

*New Perspectives*  
**Malaria Diagnosis**

**REPORT OF A JOINT WHO/USAID INFORMAL CONSULTATION  
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# Executive Summary

# 1

In malaria patients, a prompt and accurate diagnosis is the key to effective disease management. The two diagnostic approaches currently used most often, however, do not allow a satisfactory diagnosis of malaria. Clinical diagnosis, the most widely used approach, is unreliable because the symptoms of malaria are very non-specific. Microscopic diagnosis, the established method for laboratory confirmation of malaria, presents technical and personnel requirements that often cannot be met, particularly in facilities at the periphery of the health care system. In addition, delays in the provision of the microscopy results to the clinician mean that decisions on treatment may be taken without the benefit of the results.

Thus, the recent introduction of rapid diagnostic tests (RDTs) for malaria is of considerable interest. Such tests use immunochromatographic methods to detect *Plasmodium*-specific antigens in a finger-prick blood sample. The tests can be performed in approximately 15 minutes by individuals with minimal training, using test kits (available from several manufacturers) that require no electricity and no special equipment. The RDTs have detection capabilities that are in general comparable to those generally achieved by microscopy in the health services. Compared to microscopy, the main disadvantages of currently available RDTs are: lack of sensitivity at low levels of parasitaemia; inability to quantify parasite density; inability to differentiate between *P. vivax*, *P. ovale* and *P. malariae*, as well as between the sexual and

asexual stages of the parasite; persistently positive tests (for some antigens) in spite of parasite clearance following chemotherapy; and relatively high cost per test.

Diagnostic tests (microscopy and RDTs), used correctly, can contribute to better and more cost-effective disease management and can reduce the unnecessary and irrational use of antimalarial drugs.

In areas with high rates of transmission (mostly in Africa south of the Sahara), where asymptomatic infections are frequent and health infrastructures are often inadequate, most malaria treatment is based on clinical diagnosis alone. In some situations, however, the clinical diagnosis would benefit from laboratory confirmation by microscopy or RDTs. Such situations include suspected cases of severe malaria; suspected treatment failures; disease management by private-sector health providers in urban areas; and multidrug resistance (which is not yet a problem in Africa south of the Sahara).

In areas with low to moderate rates of transmission (mostly in Asia and the Americas, and in parts of Africa), most infections are symptomatic and multidrug resistance occurs in some areas (especially South East Asia). These factors are strong incentives for laboratory confirmation of malaria as a component of disease management. While microscopy is generally available at the more central levels, it is often absent or unreliable in remote areas. In such isolated localities, RDTs performed by local health workers or community volunteers can be used to diagnose malaria, which can then be treated immediately, with the aim of reducing morbidity and mortality and the incidence of severe malaria. Where multidrug resistance occurs, the cost of the recommended antimalarial drugs is higher, thus justifying the use of RDTs when microscopy is not available.

Certain other circumstances offer a potential role for RDTs in support of microscopy. These include complex health emergencies where malaria is a risk, suspected malaria epidemics, and the diagnosis of malaria in travellers and in military forces and organized workforces.

However, the microscope is a key tool in the integrated management of disease in resource poor settings, and the optimal role and conditions

for the use of RDTs in relation to microscopy remain to be determined. Several issues need to be addressed through laboratory or field research, situation analysis, modelling and institutional strengthening. These issues include: further improvement of the technical characteristics of RDTs (e.g. sensitivity, specificity, ease of performance by users and robustness); a system of international quality control and quality assurance outside the commercial sector, including the development of a bank of reference reagents and a network of field test sites; and a multidisciplinary analysis of the cost of deploying RDTs in various situations, as well as their potential for reducing malaria morbidity and mortality and delaying the emergence of drug resistance.

# Introduction



Prompt and accurate diagnosis is the key to effective disease management, one of the main interventions of the Global Malaria Control Strategy (1). It is thus of concern that poor diagnosis continues to hinder effective malaria control. This is due to a combination of factors, including non-specific clinical presentation of the disease, high prevalence of asymptomatic infection in some areas, lack of resources and insufficient access to trained health care providers and health facilities, and widespread practice of self-treatment for clinically suspected malaria.

One major contributing factor, however, is that the laboratory diagnosis of malaria has up to now relied nearly exclusively on microscopy, a valuable technique when performed correctly but unreliable and wasteful when poorly executed. A better utilization of microscopy and the development of alternative diagnostic techniques could substantially improve malaria control (2). Such objectives prove particularly relevant to the Roll Back Malaria initiative, a global movement that emphasizes better application of existing tools and the development of new ones.

Of great interest in this context is the development during the past ten years of rapid diagnostic tests (RDTs) for malaria using immunochromatographic test strips, which might offer a valid alternative to or complement microscopy (3). Various RDTs have been tested in clinical

and field situations. Test kits have been marketed and have found limited use in some malaria control programmes, as well as in special situations such as complex emergencies, epidemics and the diagnosis of malaria in returning travellers. The overall results have been encouraging, and several manufacturers are currently developing improved kits and offering them on the global market. The strong market presence of such kits is illustrated by the fact that one manufacturer alone reports having introduced 3–6 million tests to date.

The time has thus come for serious consideration of how RDTs can most effectively be applied to the very diverse situations in which malaria occurs. To that effect, an informal consultation was convened in Geneva on 25–27 October 1999, bringing together the developers, manufacturers and potential users of RDTs, and representatives of other interested agencies, to discuss future actions to ensure their optimal deployment to control malaria.

