

# Rapid diagnostic tests can improve the quality of malaria case management

William R Brieger looks at how new technologies might remove the wait and uncertainty of tried and not so trusted laboratory investigations

One of the pillars for rolling back malaria is prompt and appropriate treatment of malaria episodes with a safe and effective antimalarial drug. Malaria control efforts were seriously set back when parasites developed widespread resistance to cheap and easily produced medicines like chloroquine (CQ) and sulphadoxine-pyrimethamine (SP). According to World Health Organization (WHO) guidelines,<sup>1</sup> current recommended first line treatment is an artemisinin-based combination therapy (ACT) medicine where one of the components of the combination derives from the *Artemisia annua* plant and the other is an antimalarial drug for which no parasite resistance has been demonstrated. The two most common combinations are artemether-lumefantrine (AL) and artesunate-amodiaquine (AA).

The idea of combining two medicines, neither of which exhibits any parasite resistance, was intended to prevent the development of resistance that easily occurs when one drug is used alone (monotherapy). Although monotherapy artesunate drugs did become available in the early part of this decade, WHO has issued stern warnings to remove these from the market lest resistance develop to the main current hope for controlling malaria through prompt treatment be lost.

The challenge of malaria case management today is that the retail cost for ACTs is in the US\$5–10 range compared with US\$0.20 for a course of CQ. No longer is presumptive treatment of fevers based on clinical diagnosis recommended or affordable in our health systems, especially when treating children over 5 years of age and adults.

WHO notes that, 'The introduction of ACTs has increased the urgency of improving the specificity of malaria diagnosis.<sup>1</sup> The relatively high cost of these drugs makes waste through unnecessary treatment of patients without parasitaemia unsustainable.' Studies have shown that often less than 50% of clinically diagnosed malaria (that is diagnosis based on signs, symptoms and history) actually can be verified as malaria in the laboratory. During our field work in Nigeria we observed that caregivers of children are no better at 'guessing' whether a child has malaria than a clinician.

Unfortunately each health post, clinic, or health centre in most of Africa lacks laboratory facilities to confirm the presence of malaria parasites in someone suspected of having malaria. The problem is compounded when

community-based treatment (medicine shops, home management) accounts for a large portion of malaria treatment.

A hopeful note is the development of rapid diagnostic tests (RDTs) which are antigen based and can be administered by front line health staff. A rapid diagnostic test detects a specific protein – parasite-specific antibodies or antigens in the blood.<sup>2</sup> RDTs are relatively simple to use, specific enough to direct treatment, and detect the vast majority of malaria cases.<sup>3</sup> These are ideal for front-line health facilities without laboratory support as well as hospital clinics during hours when laboratories are not open. We should even consider how to incorporate RDTs into village health programmes.

## The problems with clinical diagnosis

Several studies stress the fact that clinical diagnosis is not an accurate way to determine whether a patient has malaria. These studies vary by location and the way their results are presented but some key lessons can be drawn from them. A key concern according to Bell and Perkins is that, 'Treatment on the basis of symptoms alone results in massive mistreatment.'

Chandler and colleagues<sup>4</sup> in Tanzania tried to understand clinicians' behaviour when it comes to treating malaria. They found a high level of presumptive diagnoses such that 'malaria diagnosis was routine with patients presenting with symptoms including any



Laboratory testing in an urban poly clinic in Ghana

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of fever, vomiting, headache, or joint pain.’ They were often given a prescription for malaria drugs and sent on their way, but even when they were sent to the lab, the test results did not always dictate what kind of treatment was given. Malaria appeared to be the clinical diagnosis of first resort, and this reduced the time clinicians took with their clients. Consultations ending in non-malarial diagnoses took on average 5 minutes, while those resulting in malaria diagnoses were 4 minutes on average.

In Chandler’s study less than 5% of those who had been prescribed a malaria drug had a positive test result. In Mozambique, Hume and co-workers<sup>5</sup> found better results, but accuracy of clinical diagnosis was not perfect. Among the Mozambican patients 74% of adults and 71% of children who had been clinically diagnosed as having malaria actually had a positive blood-slide during laboratory testing.

Keyburn and colleagues<sup>6</sup> found in Tanzania that altitude (as a proxy measure for malaria endemicity) and age of patient influenced the accuracy of clinical diagnosis. In low altitudes where malaria was highly endemic 69% of children below 6 years of age, who were admitted on suspicion of malaria, had a blood-slide that tested positive for malaria parasites. In that same environment, only 19% of patients older than 5 years who were admitted for suspected malaria actually had positive blood-slides. Accuracy in clinical diagnosis decreased to only 22% for children below 6 years of age at higher altitudes where malaria was more rare, and did not differ from the accuracy for older patients – also 22%. In simple terms, unless you are a small child living in a highly endemic area, your admission to hospital for malaria is likely to be incorrect about four times out of five. Even if you are that small child in the highly endemic area, your admission would have been incorrect at least one-third of the time.

