



in young children in endemic areas [8], as is the detection of circulating *P. falciparum* schizonts, which warn of progression to severe disease. Microscopy can also be used to diagnose infections with blood-dwelling helminths, and the use of differential white cell counts can help identify viral and bacterial infections. However, the reading of blood slides requires a functioning microscope and skilled microscopist which, for health facilities that are often located in remote and rural settings, may be challenging in terms of availability, affordability, quality control and maintenance. Realistically, it may only be feasible to retain expert malaria microscopy in major hospitals and reference centers in much of the malaria endemic and nonendemic world.

“RDTs are relatively quick and simple to use, but their cost ... is an important consideration, as are issues of quality control ... the safe disposal of used tests and related paraphernalia, appropriate storage and delivery of tests, staff training and capacity of the health staff and health system to appropriately manage positive and negative results.”

Molecular techniques, including PCR, have been deployed in developed country settings [9], and discussed in the context of pretreatment screening, for example in efforts to contain the threat of artesunate resistance in Cambodia [103]. The challenge of making molecular technology available in remote settings precludes its widespread adoption for routine diagnosis in most settings. The Foundation for Innovative New Diagnostics (FIND) [104] is working with the WHO and many in-country partners in Africa, Southeast Asia and South America to support research into malaria RDTs, as well as novel diagnostic products, including heat-stable point-of-care tests, and highly sensitive tests for malaria endemic countries.

### Rapid diagnostic tests

The development of RDTs in recent years has created the potential to revolutionize malaria diagnosis. Inexpensive, self-contained, single-use, disposable tests have been developed that detect, with reasonable sensitivity and specificity [105], the presence of *P. falciparum* and, depending on the test, *P. vivax* and other plasmodia, in the blood. The tests generally require a drop of blood to be placed on a disposable

cassette, a few drops of buffer to be added, and the test then read after a defined period of time (e.g., 15 min). A control line appears to confirm that the test has worked, and the test is positive if a second line appears. Two broad groups of tests exist: those detecting species-specific parasite lactate dehydrogenase (pLDH) and those detecting the *P. falciparum*-specific histidine-rich-protein (HRP)-2, often combined with pan-specific plasmodial aldolase (‘panmalarial antigen’). pLDH-based tests have the advantage of becoming negative once the infection has been successfully treated, enabling an assessment to be made of the efficacy of the treatment. In contrast, HRP-2 may remain detectable in the circulation for more than a month after an active infection has been cured, resulting in reduced specificity of HRP-2-based tests, especially in high-transmission settings. Currently available RDTs are not able to indicate parasite density. RDTs are relatively quick and simple to use, but their cost, at US\$0.6–1.5 per test [10,106], is an important consideration, as are issues of quality control, including lot testing and the development of positive control wells, the safe disposal of used tests and related paraphernalia, appropriate storage and delivery of tests, staff training and capacity of the health staff and health system to appropriately manage positive and negative results [11].

Recent years have seen progress with improved intra- and inter-batch quality and shelf life under tropical conditions, but there is still a need to identify further suitable antigens to improve on *Plasmodium ovale*, *Plasmodium vivax* and, possibly, *Plasmodium knowlesi* diagnosis. The performance of RDTs has been evaluated in a number of reviews, although only recently has a comprehensive assessment been completed [105], and some of the public health issues and possible impact on malaria management as a whole been taken into account [12,13]. Despite existing technical limitations, RDTs have the potential to reduce overtreatment of malaria and improve the management of nonmalaria febrile illness.

### Compliance with malaria diagnostic test results

Reyburn and colleagues [6] drew attention to the major overtreatment of malaria in Northern Tanzania, a phenomenon documented in several other settings [14,15]. Working in an environment where blood-slide microscopy was available, Reyburn found that approximately half of the patients with a negative blood slide were nevertheless treated with antimalarial drugs.

Such prescribing practice has been attributed to concerns over the quality of blood-slide results, recognizing the absence of external quality assurance mechanisms and the possibility of 'slide-negative' malaria. A subsequent controlled trial randomized individuals to receive a diagnostic test with either microscopy or an RDT and monitored prescribers' practice [16]. The prescribers and patients were aware that a single line on the RDT cassette indicated a negative result and a double line reflected a positive result. Surprisingly, even with these relatively clear diagnostic test results, approximately half of those with a negative malaria test result were still prescribed an antimalarial drug. Subsequent work has suggested that the poor compliance to test results may be due to perceived patient pressure [17–19]. Traditionally, antimalarials have been inexpensive and safe, and it has been common practice to make presumptive diagnoses and provide antimalarial treatment. It is likely to take a concerted behavior change communication program directed at prescribers and communities to change these common practices. It is important to be realistic about the likely time-frame involved: campaigns have been running for decades in Europe and North America to reduce unnecessary prescribing of antibiotics to patients presenting with viral conditions.

### Access to antimalarial treatment & diagnosis

A large proportion, sometimes the majority, of antimalarial treatments are obtained through the private sector. In many settings, a local shop will be a more immediately available source of

antimalarial treatment than the local health facility. In order to improve access to ACTs, a global subsidy – The Affordable Medicines Facility for Malaria (AMFm) [107] – will facilitate the availability of inexpensive, quality antimalarial treatments in both the public and private sectors. Studies are underway to explore the feasibility of also introducing RDTs into the private sector, for example at licensed drug shops, and at the community level, in settings where home-based management of fever is being deployed [108]. It will be necessary to address financing issues of the diagnostic tests in these settings in order to ensure an incentive exists to perform a test before dispensing malaria treatment.

### Conclusion

Universal parasitological diagnosis prior to treatment will need RDT deployment in a sustainable, quality-assured and safe manner, accompanied by adequate behavior-change communication programs that target prescribers' behavior and communities' acceptance of a negative malaria test result. Trials are underway to explore the feasibility of, and to generate operational experience on, these critical issues.

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*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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