## Objectives of the meeting

# 3

The objectives of the informal consultation were:

- to define the rational use of microscopy and of RDTs for malaria control;
- to identify factors that determine the choice of approaches to the diagnosis of malaria;
- to define the desired specifications for new diagnostic tests; and
- to outline outstanding research questions and plan a research agenda.

# Approaches to the diagnosis of malaria

# 4

Several approaches to the diagnosis of malaria (defined for the purpose of this document as disease caused by infection with malaria parasites) can be adopted. Each approach presents characteristics such as cost, ease of performance and accuracy, which will determine its applicability to different situations.

## 4.1. CLINICAL DIAGNOSIS

Clinical diagnosis is the most widely used approach. It has been the only feasible one in many situations, particularly in rural areas and at the periphery of the health care system where laboratory support to clinical diagnosis does not exist. Among the many clinical signs and symptoms associated with malaria, the most prominent is fever, which is often accompanied by chills, perspiration, anorexia, headaches, vomiting and malaise. Residents of endemic areas are often familiar with this combination of symptoms, and frequently self-diagnose malaria based on symptoms alone. In addition to these symptoms of uncomplicated malaria, other manifestations may develop that signal severe malaria, which is almost always due to *Plasmodium falciparum*. These include confusion or drowsiness with prostration together with severe manifestations such as cerebral malaria, severe anaemia and others.

Clinical diagnosis is inexpensive to perform, and requires no special equipment or supplies. However, the symptoms of malaria are very

non-specific and overlap with those of other febrile illnesses. A diagnosis of malaria based on clinical grounds alone is therefore unreliable, and when possible should be confirmed by laboratory tests. In spite of this lack of specificity, in some settings (see section 5.2) disease management based on clinical diagnosis alone is justifiable.

## 4.2. MICROSCOPIC DIAGNOSIS

Conventional light microscopy is the established method for the laboratory confirmation of malaria. The careful examination by an expert microscopist of a well prepared and well stained blood film remains currently the “gold standard” for detecting and identifying malaria parasites. In most settings, the procedure consists of: collecting a finger-prick blood sample; preparing a thick blood smear (in some settings a thin smear is also prepared); staining the smear (most frequently with Giemsa); and examining the smear through a microscope (preferably with a 100X oil-immersion objective) for the presence of malaria parasites (4).

Microscopy offers many advantages.

- It is sensitive. When used by skilled and careful technicians, microscopy can detect densities as low as 5–10 parasites per  $\mu\text{l}$  of blood (5). Under general field conditions, however, the detection capabilities of a typical microscopist might be more realistically placed at 100 parasites per  $\mu\text{l}$  of blood (6).
- It is informative. When parasites are found, they can be characterized in terms of their species (*P. falciparum*, *P. vivax*, *P. ovale*, and/or *P. malariae*) and of the circulating stage (e.g. trophozoites, schizonts, gametocytes). Occasionally, expert microscopists can detect morphological alterations induced by recent drug treatment. In addition, the parasite densities can be quantified (from ratio of parasites per number of leukocytes or erythrocytes). Such quantifications are needed to demonstrate hyperparasitaemia (which may be associated with severe malaria) or to assess parasitological response to chemotherapy.
- It is relatively inexpensive. Cost estimates for endemic countries range from about US\$ 0.12 to US\$ 0.40 per slide examined

(Palmer K, personal communication, 1999). Such figures, however, do not reflect the true cost to the health system or to the patient, which may be substantially higher. In addition, the cost per test will increase if utilization is low, or if microscopy in the health facility is used only for malaria diagnosis.

- It is a general diagnostic technique that can be shared with other disease control programmes, such as those against tuberculosis or sexually transmitted diseases.
- It can provide a permanent record (the smears) of the diagnostic findings and be subject to quality control.

Microscopy suffers from three main disadvantages.

- It is labour-intensive and time-consuming, normally requiring at least 60 minutes from specimen collection to result.
- It is exacting and depends absolutely on good techniques, reagents, microscopes and, most importantly, well trained and well supervised technicians. Unfortunately these conditions are often not met, particularly at the more peripheral levels of the health care system. In these circumstances, microscopic diagnosis risks becoming an unreliable tool that uses up scarce resources for doubtful results.
- There are often long delays in providing the microscopy results to the clinician, so that decisions on treatment are often taken without the benefit of the results.

#### 4.3. RAPID DIAGNOSTIC TESTS (RDTs)

These tests are based on the detection of antigens derived from malaria parasites in lysed blood, using immunochromatographic methods. Most frequently they employ a dipstick or test strip bearing monoclonal antibodies directed against the target parasite antigens. The tests can be performed in about 15 minutes. Several commercial test kits are currently available. The field is evolving rapidly, and technical improvements are continually being announced that will undoubtedly enhance the capabilities of RDTs for malaria diagnosis.

