



Is there a role for malaria rapid diagnostic tests in Africa?



Dr David Bell

Roll Back Malaria Department, World Health Organization, Geneva

Rapid diagnostic tests (RDT) are of increasing interest to malaria programmes in Africa as rising costs of anti-malaria drugs increase the need for diagnostic accuracy. RDTs hold great promise for disease management, but their usefulness will depend on local epidemiology, existing health service capacity, local cost of both RDTs and treatment, and the quality of planning devoted to their introduction and use.

When chloroquine and other low-cost drugs were highly effective, treatment of malaria based on symptoms alone was widely seen to be cost-effective. However, the introduction of Artemisinin-based combination therapies (ACT), increases the importance of minimising unnecessary drug use. As microscopy is difficult to maintain in remote and poorly resourced areas,^{1,2} RDTs offer the possibility to extend accurate parasite-based malaria diagnosis to people in remote areas for the first time (see Table 1).

Table 1 RDTs and microscopy

RDTs are best viewed as a means of extending parasite-based diagnosis to areas where good microscopy cannot be maintained. Microscopy can provide accurate quantitation of parasite density, accurate identification of species, and high sensitivity. RDTs are likely to be cheaper than microscopy where caseload is low and a microscopist would not otherwise be active. They offer the potential to provide accurate diagnosis at a household level.

Most RDTs are relatively simple to operate, giving a result about 15 minutes after finger-prick blood sampling. They have potential applications in case management, epidemic investigation, and surveillance. Ten years after the introduction of the first commercially-available product, a rapid proliferation in products on the market, variability of results in field trials,³⁻⁶ uncertainty over the relationship between cost and benefits in high-prevalence areas, and the vulnerability of biological tests to degradation by temperature and moisture have resulted in continued uncertainty as to when they should be used.

Types of RDTs

Malaria RDTs are available as a simple dipstick, a cassette (dipstick in a plastic holder), or in a card format. Simplicity of format (e.g. cassettes) may be important to overall sensitivity.⁷ All products detect *P. falciparum*-specific protein, either histidine-rich protein-2 (HRP2) or parasite-specific lactate dehydrogenase (pLDH). Some, which also detect pan-specific aldolase or pLDH, distinguish a

non-*P. falciparum* infection from *P. falciparum* or mixed-species infections. Other species-specific RDTs are becoming available. Tests detecting *P. falciparum*-only are priced from about US\$0.60, whereas pan-specific tests are commonly about 40% more expensive.

Ensuring RDTs are beneficial

Misdiagnosis remains a major contributor to malaria morbidity and mortality.⁸ The usefulness of RDTs in case management will depend on whether this can be reduced and on the level of cost savings accrued by health services and patients. Cost-benefit ratios depend on the cost of the RDT, the cost of treatment, parasite prevalence, and the effect of the RDT on treatment practice. In epidemic-prone areas and areas of low endemicity, such as highlands, southern Africa, and Ethiopia, it is clear that spending US\$1.00 on treatment would be worthwhile if it avoided giving ACT worth US\$2.80 to up to 90% of febrile patients who are not parasitaemic. Where prevalence is high in many sub-Saharan countries, benefits are less clear (see Table 2). If a high proportion of febrile patients have parasitaemia, the additional cost of diagnosis may not be recouped through treatment saved.

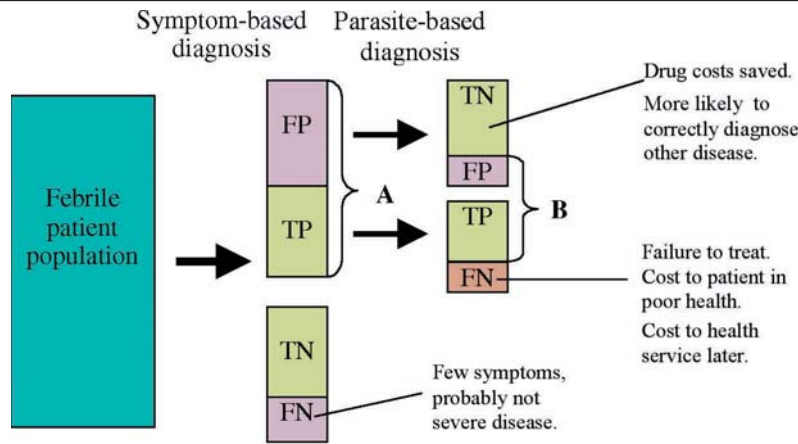
Table 2 RDTs and high parasite prevalence

To be clinically useful, it is recommended that RDTs should reliably detect infections of at least 100 parasite/μl.¹⁰ It is sometimes suggested that RDTs of reduced sensitivity would be of advantage in sub-Saharan Africa, as they would be negative in fever cases with high immunity in which a low parasite density is incidental and not the cause of illness. This overlooks the need to detect and treat low-density parasitaemia in children and recent immigrants or travellers, and the possibility that treating any parasitaemia in a sick person may be helpful. Reliance should be placed on good case selection for testing, rather than on an insensitive test.¹⁰

RDTs will be of no benefit if the result is ignored. However, if health workers are to be expected to withhold anti-malarial treatment from a febrile patient with a negative RDT result, both health worker and patient must have confidence in the diagnosis. Reliance on a poorly sensitive RDT will inevitably result in failures of malaria case management with resultant loss of confidence in RDT use and loss of the benefits in reduced morbidity and mortality that ACT should provide (see Figure 1).

