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# COCHRANE COLUMN

**Taryn Young**

The Cochrane Collaboration (http://www.cochrane.org) is an international, non-profit organization that prepares and disseminates up-to-date systematic reviews on the effects of healthcare interventions in order to help people make well-informed decisions. Systematic reviews aim to answer focused healthcare questions by systematically identifying and evaluating all relevant research studies and synthesizing their results.

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In this issue, we feature the Cochrane Diagnostic Review on Rapid diagnostic tests for diagnosing uncomplicated *Plasmodium falciparum* malaria in endemic countries, conducted by Abba *et al.* This column highlights Cochrane Reviews of relevance to public health, and aims to stimulate debate on relevance, feasibility and acceptability. We asked Emmanuel Bottieau and colleagues to comment on and put the review in context, and Mariska Leeflang provides an overview of the approach to conducting diagnostic reviews.

# Rapid diagnostic tests can extend access of diagnostic services for uncomplicated *Plasmodium falciparum* malaria

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Rapid diagnostic tests (RDTs) for malaria use antibodies to detect malaria parasite antigens in a drop of blood. They take only a few minutes to perform and require little training to use. If sufficiently accurate, they could prove useful for diagnosing malaria in areas where microscopy diagnosis is unavailable or of poor quality.

A team from the UK, Malaysia and the World Health Organization have undertaken a Cochrane review to assess the accuracy of RDTs for detecting *Plasmodium falciparum* parasitaemia in people attending ambulatory healthcare facilities in areas where malaria is endemic.

The authors carried out a systematic and comprehensive search up to 14 January 2010. They included studies that compared RDTs to malaria microscopy or polymerase chain reaction. Included studies were of patients from a random or consecutive series of patients attending ambulatory health facilities with symptoms of malaria in endemic areas. Studies including only travellers from non-endemic areas were excluded, and a total of 74 studies were included.

Data were analysed by type of test, categorized by the antigens used to detect *P. falciparum* and in the case of test Types 2–5, other malaria parasite species on another test line. This review examined *P. falciparum* detection. Table 1 shows the types of tests included in the review, the antigens they use and the combinations of malaria parasites that they are designed to detect.

For both categories of test, there was substantial heterogeneity in the study results. Quality of the microscopy reference standard could only be assessed in 40% of studies due to inadequate reporting, but results did not seem to be influenced by the reporting quality.

Overall, HRP-2 antibody-based tests were less specific than pLDH-based tests, although the point estimate suggests that they may be slightly more sensitive. If the point estimates for Type 1 (HRP-2) and Type 4 (pLDH) tests are applied to a hypothetical cohort of 1000 patients where 30% of those presenting with symptoms have *P. falciparum*, Type 1 tests will miss 16 cases, and Type 4 tests will miss 26 cases. The number of people wrongly diagnosed with

**Table 1** Description of RDT types included in the review

| Type of test | Antibody combinations | Possible results |
|---|---|---|
| Type 1 | HRP-2 (*P. Falciparum*-specific) | No Pf; Pf; invalid |
| Type 2 | HRP-2 (*P. Falciparum*-specific) and aldolase (pan-specific) | No malaria; Pf or mixed; Pv, Pf and/or Pm; invalid |
| Type 3 | HRP-2 (*P. Falciparum*-specific) and pLDH (pan-specific) | No malaria; Pf or mixed; Pv, Pf and/or Pm; invalid |
| Type 4 | pLDH (*P. Falciparum*-specific) and pLDH (pan-specific) | No malaria; Pf or mixed; Pv, Pf and/or Pm; invalid |
| Type 5 | pLDH (*P. Falciparum*-specific) and pLDH (*P. vivax*-specific) | No malaria; Pf; Pv; Pf and Pv; invalid |

**Table 2** Average sensitivities and specificities in meta-analyses by type of test and by antibody

| RDT type | Number of studies | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|
| HRP-2 (Types 1–3) | 75 | 95.0 (93.5–96.2) | 95.2 (93.4–99.4) |
| Type 1 | 65 | 94.8 (93.1–96.1) | 95.2 (93.2–96.7) |
| Type 2 | 8 | 96.0 (94.0–97.3) | 95.3 (87.3–98.3) |
| Type 3 | 5 | 99.5 (71.0–100) | 90.6 (80.5–95.7) |
| pLDH (Types 4 and 5) | 19 | 93.2 (88.0–96.2) | 98.5 (96.7–99.4) |
| Type 4 | 16 | 91.5 (84.7–95.3) | 98.7 (96.9–99.5) |
| Type 5 | 3 | 98.4 (95.1–99.5) | 97.5 (93.5–99.1) |

CI: confidence interval.

*P. falciparum* would be 34 with Type 1 tests, and 9 with Type 4 tests.

The results show that sensitivity and specificity of all RDT types is such that they can be used to extend the access of diagnostic services for uncomplicated *P. falciparum* malaria. Difference in accuracy between tests is small and choice of test should be guided by the malaria epidemiology of a site combined with the cost and availability of the test. The HRP-2 antigen persists even after effective treatment and so pLDH tests should be chosen for treatment failure detection.