##### 4.3.1. Antigens targeted by currently available RDTs

- Histidine-rich protein II (HRP-II) (7) is a water-soluble protein produced by trophozoites and young (but not mature) gametocytes of *P. falciparum*. Commercial kits currently available detect HRP-II from *P. falciparum* only.
- Parasite lactate dehydrogenase (pLDH) (8) is produced by asexual and sexual stages (gametocytes) of malaria parasites. Test kits currently available detect pLDH from all four *Plasmodium* species that infect humans. They can distinguish *P. falciparum* from the non-*falciparum* species, but cannot distinguish between *P. vivax*, *P. ovale* and *P. malariae*.
- Other antigen(s) that are present in all four species are also targeted in kits that combine detection of the HRP-II antigen of *P. falciparum* together with that of an, as yet unspecified, “pan-malarial” antigen of the other species.

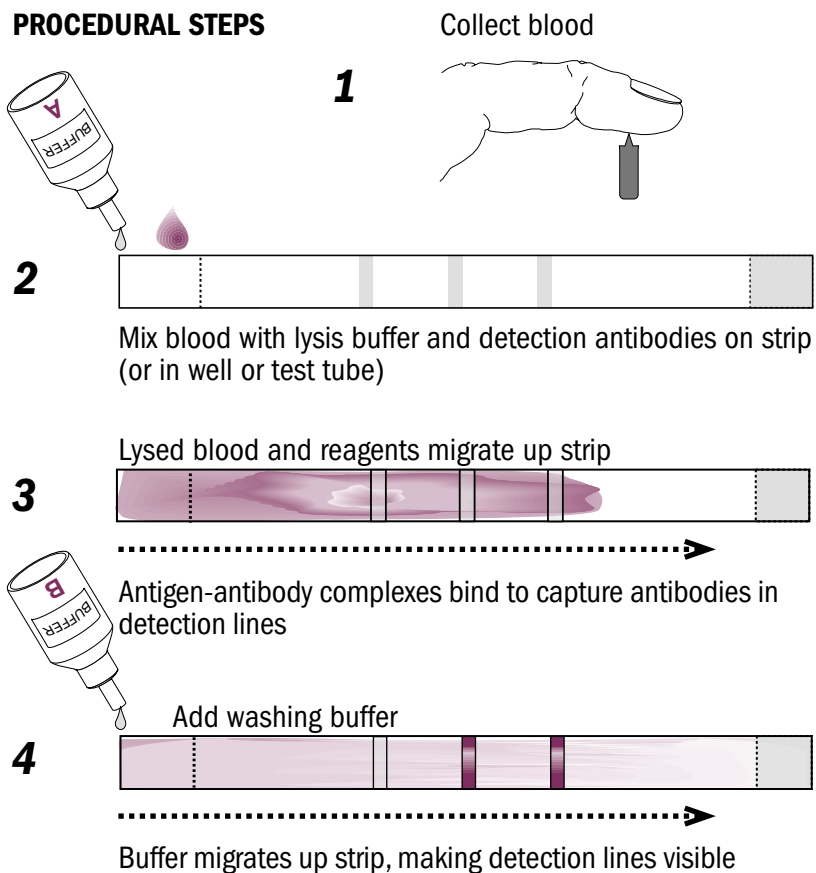
Some kits that detect all four *Plasmodium* species mention in their brand name or their marketing material only two species (e.g. “PF/PV”). This can lead to confusion about their diagnostic capabilities.

##### 4.3.2. General test procedure (varies between kits) (Fig. 1)

- A finger-prick blood specimen is collected (2–50 µl, depending on the kit), using a variety of microcapillary tubes. Some manufacturers state that anticoagulated blood or plasma can also be used.
- The blood specimen is mixed (in a separate test tube or a well, or on a sample pad) with a buffer solution that contains a haemolysing compound as well as a specific antibody that is labelled with a visually detectable marker (such as colloidal gold). If the antigen under investigation is present, an antigen/antibody complex is formed. In some kits, the labelled antibody is pre-deposited during manufacture on to the sample pad or in the well, and only a lysing/washing buffer is added to the blood.
- The labelled antigen-antibody complex migrates up the test strip (most often nitrocellulose/glass fibre) by capillary action towards test-specific reagents that have been pre-deposited during manufac-

FIGURE 1. GENERAL TEST PROCEDURE

PROCEDURAL STEPS



EXAMPLE RESULTS (SPECIFIC TEST FORMATS VARY)

