REVIEW 10.1111/1469-0691.12152

Malaria rapid diagnostic tests in travel medicine

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Abstract

Malaria is a serious condition in the non-immune traveller, and prognosis depends on timely diagnosis. Although microscopy remains the cornerstone of diagnosis, malaria rapid diagnostic tests (RDTs) are increasingly used in non-endemic settings. They are easy to use, provide results rapidly and require no specific training and equipment. Reported sensitivities vary between different RDT products but are generally good for *Plasmodium falciparum*, with RDTs detecting the *P. falciparum* antigen histidine-rich protein-2 (PfHRP2) scoring slightly better than *P. falciparum*-lactate dehydrogenase (Pf-pLDH)-detecting RDTs. Sensitivity is lower for *Plasmodium vivax* (66.0 – 88.0%) and poor for *Plasmodium ovale* (5.5 – 86.7%) and *Plasmodium malariae* (21.4 – 45.2%). Rapid diagnostic tests have several other limitations, including persistence of the PfHRP2 antigen, cross-reactions of *P. falciparum* with the non-falciparum test line and *vice versa* and (rare) false-positive reactions due to other infectious agents or immunological factors. False-negative results occur in the case of low parasite densities, prozone effect or *pfhrp2* gene deletions. In addition, errors in interpretation occur, partly due to inadequacies in the instructions for use. Finally, RDTs do not give information about parasite density. In the diagnostic laboratory, RDTs are a valuable adjunct to (but not a replacement for) microscopy for the diagnosis of malaria in the returned traveller.In malaria endemic settings, special groups of travellers (those travelling for long periods, expatriates and short-stay frequent travellers) who are remote from qualified medical services may benefit from self-diagnosis by RDTs, provided they use correctly stored RDT products of proven accuracy, with comprehensive instructions for use and appropriate hands-on training.

Keywords: Diagnosis, malaria, plasmodium, rapid diagnostic test, travel medicine, traveller
Article published online: 14 January 2013
Clin Microbiol Infect 2013; **19:** 408–415

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Malaria in the Returned Traveller: a Serious Condition with Difficult Diagnosis

Yearly, approximately 10 000 cases of imported malaria are reported, but the actual number may be as high as 30 000 [1]. Imported malaria is a potentially fatal condition and the outcome depends largely on timely diagnosis and treatment [2]. In malaria non-endemic settings, competence in the microscopic diagnosis of malaria is often lacking because of low exposure to malaria-positive samples [3]. Malaria rapid diagnostic tests (RDTs) may be an alternative: RDTs are simple, hand-held diagnostic devices that offer a quick (within 20 min) diagnosis. Results are visually read as coloured lines on a strip, and no particular expertise is required.

Malaria Rapid Diagnostic Tests: Mechanism, Target Antigens and Formats

Malaria RDTs consist of a nitrocellulose strip mostly embedded in a plastic cassette; occasionally, this strip may present as a dipstick (self-standing strip to be dipped in a tube) or be enclosed in a cardboard format. The mechanism of action is explained in Fig. 1.

The following antigens may be detected: histidine-rich protein-2 (PfHRP2) and *P. falciparum*-specific parasite lactate dehydrogenase (Pf-pLDH) (which are both specific for *P. falciparum*), *P. vivax*-pLDH (Pv-pLDH, specific to *P. vivax*) and pan-pLDH and aldolase (common to all human *Plasmodium* species). Malaria RDTs are categorized as two-, three- or