The full text of the Cochrane Review is available in *The Cochrane Library*: Abba K, Deeks JJ, Olliaro PL, Naing CM, Jackson SM, Takwoingi Y, Donegan S, Garner P. Rapid diagnostic tests for diagnosing uncomplicated *P. falciparum* malaria in endemic countries. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.: CD008122. DOI: 10.1002/14651858.CD008122.pub2.

# Commentary: Rapid diagnostic tests for diagnosing uncomplicated *Plasmodium falciparum* malaria in endemic countries (Review)

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Major progress in prevention, diagnosis and treatment, as well as growing international financing and renewed global political commitment have had an impact on the prevalence of malaria.[1] However, global malaria deaths (almost exclusively attributable to *Plasmodium falciparum*) still reached 1 238 000 (929 000–1 685 000) in 2010,[2] far beyond the World Health Organization (WHO) estimates,[1] the difference being explained by the large underestimation of malaria mortality, in particular in children aged >5 years and in adults.

Early, prompt and accurate diagnosis of malaria, followed by adequate treatment, reduce morbidity and mortality. Microscopy is technically demanding, so simple Rapid diagnostic tests (RDTs) are potentially important. These tests mainly detect histidine-rich protein-2 (HRP-2) or plasmodium lactate dehydrogenase (pLDH) specific to *P. falciparum* (Pf), alone or in combination with other antigens. Since any patient suspected of malaria should be tested either by microscopy or RDT before treatment,[3] the systematic review of Abba *et al.* assessing the performances of current RDTs in diagnosing *P. falciparum* malaria is most welcome. After having analysed 111 test evaluations in 74 unique studies assessing 21 different RDT brands and 60 396 RDT results, the conclusion is straightforward: performance of RDTs is such nowadays that it may replace microscopy for patient care. Readers are also elegantly provided tables for interpreting RDT performances in different epidemiological scenarios.

The review findings are particularly robust for the RDTs targeting HRP-2 or Pf-pLDH alone (of note, pLDH, if not clearly defined, may also refer to pan-pLDH, common to all *Plasmodium* species). As acknowledged by the authors, the number of studies evaluating combined RDTs is much smaller, resulting in large 95% confidence intervals and unsatisfactory diagnostic accuracy when considering the lowest ranges. Such RDTs are more expensive and also more difficult to interpret by less educated caregivers. Another limitation is that the rare, but worrying prozone phenomenon (false-negative or low results in case of high parasite density) has not been explored.[4] According to a study published after January 2010, prozone only affects HRP-2-based RDTs at variable frequency and intensity but may account for up to 1% of false-negative results in patients with *P. falciparum* malaria (unfortunately those with hyperparasitaemia, at highest risk of complication).[4] Finally, no RDT type was clearly superior to another in terms of sensitivity, but HRP-2-based RDTs were less specific. The long persistence of HRP-2 after parasite clearance is indeed of concern in areas of high malaria transmission.[5] Side-to-side comparisons of both types of RDTs are now required in different epidemiological settings, to refine their respective positioning. No universal 'one-size-fits-all' RDT is to be expected for all variable and evolving malaria contexts. Meanwhile, the authors must be congratulated for this impressive piece of work that provides reassurance for the caregivers and policy makers of the many endemic countries where RDTs have already been deployed towards the most peripheral health facilities.

## References


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# Approach to conducting Cochrane Diagnostic Test Accuracy Reviews


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Cochrane diagnostic test accuracy (DTA) reviews assess the accuracy of diagnostic medical tests. The accuracy of a test determines how well a test is able to differentiate between people with and without the target condition. Accuracy is often expressed in sensitivity (the proportion of persons with the target condition who test positive) and specificity (the proportion of persons without the target condition who test negative).

As for all systematic reviews, a DTA review starts with a research question. This question leads the rest of the review and is of utmost importance. Most questions will be comparative questions: is MRI better than CT to detect stroke in elderly

patients? In order to answer any review question, it is necessary to include the intended role of the test in the question, or at least the setting in which the test will be used. For example, a test that will be used to refer patients from general practice to a more specialized setting, will have to meet other requirements than a test that will be used to confirm a previously made diagnosis in an academic hospital.

The question will not only guide retrieval of studies and data extraction, but also quality assessment. The current tool that should be used for the assessment of quality is QUADAS-2. QUADAS-2 assesses both the internal and external validity of a study in four domains: patient population, index test, reference standard and flow and timing. Older reviews used QUADAS-1, in which the internal and external validity were sometimes mixed. External validity (the applicability of the results of a study to practice) very much depends on the actual research question.

The most prominent part of a systematic review is often the meta-analysis. In DTA reviews, there are two outcomes that should be meta-analysed simultaneously: sensitivity and specificity. Because sensitivity and specificity are correlated with each other, they should not be pooled separately. Thus, meta-analysis of these data requires sophisticated statistical packages, like SAS, STATA or R.

The final part of a DTA review is the presentation and interpretation of the results. Here again, the research question guides the interpretation. If the question was whether a test can be used to refer patients for further work-up, the results from the meta-analysis can be used to explain how many patients will be missed by using one test or the other (the false negatives); and how many patients will be referred when this was not necessary (the false positives).

For more information on the Cochrane Diagnostic Test Accuracy Reviews, visit http://srdta.cochrane.org/