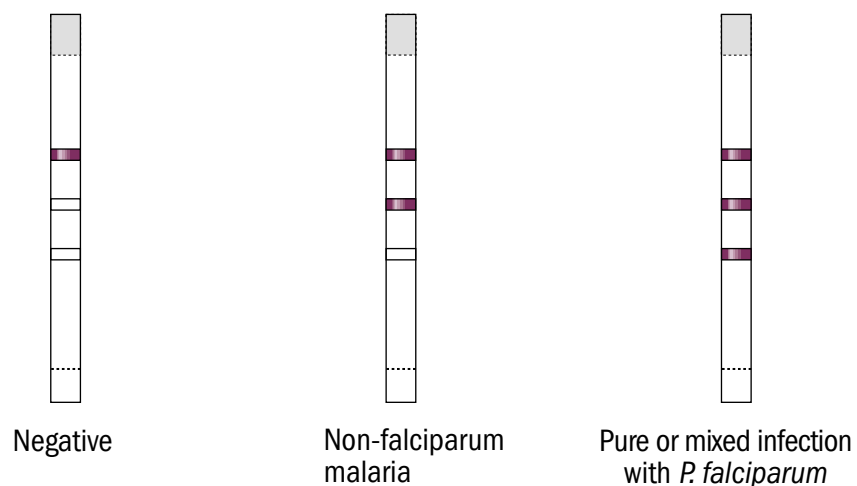
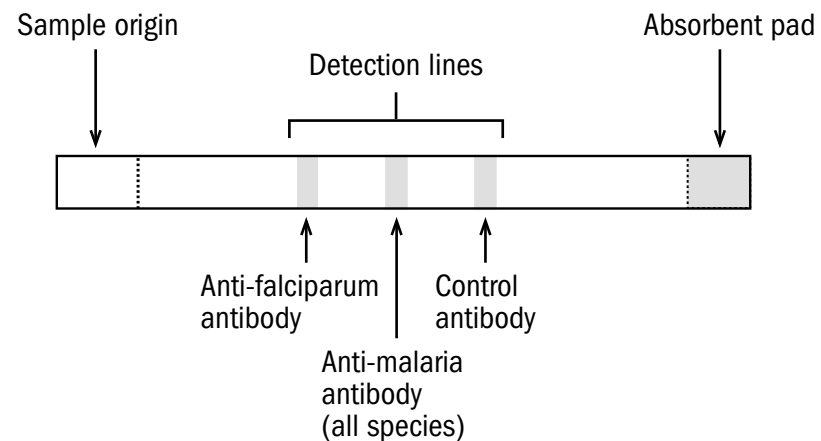
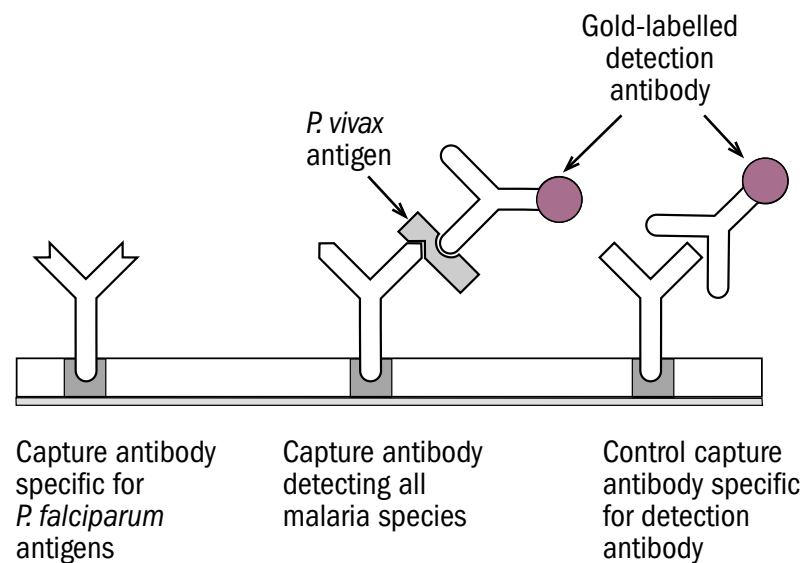


FIGURE 1. GENERAL TEST PROCEDURE

COMPONENTS OF ANTIGEN DETECTION TEST BEFORE USE



SCHEMATIC REPRESENTATION OF IMMUNOLOGIC REACTION ON A POSITIVE STRIP (EXAMPLE *P. VIVAX* INFECTION)





ture. These include (a) a line of capture antibody specific for the antigen under investigation (several lines are used if several antigens are being investigated) and (b) a procedural control line, with an antibody that will capture the labelled antibody.

- A washing buffer is then added to remove the haemoglobin and permit visualisation of any coloured line on the strip. The buffer is added by depositing it directly on the strip, by placing it in a well from which it migrates up the strip, or by washing the entire strip in a test tube.
- If the blood contains the antigen under investigation, the labelled antigen-antibody complex will be immobilized at the pre-deposited line of capture antibody and will be visually detectable. Whether the blood contains antigen or not, the control line will become visible as labelled antibody is captured by the predeposited line of antibody directed against it. (*Note*: this design results in the control line appearing even if no blood is mixed with the haemolysing buffer.) The complete test run time varies from 5 to 15 minutes.

#### 4.3.3. Test performance of RDTs

- Test performance of RDTs has been assessed extensively in diverse clinical situations, in both endemic and non-endemic countries. The utility of these assessments has been compromised somewhat by variations in methodologies and commonly small sample size. The continuation of such assessments will be made necessary by the introduction of technically improved or newly developed kits.
- RDTs variably detect the four *Plasmodium* species that infect humans, depending on the antigens on which they are based (see section 4.3.1). Some RDTs detect *P. falciparum* only, while others detect *P. falciparum* and the other malaria parasites on two separate bands. To date, no commercial RDT has been reported to differentiate reliably between *P. vivax*, *P. ovale* and *P. malariae*, although research to develop such a test is continuing.
- The sensitivity of the RDTs has been most studied for *P. falciparum*, since the *P. falciparum* kits (targeting mostly *P. falciparum* HRP-II) have been available for a longer time. Compared with expert

microscopy (sometimes complemented by the polymerase chain reaction), RDTs generally achieve a sensitivity of >90% in the detection of *P. falciparum* at densities above 100 parasites per  $\mu\text{l}$  blood (9.24 and reports presented at the meeting). Below the level of 100 parasites per  $\mu\text{l}$  blood, sensitivity decreases markedly.

