Malaria rapid diagnostic tests: A revolution and challenge for management of febrile disease

Rapid, accurate diagnostic testing is essential in malaria-endemic areas.

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Febrile patients in malaria-endemic areas need rapid and accurate diagnosis to ensure prompt access to antimalarial treatment to avoid severe disease. As most fevers in malaria-endemic areas of South Africa are not caused by malaria, and symptom-based diagnosis is highly nonspecific, rapid demonstration of the presence or absence of malaria parasites reduces delays in appropriate management of non-malarial fever, saves resources by reducing use of antimalarial drugs, and helps to determine true malaria prevalence. The introduction of malaria antigen-detecting rapid diagnostic tests (RDTs) has extended the possibility of such accurate, rapid diagnosis to the whole population for the first time.

Malaria RDTs provide a quick diagnosis, usually within 15 - 20 minutes. These tests require only a drop of blood from a finger prick, and can be used in a variety of settings – from a rural community to a hospital laboratory or a doctor's office. It is essential to carefully consider the role of the RDT for each setting, and to ensure comprehensive training and competency assessment of end-users. Job-aids are being developed and tested by the World Health Organization (WHO) and other agencies for the most common RDTs (Table I). Community education may also be necessary, particularly with regard to the management of fever where malaria is excluded.

Table I. List of web-based resources for malaria RDTs

Website URL	Description of resource
http://www.wpro.who.int/sites/rdt	Definition of an RDT; mechanism of action; using RDTs; list of RDT products and manufacturers; choosing an RDT; RDT job-aid and training manual; list of published reviews and trials
http://www.rapid-diagnostics.org	Rapid test technologies; appropriate use and accuracy
http://www.malaria.org.zw/index.html	East and southern African malaria control

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RDTs do not replace expert microscopy, but extend parasite-based diagnosis to new settings where good-quality microscopy cannot be sustained. Microscopy is necessary to monitor response to treatment in patients with severe malaria, for drug efficacy monitoring, species determination, and quantitation of parasites, particularly to confirm very high parasite densities – one of the many criteria that define severe disease.

Malaria RDTs are available in three main formats: dipstick, card and cassette. Most RDTs detecting *Plasmodium falciparum* target its histidine-rich protein 2 (HRP2). This antigen is present in asexual *P. falciparum* blood stages and early gametocytes. However, HRP2 remains detectable for weeks after effective treatment, limiting the use of this type of RDT in monitoring response to treatment, and complicating the interpretation of results in recently treated patients.[1] The antigen structure is also highly variable, which may reduce RDT sensitivity.[2]

Combination RDTs are available that detect both *P. falciparum* and usually a pan-malarial antigen common to all human malaria species. The *P. falciparum*-specific antibody targets either HRP2 or *Plasmodium* lactate dehydrogenase (pLDH), while the pan-specific antibody targets either pLDH or aldolase. pLDH-based RDTs may have some role in monitoring treatment efficacy, as this antigen becomes undetectable after parasite clearance. However, they often have limited sensitivity at low parasite densities and decreased sensitivity for *P. malariae* and *P. ovale*.[1]

The interpretation of an RDT can be challenging. All RDTs contain a control line and the test is regarded as invalid if this line does

not appear. However, an intact control line does not guarantee that the test line is working properly. Combination RDTs are more complicated to interpret, and usually don't distinguish between *P. falciparum*-only infections and those also involving other species.

A number of factors affect RDT performance, including transport and storage conditions, manufacturing quality, parasite density in the patient, and test preparation and interpretation. Some RDTs achieve a sensitivity similar to good field microscopy (~100 parasites/µl), but may deteriorate with high humidity and temperature.[3] False-negative results may occur in some circumstances.[1] RDT-based diagnostic health care systems should include at a minimum: careful procurement, quality checks before distribution to the end-user, appropriate transport and storage practice, comprehensive training and supervision of end-users, an appropriate management algorithm for positive and negative RDT results, and community education. The algorithm should be modelled to the national malaria treatment policy and the major causes of non-malarial febrile illness (and consistent with IMCI protocols in children).

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The following should be considered when choosing a malaria RDT: manufacturing quality, stability, cost, malaria prevalence and species, sensitivity and specificity, and likely end-users.[4] *P. falciparum* is the predominant malaria species in South Africa, but determining whether to use a test detecting *P. falciparum* only or a combination test is a difficult issue. HRP2 tests are cheaper (about US$0.65 compared with US$0.90 - 1.30 for a combination test) and simpler to interpret. However, failure to detect the less common *Plasmodium* species will complicate management of RDT-negative patients and may harm confidence in RDT-based malaria diagnosis.

Malaria RDTs have the potential to greatly enhance management of febrile disease and allow prompt access to antimalarial drugs. The degree of thought and care that goes into RDT introduction and implementation will determine whether their potential is realised or not.

References

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In a nutshell

- Good-quality, antigen-detecting rapid diagnostic tests (RDTs) can provide rapid and accurate malaria diagnosis.
- RDTs do not replace expert microscopy, but extend malaria diagnosis to new settings.
- The widely used RDTs remain positive for weeks after successful treatment and therefore rapid tests are used only for initial diagnosis of malaria and not to monitor treatment response or diagnose malaria in recently treated patients.
- Consider the following when choosing a malaria RDT: manufacturing quality, stability, cost, malaria prevalence and species, sensitivity and specificity, and the likely end-users.
- A health care system should procure carefully; check quality before distribution; store and transport appropriately; train and supervise end-users; have a strategy to manage negative RDT results; and ensure community understanding and acceptance.

Single Suture

You are what you pee

Your urine could provide more than just information about what you have been eating and drinking, according to a team at Imperial College, London. They have found a new way to monitor human metabolism after screening urine from 4 000 people from the UK, the USA, China and Japan. They used nuclear magnetic resonance to identify metabolites in the urine and showed that specific metabolites are linked to certain ethnic groups, nationalities, genders and diseases.

They also found 4 molecules that appear to be correlated with hypertension – one of which is formate, suggesting that a kidney ion pump is involved. If this is confirmed it could lead to new treatments for hypertension.

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