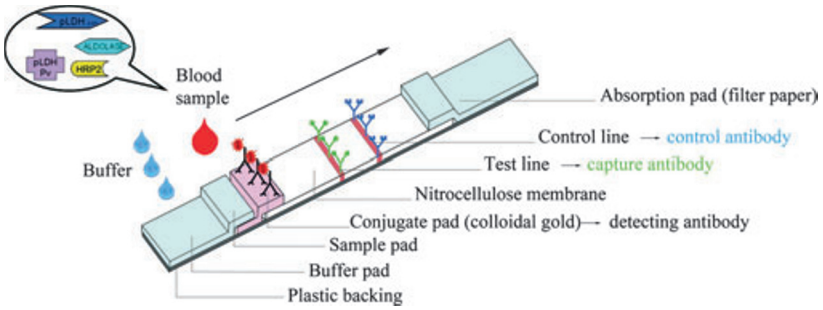

FIG. 1. Schematic drawing of a malaria rapid diagnostic test. Sequence of events when performing an MRDT. Blood and buffer are applied, respectively, to the sample and buffer pad. They are attracted by the capillary action of the absorption pad and start to migrate. First, they pass the conjugate pad, which contains a detection antibody targeting a *Plasmodium* antigen, such as PfHRP2, Pf-pLDH, Pv-pLDH, pan-pLDH or aldolase (for abbreviations see text). This detection antibody is a mouse-antibody that is conjugated to a signal, mostly colloidal gold. If present in the sample, the *Plasmodium* antigen is bound to this detection antibody-conjugate. Next, the antigen-antibody-conjugate complex migrates further until it is bound to the capture antibody, which binds to another site of the *Plasmodium* target antigen. As the capture antibody is applied on a narrow section of the strip, the complex with the conjugated signal will be concentrated and by virtue of the colloidal gold will become visible as a coloured line. The excess of detection antibody-conjugate that was not bound by the antigen and the capture antibody moves further until it is bound to a goat-raised anti-mouse antibody, thereby generating a control line.

four-band products, depending on the number of lines ('bands') that may become visible on the strip, with the control line standing for one band. Two-band RDTs detect a single antigen (mostly PfHRP2), whereas three-band RDTs detect *P. falciparum* (PfHRP2 or Pf-pLDH) and in addition mostly a pan-malaria antigen (pan-pLDH or aldolase); four-band RDTs detect a *P. falciparum*-specific antigen, a pan-malaria antigen and a *P. vivax*-specific antigen (Fig. 2).

Key-points of the Laboratory Diagnosis of Malaria in Returned Travellers

Microscopy represents the cornerstone of malaria diagnosis as it provides all relevant information: confirmation of the diagnosis of malaria; species differentiation (which is important because *P. falciparum* is life-threatening and because treatment is not the

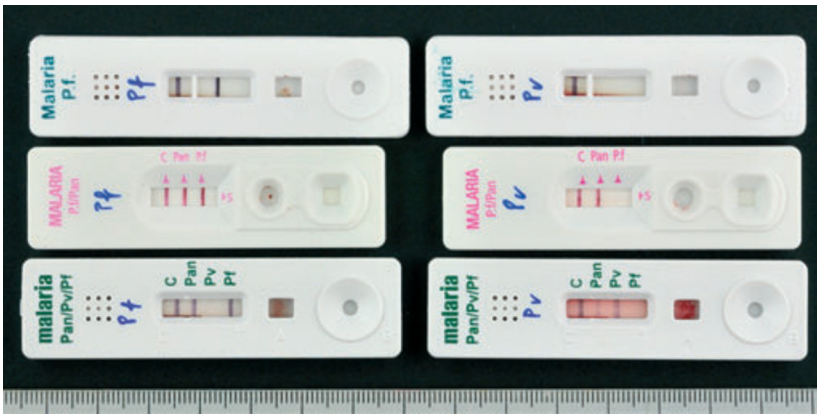

FIG. 2. Two-, three- and four-band malaria RDTs (above, middle and below, respectively) run with a *P. falciparum* sample (left) and a *P. vivax* sample (right). The two-band RDT shows the control line and a *P. falciparum* (PfHRP2)-line for the *P. falciparum* sample and only a control line for the *P. vivax* sample: correct reporting is '*P. falciparum*' and 'no *P. falciparum* detected', respectively. The three-band RDT shows, apart from the control line, PfHRP2 and pan-pLDH test lines for *P. falciparum*: correct reporting is '*P. falciparum*, mixed infection with non-*falciparum* species not excluded'. The *P. vivax* sample shows only a pan-pLDH test line: correct reporting is 'non-*falciparum* species'. For the *P. falciparum* sample, the four-band RDT shows test lines for the pan-pLDH and PfHRP2 test lines: correct reporting is '*P. falciparum*, mixed infection with *P. ovale*/*P. malariae* not excluded'. For the *P. vivax* sample, pan-pLDH and Pv-pLDH test lines are visible: correct reporting is '*P. vivax*, mixed infection with *P. ovale*/*P. malariae* not excluded'.