- RDT sensitivity for non-*falciparum* species has been less extensively studied. Investigations conducted to date indicate that the pLDH kits may achieve a sensitivity for *P. vivax* comparable to that for *P. falciparum* (25–28). This is not yet the case for kits that target different “pan-malarial” antigens (29).
- The specificity of RDTs, measured in the same investigations, is uniformly high (mostly >90%). However, false positive results have been reported in blood from patients with rheumatoid factor, especially in an earlier version of one HRP-II kit (30); the problem, possibly associated with cross reactivities with the labelled monoclonal antibody, has reportedly been corrected in more recent kits versions. In addition, HRP-II tests can remain positive for 7–14 days following chemotherapy in a substantial proportion of individuals, even though these patients no longer have symptoms or parasitaemia (as assessed by blood smears) (9). Such degrees of persistent positivity are apparently not encountered in tests targeting other antigens (28).
- The predictive values, both positive and negative, vary with parasite prevalence and are often found to be acceptable.
- The RDTs are uniformly reported to be easier to perform than all other malarial diagnostic techniques, with some RDT formats being found more user-friendly than others. Health workers with minimal skills can be trained in RDT techniques in periods varying from three hours to one day (31, 32).

#### 4.3.4. Currently available RDTs: advantages over microscopy (see Table 1)

- RDTs are simpler to perform and to interpret. They do not require electricity, special equipment or training in microscopy. Peripheral health workers (and other health providers as well as community volunteers) can be taught the procedure in a matter of hours, with good retention of skills over a one-year period.

- RDTs are relatively robust and test performance and interpretation vary relatively little among individual users. Moreover, most kits can be shipped and stored under ambient conditions.
- Since RDTs detect circulating antigens, they may detect *P. falciparum* infection even when the parasites are sequestered in the deep vascular compartment and thus undetectable by microscopic examination of a peripheral blood smear. In women with placental malaria (as demonstrated by placental smears), RDTs have detected circulating HRP-II even though the blood smears were negative due to sequestration of *P. falciparum* in the placenta (33).

#### 4.3.5. Currently available RDTs: disadvantages

- Commercially available RDTs targeting HRP-II can detect only *P. falciparum*. Such kits will detect only a portion of cases in areas where other *Plasmodium* species are co-endemic. They are not suitable for diagnosing cases of imported malaria from areas where *P. falciparum* is not necessarily the most prevalent species.
- RDTs that target HRP-II of *P. falciparum* can give positive results for up to two weeks following chemotherapy and parasite clearance as confirmed by microscopy. The reason for this antigen persistence needs to be clarified. Pending such clarification, RDTs targeting HRP-II might yield confusing results in relation to the assessment of treatment failure or drug resistance.
- The current RDTs are more expensive than microscopy, with costs per test varying from US\$ 0.60 to US\$ 2.50 and possibly more, depending on the marketing area.
- RDTs are not quantitative. They thus fail to provide information of possible prognostic importance and are not suitable for detailed investigations on the therapeutic efficacy of antimalarial drugs.
- Kits that detect both *P. falciparum* and non-*falciparum* species cannot differentiate between *P. vivax*, *P. ovale* and *P. malariae*, nor can they distinguish pure *P. falciparum* infections from mixed infections that include *P. falciparum* (27).

**TABLE 1. COMPARISON OF THE REQUIREMENTS, PERFORMANCE, DIRECT COSTS AND TECHNICAL SPECIFICATIONS OF MICROSCOPY AND RDTs**

	MICROSCOPY	RDTs
<b>REQUIREMENTS</b>		
Equipment	Microscope	None
Electricity	Preferred, not necessary	None
Supplies	Blood collection, staining reagents and supplies, water	Blood collection (supplied in some kits)
Training	Trained microscopist	Only minimal training required
<b>PERFORMANCE</b>		
Test duration	Usual minimum 60 minutes	15–20 minutes
Labour-intensiveness	High	Low
Subjectivity	High	Low
Robustness	Average	High
<b>DIRECT COSTS</b>		
Cost per test	US\$ 0.12–0.40	US\$ 0.60–2.50
<b>TECHNICAL SPECIFICATIONS</b>		
Detection threshold	5–10 parasites/μl blood	40–100 parasites/μl blood
Detection of all four species	Yes	Some RDTs
Quantification	Possible	Not possible
Differentiation between <i>P. vivax</i> , <i>P. ovale</i> and <i>P. malariae</i>	Possible	Not possible
Differentiation between sexual and asexual stages	Possible	Not possible
Detection of ( <i>P. falciparum</i> ) sequestered parasites	No	Yes
Antigen persistence	Not applicable	Some RDTs

- RDTs that detect antigens produced by gametocytes (such as pLDH) can give positive results in infections where only gametocytes are present. Gametocytes are not pathogenic, and gametocytes of *P. falciparum* can persist following chemotherapy without implying drug resistance. Such positive RDT results can thus lead to erroneous interpretations (false positives) and unnecessary treatment of people not suffering from malaria.
- Earlier versions of the test kits targeting HRP-II of *P. falciparum* have given false positive results in patients with rheumatoid factor; this problem has reportedly been corrected.

#### 4.4. OTHER TECHNIQUES

Other diagnostic methods are available, but they are not as suitable for wide field application as microscopy or RDTs and are unsuitable for use in routine disease management. They include microscopy using fluorochromes, polymerase chain reaction (PCR) based tests and antibody detection by serology.