### Benefits of RDTs

Hopkins, Asimwe and Bell<sup>7</sup> posit several key benefits of accurate parasitological malaria diagnosis generally over clinical diagnosis.

- Patients who are given presumptive antimalarial treatment for non-malarial disease have poor outcomes.
- Improved targeting will preserve drug supplies.
- Improved targeting is likely to preserve drug efficacy through reduction in exposure of malaria parasites to low levels of artemisinin derivatives circulating in communities
- parasite-based diagnosis is essential to monitor trends in malaria prevalence
- Improving the accuracy of diagnosis is expected to reduce unnecessary expenses incurred by patients. They conclude that ‘Micro-scop-

is likely to remain essentially confined to hospitals and large clinic settings. Rapid diagnostic tests, which do not require the laboratory infrastructure or expertise of microscopy, are increasingly seen as a reliable alternative for case management in virtually all endemic settings.’

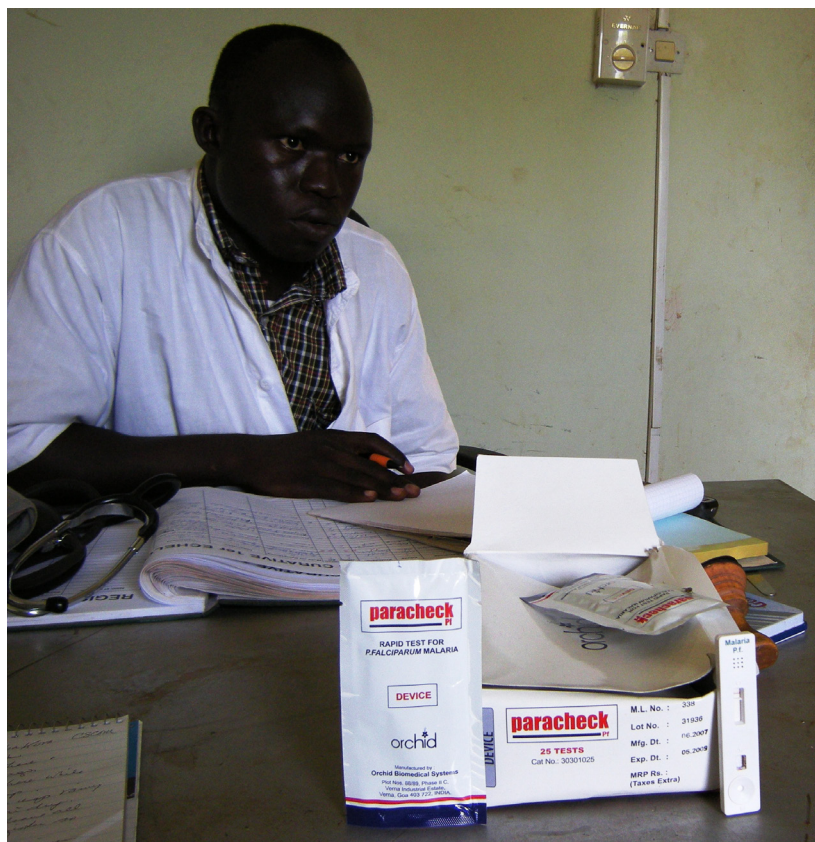
From the economic viewpoint, research in Zambia found that, ‘RDTs were the most cost-effective method at correctly diagnosing malaria in primary health facilities in Zambia when compared to clinical and microscopy strategies.’<sup>8</sup> The researchers concluded that scale up of RDTs would be cheaper than microscopy.

### Challenges in Using RDTs

Reasons for a reliance on inaccurate clinical diagnoses obviously rest on availability of appropriate testing supplies and equipment. Unfortunately availability of diagnostic capacity at a clinic does not mean that clinicians will use it.<sup>9</sup> Three other social factors have been identified by Chandler’s team:<sup>4</sup>

1. the influence of initial training within a context where the importance of malaria is strongly promoted;
2. the influence of peers, conforming to perceived expectations from colleagues;
3. pressure to conform to perceived patient preferences.

Sometimes national treatment guidelines create ambiguity. It is not uncommon to see a description of parasitological diagnostic procedures followed by a caveat such as, ‘even with a negative specimen, without other causes of fever do not rule out the diagnosis of malaria.’ This reinforces health workers’ own beliefs in the efficacy of their clinical diagnostic instincts.



RDTs on the desk of a doctor at a rural clinic in Mali

In Zambia, Chanda et al<sup>8</sup> worried that unless health worker prescribing habits changed, parasitological diagnosis would not achieve these potential benefits and savings. During discussions with a nurse in a Mozambican antenatal clinic we were happy to find RDTs on her table. She used them for any suspected case of malaria. We asked her what she would do if the test result was negative. She said she would send the client to the lab. What if the lab results were negative? She would still treat because one can never be sure if the client has malaria or not. Lack of trust in diagnostic test results negates all the benefits outlined above.