Good quality assurance is therefore a vital component of the use of RDTs. This must extend from procurement (see Table 3) to point of use.

Figure 1 Effects of introducing parasite-based diagnosis as an addition to a symptom-based algorithm to guide the use of ACT. While low RDT specificity (high false positive rate) will reduce cost-savings, low sensitivity (high false negative rate) may lose the health benefits that ACT would provide.



FP: False positive. FN: False negative. TP: True positive. TN: True negative
 A: Would have been treated with antimalarial drugs on basis of symptoms.
 B: Treated with antimalarial drugs on basis of RDT result.

Incorporating RDTs into disease management

RDTs should be seen as part of the diagnostic process, not the sole basis for treatment. A good treatment algorithm that takes the inherent fallibility of RDTs into account will guide health workers to:

1. Treat cases with anti-malarial drugs that are RDT negative but have symptoms consistent with severe malaria (while assessing for other causes).
2. Re-test after 1 or 2 days if significant symptoms persist.
3. Consider further investigation whether the RDT negative or positive.

RDTs should be incorporated into established treatment protocols such as IMCI,⁹ rather than used as a stand-alone test.

Table 3 Issues to consider when purchasing an RDT

- Plasmodium species to be detected (*P falciparum* only, or pan-specific).
- Shelf-life and temperature stability in intended conditions of storage and use.
- Ease of use, including format of the test (i.e. cassette dipstick, card).
- Requirement for post-treatment testing of patients.
- Cost (including transport, training, and quality control).
- Accuracy.
- Evidence of good manufacturing practice.

Most manufacturers specify storage below 30°C, which is not possible in many endemic areas. However, maintaining in centralised storage as long as possible, care during transport, and storage in shade or under thatch roofs will help minimise degradation. Monitoring sensitivity in remote locations has been difficult, but new innovations such as positive control wells and temperature monitors may address this adequately in the near future. Although the RDT technique appears simple, mistakes in preparation or reading are common so good training and clear instructions in local languages are essential.⁷

Once quality and confidence are established, further possible benefits include:

- improvement in compliance to treatment
- improvement in treatment-seeking behaviour
- search for alternative diagnosis in case of a negative result.

Operational research to define these effects is important in determining the total long-term cost-benefits to health programmes.

Further reading

WHO is assisting in the development of methods for prequalification and quality assurance of RDTs, and assessing cost-benefits. Present advice is summarised in the WHO RDT website www.wpro.who.int/rdt and recent publications.^{10,11}

References

1. Durrheim DN, Becker PJ, Billingham K. Diagnostic disagreement – the lessons learnt from malaria diagnosis in Mpumalanga. *S Afr Med J* 1997; 87: 1016.
2. Kachur SP, Nicolas E, Jean-François et al. Prevalence of malaria parasitemia and accuracy of microscopic diagnosis in Haiti, October 1995. *Rev Panam Salud Publica* 1998; 3: 35–9.
3. Rubio JM, Buhigas I, Subirats M et al. Limited level of accuracy provided by available rapid diagnosis tests for malaria enhances the need for PCR-based reference laboratories. *J Clin Microbiol* 2001; 39: 2736–7.
4. Coleman RE, Maneechai N, Rachapaew N et al. Field evaluation of the ICT Malaria Pf/Pv immunochromatographic test for the detection of asymptomatic malaria in a Plasmodium falciparum/vivax endemic area in Thailand. *Am J Trop Med Hyg* 2002; 66: 379–83.
5. Huong NM, Davis TM, Hewitt S et al. Comparison of three antigen detection methods for diagnosis and therapeutic monitoring of malaria: a field study from southern Vietnam. *Trop Med Int Health* 2002; 7: 304–8.
6. Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. *Jama* 2003; 289: 959–62.
7. Tavrow P, Knebel E, Cogswell L. *Using quality design to improve malaria rapid diagnostic tests in Malawi*. Quality Assurance Project (QAP) for the United States Agency for International Development. Bethesda, Maryland, 2000.
8. Ghebreyesus TA, Witten KH, Getachew A et al. Community-based malaria control in Tigray, northern Ethiopia. *Parasitologia* 1999; 41: 367–71.
9. WHO. *IMCI Information Package*. WHO/CHS/CAH/98.1 A-M. Accessed: 2004. <http://www.who.int/child-adolescent-health/publications/pubIMCI.htm>.
10. WHO. *Malaria Rapid Diagnosis: Making it Work*. Meeting report 20–23 January 2003. World Health Organization, Manila, 2003.
11. WHO. *The Use of Malaria Rapid Diagnostic Tests*. Accessed: 2004. www.wpro.who.int/rdt.