- Microscopy using fluorochromes such as acridine orange, either on blood smears (34) or on centrifuged blood specimens (QBC<sup>®</sup> technique) (35) is expensive and requires special equipment and supplies (centrifuge and centrifuge tubes, special light sources and filters).
- PCR (36) is more sensitive and specific than all other techniques. It is, however, a lengthy procedure that requires specialized and costly equipment and reagents, as well as laboratory conditions that are often not available in the field.
- Antibody detection by serology (37) only measures prior exposure and not specifically current infection.

## Diagnostic practices

# 5

#### 5.1. OVERVIEW

Several factors determine the choice of diagnostic practices to be used in a given geographical area. They include (a) level of endemicity, (b) prevalence and type of drug resistance, (c) geographical accessibility, (d) social and economic characteristics, (e) underlying health infrastructure and (f) available diagnostic tools. Until recently, the options for diagnosing malaria were essentially limited to clinical diagnosis and microscopy, but this situation has changed decisively with the advent of RDTs. Section 5 discusses diagnostic practices in selected epidemiological situations, focusing on the potential role that RDTs may play in support of clinical diagnosis and microscopy.

#### 5.2. AREAS OF HIGH MALARIA TRANSMISSION

High malaria transmission occur mostly in Africa south of the Sahara, where *P. falciparum* predominates and causes an estimated 90% of the deaths attributable to malaria worldwide. High transmission also occurs in other areas of the world (e.g. Papua New Guinea), however, and not all endemic areas in Africa south of the Sahara are characterized by high rates of transmission (see section 5.3). In 1999, it was estimated that there were some 261 million cases of malaria in areas with high transmission (87% of the global total of 300 million) and 870 000 deaths (87% of the global total of >1 million).

In areas with high transmission, malaria occurs frequently and predominantly in young children, communities are familiar with the disease, and access to health care facilities is often difficult. Thus, the great majority of cases are self-treated based on clinical signs and symptoms alone (38). Such practices occur outside the established health care system and patients are often treated – if indeed they are treated – with non-recommended and inadequate regimens.

Most health care providers in these areas also rely on clinical diagnosis, using as their main criterion the presence of fever or a history of fever. While such an approach might first appear undesirable, it is justified because in these situations the demonstration of parasites by microscopy (or by other means such as RDTs) would be of limited diagnostic help. The majority of the population – including asymptomatic individuals – have parasitaemia most of the time. Thus the detection of malaria parasites does not necessarily mean that they are responsible for the patient's illness, since they may reflect only a coincidental infection (39). In addition to being only marginally useful, laboratory diagnosis is often not possible owing to severe limitations on resources, particularly at the peripheral level of the health care system. Treatment based on clinical diagnosis alone is therefore a justifiable approach to the management of most cases of malaria in areas with high rates of transmission.

Algorithms have been developed to attempt to improve the clinical diagnosis of malaria, and especially to distinguish it from other febrile illnesses. Such algorithms have met with only limited success, owing mainly to the high degree of overlap between the various febrile illnesses. Clinical diagnosis, as currently practised, uses a broad definition of malaria and will result in high sensitivity at the cost of low specificity. The latter occurs especially when the prevalence of malaria decreases, such as during seasonal reductions in transmission. However, high sensitivity is given precedence because malaria is a potentially fatal though treatable illness (40). This position is reflected in the algorithms developed for the integrated management of childhood illness: in areas of high malaria risk any child with fever or a recent history of fever will be treated with anti-malarial drugs even if other causes of fever are present (41).

Treatment based on clinical diagnosis alone does result in unnecessary and irrational drug use, though this might be acceptable in the case of drugs such as chloroquine or sulfadoxine/pyrimethamine, which are cheap and safe with few adverse reactions. It has been argued that confirming the clinical diagnosis with microscopy or RDTs might, by reducing drug use, decrease the potential selection of drug-resistant parasites. This remains to be proven, however, because no data exist to date to quantitatively correlate patterns of drug use with emergence of resistance. In addition, most drug pressure occurs through self-medication in the community, a practice that is difficult to regulate effectively. Thus, whether confirmatory diagnostic tests can decrease the emergence of drug resistance is an issue that needs to be investigated.

In most areas with high rates of transmission, treatment based on clinical diagnosis alone is incorporated in malaria treatment guidelines, drug resistance is still manageable, and chloroquine and sulfadoxine–pyrimethamine remain the drugs of choice. In such situations, there is no immediate need for large-scale use of confirmatory diagnosis. In some circumstances, however, the clinical diagnosis of malaria should be confirmed by microscopy or alternative tests. These circumstances include those set out below.

- In cases of suspected severe malaria, laboratory confirmation can guide initial therapy. In facilities at the central and district levels, microscopy should be the confirmatory diagnostic test of choice. In peripheral locations where microscopy is not available, RDTs might prove particularly useful since they can be performed by health workers with limited training and skills. Compared to blood smears, RDTs provide more timely results for disease management. Theoretically, by measuring circulating antigen, RDTs may also reflect parasite load more accurately. Unlike microscopy, however, currently available RDTs do not yield quantitative results and thus fail to provide a valuable element for prognosis and patient follow-up.
- Where persistence of parasites must be proved to confirm treatment failure (42), microscopy might be preferable because parasite quantification is used to define one type of early treatment failure. If microscopy is not available and RDTs are used, those that detect persistent antigenaemia in spite of parasite clearance should be avoided.