Of course, trust in a diagnostic tool must be earned. According to TDR,<sup>2</sup> a lot of public money is being spent on RDTs. We must ensure that there is a process for determining RDT quality so that this public money is not wasted. Recently WHO and partner agencies tested the tests. They examined and compared different lots of 41 products from 21 manufacturers against prepared blood panels of cultured *Plasmodium falciparum* parasites and patient-derived *P falciparum* and *P vivax* parasites, and a parasite-negative panel.<sup>10</sup> Factors such as temperature and parasite density were found to be important influences on accuracy.

Overall among the 41 products tested thirty-six had a detection rate of at least 90% in areas where people are likely to have high parasite densities. Only nine products had a detection rate of at least 90% if there was low parasite density. A second round of testing additional products is underway. The take away message from the report is that countries carefully need to consider their own epidemiological and climatic conditions before choosing an RDT. Countries that have internal variations in their malaria patterns may need more than one product.

### Setting up for RDT use

Malaria programme planners must consider is the cost of the total RDT implementation package. TDR<sup>2</sup> remind us that these costs include training health workers to use the tests and additional supplies such as gloves, sharps boxes, job aids, and community health education. Bell and Perkins<sup>3</sup> show that

actual procurement of the RDTs may be just half, or a little less than the total cost of implementing diagnosis by rapid test. Other costs in addition to those just mentioned include transport, supervision, lot quality testing, and monitoring accuracy in the field.

WHO<sup>11</sup> suggests the following conditions be in place for integrating and scaling-up the use of RDTs into malaria control and primary health services:

- quality control testing of a designated sample of the product;
- 'cool chain' for transport and storage;
- health worker training and monitoring;
- clear guidelines on action to follow – a diagnosis and treatment algorithm that includes RDTs.

Front-line health facilities are the ideal place to use RDTs, but will health workers use and trust them? Williams et al<sup>12</sup> implemented an RDT training programme at six Tanzanian dispensaries where the problem of overuse of antimalarial drugs based on clinical diagnosis had been seen. The proportion of 'over-prescriptions', drugs given to people without malaria parasites out of those suspected of malaria, decreased from 55% before training to 16% afterwards. Generally both clinicians and clients liked the RDTs and thought they improved the quality of care. A few community members were suspicious that these were HIV tests, and a few health staff complained about the extra work required, but these are factors that a continued health education



*A rural/district health centre in Ghana: the health worker in charge of distributing RDTs (although they were out of stock at the time).*

effort can address.

The experiences of Reyburn and colleagues in promoting RDT use in hospital clinics were not as encouraging. They found that the promoting the use of RDTs with basic training for clinical staff, did not in itself lead to any reduction in over-treatment for malaria. They concluded that interventions to improve clinicians' management of febrile illness are essential but will not be easy. One factor may have been the division of labour. This study took place in public hospitals in Tanzania, and the clinicians sent the patients to the laboratory for the tests. They were not directly involved in the testing as was the case with the frontline facility staff. Although they received information during training on the accuracy and usefulness of RDTs, the lack of hands-on experience may have made it less easy for them to break with their former dependence on their clinical acumen.

In contrast Rennie and co-workers<sup>14</sup> first observed how Filipino front-line health staff used RDTs and based training on common mistakes they observed. They were concerned that malaria RDTs will frequently be used in remote areas with little supervision or support, so such training is crucial. Instructions in the package were not found to be helpful to the health workers, so a job aid was designed to accompany the instructions. This was found to bring about a 17% improvement in performance of RDTs. Still there were mistakes, and a follow-up orientation added another 10% to the accuracy of the trainees. We can see clearly that appropriate training is a crucial element of the RDT implementation package.

### RDT use at the community level

The preceding sections have focused on diagnosis of malaria in clinical settings. In many African communities where 50–75% of people seek malaria treatment outside the formal health sector, and in particular obtain their drugs from patent medicine vendors, the challenge of diagnosis is equally troublesome.<sup>15</sup>

At the community level in Zambia, Harvey and colleagues<sup>16</sup> found that Manufacturer's although instructions like packet inserts provided with RDTs are

insufficient to ensure safe and accurate use by volunteer community health workers (CHWs). They learned this after testing three groups of CHWs, one using the package insert instructions, a second using the job aid they developed, and the third that had both the job aid and training. The well-designed job aid plus training ensured high performance.

### Conclusions

With the advent of more expensive artemisinin-based combination therapy (ACT) treatment for malaria as first-line medicines, there is an urgent need to ensure that malaria treatment is prescribed only when needed. Clinical diagnosis based on signs and symptoms results in wastage of ACTs, and laboratory diagnosis is therefore preferred. Most front-line health facilities in Africa lack laboratory services, but rapid diagnostic tests can be used successfully at this level as well as in the community and at hospital clinics during hours when labs are closed. To implement RDT use as part of comprehensive malaria and primary healthcare services, malaria programme planners must account for more than procurement and supply. Of particular concern is training of health staff and health education of the community to understand and accept RDT use as the best way to provide quality malaria care.

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