table), with approximately 1% to 2% of noncases being false-positives when compared with microscopy. Conversely, mean sensitivities were low, with false-negative rates for nonfalciparum species between 11% and 22%.

Evidence Profile

No. of studies: 37 publications reporting 47 study cohorts

Study years: Conducted, 1998–2011; published, 1999–2013

Last search date: December 31, 2013

No. of participants: 22 862 with symptoms suggestive of uncomplicated malaria

Men: 8304 (56%) **Women:** 6399 (44%); only 34 studies (14 703 participants) reported sex

Race/ethnicity: Unavailable

Age range: 0-94 years; 5 studies did not report age

Settings: Ambulatory health care settings in nonfalciparum malaria endemic areas

Countries: 18 countries in Asia, Africa, and South America

Discussion

In *P vivax* endemic areas, vivax-specific RDTs have higher sensitivity for malaria than pan-specific RDTs. Pan-specific RDTs may be useful in areas where the majority of malaria is caused by *P falciparum* or mixed infection because they are sensitive for the detection of *P falciparum*.[3]

When we updated our search in December 2014, we found 4 additional studies that meet the review inclusion criteria. Three of the studies, with sample sizes of 677 participants,[4] 1762 participants,[5] and 200 participants,[6] respectively, compared vivax-specific RDTs with microscopy. Their findings were consistent with those for studies included in the published review, although Vyas et al[4] found a lower specificity (90%). Inclusion of the 3 new studies in an updated meta-analysis of vivax-specific RDTs gave a mean sensitivity of 94% (95% CI, 86%-98%) and a mean specificity of 99% (95% CI, 98%-100%), similar to those of the original meta-analysis. The fourth new study by Chong et al,[7] with a sample size of 185 participants assessed a type 3 pan-specific RDT against microscopy and polymerase chain reaction for detection of nonfalciparum malaria. The study by Chong et al was consistent with the included studies for type 3 RDTs, and is unlikely to change the conclusions of the review.

Table. Summary of Accuracy of Rapid Diagnostic Tests for Diagnosing *Plasmodium vivax* and Nonfalciparum Malaria

RDT[a]	RDT Target Antigen	No. of Studies	Malaria Cases	No. of Participants	Median Prevalence (Range), %	Mean Sensitivity (95% CI), %	Mean Specificity (95% CI), %
RDTs for *P vivax* Malaria (With or Without Other *Plasmodium* Species) Verified by Microscopy							
Vivax-specific	Pf HRP-2 and pLDH-Pv	8	580	3682	19 (2-45)	95 (86-99)	99 (99-100)
Pan-Specific RDTs for Nonfalciparum Malaria							
Verified by microscopy							
Type 2	Pf HRP-2 and aldolase	11	958	6879	14 (7-32)	78 (73-82)	99 (97-99)
Type 3	Pf HRP-2 and pLDH-pan	23	1537	11 234	10 (7-36)	78 (69-84)	99 (98-99)
Type 4	pLDH-Pf and pLDH-pan	10	986	3831	27 (8-33)	89 (79-95)	98 (97-99)
Verified by PCR							
Type 3	Pf HRP-2 and pLDH-pan	5	300	1639	15 (7-33)	81 (72-88)	99 (97-99)

Abbreviations: HRP-2, histidine-rich protein 2; PCR, polymerase chain reaction; Pf, *Plasmodium falciparum*; pLDH, plasmodium lactate dehydrogenase; Pv, *Plasmodium vivax*; RDT, rapid diagnostic test.

Source: Data adapted from Abba et al, 2014,[2] under the terms of the Creative Commons Attribution Noncommercial license.

[a] RDTs use different types of antibody or antibody combinations to detect *Plasmodium* antigens. Some antibodies aim to detect a particular species whereas others are panmalarial aiming to detect all *Plasmodium* species. Type 2 and type 3 RDTs use antibodies that detect the HRP-2 antigen expressed only by *P falciparum*. Both RDTs also include pan-specific antibodies: type 2 detects aldolase and type 4 detects pLDH from all *Plasmodium* species. Type 4 RDTs use antibody combinations that detect *P falciparum* specific pLDH or pLDH from any *Plasmodium* species. Seven studies assessed more than 1 RDT by giving participants all RDTs (head-to-head comparison).

Limitations

Study quality and descriptions and reporting of patient characteristics and reference standards were variable. Microscopy is imperfect, and it is possible that an RDT result may have been accurate in some cases of discordant results between microscopy and RDT. However, studies using polymerase chain reaction as the reference standard gave similar results to those using microscopy. Insufficient data were available to assess the effect of parasite density on test accuracy.

Comparison of Findings With Current Practice Guidelines

The World Health Organization recommends diagnosis by either microscopy or RDT before starting antimalarial treatment.[8] Local malaria epidemiology, geography, resources, and infrastructure will influence the decision to use microscopy or an RDT.

Areas in Need of Future Study

Research evaluating clinical algorithms using vivax-specific RDTs in endemic areas is needed.

ARTICLE INFORMATION

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Submissions: We encourage authors to submit papers for consideration as a JAMA Clinical Evidence Synopsis. Please contact Dr McDermott at mdm608@northwestern.edu.

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