- Private-sector health providers, especially those working in areas of lower transmission, such as cities, might justifiably use RDTs since the lower prevalence of malaria in these areas reduces the predictive value of clinical diagnosis and increases the correlation between parasitemia and disease. RDTs may be more acceptable than microscopy to these practitioners as well as to their clients, who may be willing to pay for the convenience of “on-the-spot” diagnosis and treatment.
- Multidrug resistance can reach a level at which drug treatment based on clinical diagnosis alone ceases to be a rational policy. Syndromic management can be justified only as long as the anti-malarial drug used is safe, cheap and effective. The two main drugs used for first- or second-line treatment in Africa south of the Sahara, chloroquine and sulfadoxine–pyrimethamine, fit these criteria. Emergence of resistance to both chloroquine and sulfadoxine–pyrimethamine would dictate the use of alternative drugs (such as quinine, mefloquine and artemisinin and its derivatives) that are substantially more expensive and less safe. Under such circumstances, increased diagnostic specificity is desirable and could be achieved through laboratory testing. There are arguments for increasing the availability of microscopy where it is cost-effective (i.e. when used for the diagnosis of other diseases as well as malaria) but there are locations where microscopy is unreliable and difficult to sustain. In such circumstances, RDTs might justifiably be used if the overall cost (including the costs to the patients and to the health care system) of their use proves lower than that of using a more expensive and less safe drug, and if an impact of test results on drug use can be demonstrated.

### 5.3. AREAS OF LOW TO MODERATE MALARIA TRANSMISSION

These areas are found mostly in Asia and the Americas, but also in substantial parts of Africa such as the highlands, desert fringes and cities, and in countries where vector control activities are well developed. In 1999, it was estimated that there were some 39 million cases of malaria in such areas (13% of the global total of 300 million) and 130 000 deaths (13% of the global total of >1 million). Areas with low to moderate transmission rates account for most of the malarial diag-

nostic smears collected worldwide (for example, over 86 million blood slides were examined in India alone in 1997).

Compared to areas of high transmission, in areas of low transmission malaria occurs less frequently, and in all age groups, and most infections are symptomatic. Multidrug resistance has developed in some of these areas, particularly in the countries of South East Asia. These factors are strong incentives for the laboratory confirmation of malaria as a component of disease management. While expert microscopic diagnosis is generally available at the more central levels of the health care system, it is often unreliable or absent in remote areas where health facility coverage is low and the population is at high risk of contracting malaria.

Situations that stand to benefit from the use of RDTs therefore include the following:

- In remote communities or highly mobile populations, where microscopic diagnosis is not available and where patients do not have adequate access to health care facilities, treatment is frequently based on clinical diagnosis alone. Here, the use of RDTs by local health workers or community volunteers has proved valuable, as illustrated by the following examples:
  - Since 1997 in northwest Thailand, peripheral health workers with three hours of training have reliably performed RDTs to confirm falciparum malaria. Test-positive individuals are treated immediately with mefloquine and a single gametocytocidal dose of primaquine. This is well accepted by the local residents, who have offered to help finance the diagnostic system (32). The approach has also been expanded to areas near the Myanmar–Thailand border, with the Border Patrol Police staff performing RDTs in remote villages.
  - In Cambodia, a WHO donation in 1996 initiated a programme whereby health workers at local health centres use RDTs. In 1997–1998, 43 000 dipsticks were distributed to the health centres (119 health centres received RDTs in 1998). A review of records and stocks indicates that, during that period, 11 000 people were treated at the health centres with mefloquine for falciparum malaria. An estimated 60 000 dipsticks were to be distributed in 1999 in

areas where artesunate–mefloquine is the recommended first-line treatment for uncomplicated falciparum malaria.

- In Madhya Pradesh State in India, remote forest villages are inaccessible during the rainy season, the main transmission period for *P. falciparum*. Following minimal training, field workers have detected *P. falciparum* successfully using RDTs in this setting (17, 43). Patients found to be positive for *P. falciparum* were treated with sulfadoxine–pyrimethamine or sulfalene–pyrimethamine.
- In gold mining communities in the state of Mato Grosso in Brazil, a programme has been successfully introduced whereby *cantina* (snack bar) staff use RDTs to diagnose falciparum malaria, which is then treated with mefloquine. The *cantina* staff learned to use and interpret the RDTs in two hours.
- Where multidrug resistance dictates the use of drugs or drug combinations that are more expensive than the diagnostic test, RDTs may prove valuable. While the direct cost of RDTs is higher than that of microscopy, the overall costs (including organization, supervision, quality control and skilled personnel) to support these diagnostic approaches are likely to be lower for RDTs than for infrequently used microscopy. In addition, in some remote areas, microscopy is simply not available. An alternative approach in such situations, which might prove cost-effective, would consist of expanding the use of microscopy for the diagnosis of other diseases, such as other parasitic diseases and tuberculosis.
- The prevention and management of severe malaria constitutes another potential application of RDTs. Owing to their low level of immunity, malaria patients in areas with low to moderate rates of transmission are at high risk of developing severe disease. In such patients, early diagnosis and treatment are critical. A recent death audit in the southern provinces of Viet Nam showed that more than 90% of the mortality due to malaria occurred in those whose admissions were delayed until the fourth to sixth day following the onset of the disease (Tran Tinh Hien, personal communication, 1999). In Myanmar, among people who experienced an attack of malaria, only 45–55% consulted qualified health personnel (Myat Phone Kyaw, personal communication, 1999). At the more peripheral levels of the health services that lack microscopy, RDTs could be used

for early diagnosis and treatment and, as a result, could reduce the incidence of severe disease. In addition, RDTs can assist in differentiating falciparum malaria from other diseases with similar clinical manifestations, such as viral encephalitis, dengue and typhoid fever. Finally, RDTs could be used in the management of severe malaria when the microscopy services are not operating, such as at night or at weekends.

#### 5.4. SPECIAL SITUATIONS

People with little or no previous exposure to malaria, who therefore often have no immunity, may become rapidly and severely ill upon infection and need prompt diagnosis and therapy. Moreover, travellers and other newly infected persons may find themselves in situations in which reliable health care is not available. In such circumstances RDTs for malaria may have a useful role, as demonstrated in the examples below.

- **Complex emergencies**, such as those caused by conflicts or environmental catastrophes, create conditions that may facilitate the introduction and spread of malaria. These include: the displacement of non-immune populations into malaria-endemic areas; environmental changes that allow breeding of malaria vectors; concurrent health problems such as malnutrition; and the unavailability, at least initially, of food, sanitation and basic health care to address general health problems, including the diagnosis and treatment of malaria. In many complex emergencies, malaria may cause up to 40–50% of all illness; if a risk exists, an assessment should be made of malaria's share as a cause of mortality and morbidity. The assessment should also include the parasite species involved and the efficacy of anti-malarial treatments. This information can be applied to facilitate targeted prevention and treatment strategies. Microscopic diagnosis being rarely possible in acute emergencies, RDTs can at least initially play a crucial role, for example, in monitoring the accuracy of clinical diagnosis, rapidly assessing malaria prevalence or the response to antimalarial drugs.
- **Malaria epidemics** may occur in complex emergencies, but can also result from environmental changes and population migration (44). Such epidemics constitute an increasing problem, and their

early detection and prevention constitutes one of the four basic technical elements of the Global Malaria Control Strategy (1). In epidemic situations where pre-existing health services can provide microscopy, this diagnostic approach should be adopted to support clinical diagnosis. In areas where such services are unavailable, the use of RDTs to confirm the epidemic in its early stages can be especially useful. This was exemplified during a recent malaria epidemic in Kisii and Gucha districts of Kenya, where random sampling with RDTs was used to assess *P. falciparum* infection rates prior to targeted interventions to control the epidemic (Allan R, personal communication, 1999).

- **Malaria in returning travellers** is a diagnostic challenge in which RDTs, if used correctly, might prove useful. Over 12 000 annual cases have recently been reported in Europe, where case fatality rates among patients with *P. falciparum* malaria can reach 3.6% (45). In non-endemic countries, the prompt and accurate detection of malaria in febrile returning travellers is critical. These individuals are often non-immune and a delay in diagnosis can prove fatal. Unfortunately, health personnel in non-endemic countries frequently lack experience in the microscopic diagnosis of malaria, or there can be appreciable delays in obtaining results. Such problems could be alleviated by the use of RDTs. Studies on returning febrile travellers, comparing the results obtained with RDTs to those obtained with expert microscopy or PCR, found that both sensitivity and specificity were in general above 90%. These initial findings are encouraging and indicate that RDTs could be used in a supporting role to identify rapidly *P. falciparum* infections when prompt microscopic diagnosis is problematic in the home country. Nevertheless, all patients with initially negative RDT results should be monitored, and RDTs should not be considered as a replacement for expert microscopy. Of greatest concern is the fact that, in non-immune individuals, symptomatic malaria can occur at parasite densities that are below the detection threshold of currently available RDTs.
- **Stand-by emergency self-treatment in travellers** constitutes another application of RDTs that has been proposed by certain groups. In this approach, the traveller is expected to self-diagnose and treat a possible malaria attack when medical attention is not

available within 24 hours of the onset of symptoms. RDT kits are marketed in several European countries for self-use by travellers, and some also contain antimalarial drugs for self-treatment. Under such conditions, the utilization of such devices has been shown to be technically problematic. Healthy volunteers at a travel clinic in Switzerland were able to learn how to perform the test, especially if the standard written instructions of the manufacturers were supplemented with verbal information; but their interpretation of prepared tests showing a range of possible test results was unsatisfactory, with an unacceptably high rate of false-negative interpretations (46, 47). In a recent study in febrile European tourists in Kenya, only 68% were able to perform the RDTs correctly, and 10 out of 11 with microscopically confirmed malaria failed to diagnose themselves accurately (48). Thus, major technical modifications are required before such RDT kits can be recommended for use by travellers.

- **Military forces (and organized workforces)** are sporadically exposed to malaria, but often do not have laboratory staff with adequate experience in malarial microscopy. RDTs could play a valuable supporting role to microscopy in garrisons, and could be the primary diagnostic tool at the front line, for use by medical auxiliaries. For such purposes, it would be important that the test kits be robust and that the packaging contain all the necessary supplies for blood collection and testing.

# Issues in the application of RDTs



## 6.1. TECHNICAL CHARACTERISTICS

RDTs should provide results at least as accurate as those derived from microscopy performed by an average technician under routine field conditions. For that purpose, RDTs must strive towards achieving the following specific technical characteristics.

### 6.1.1. Sensitivity

Sensitivity is the most critical issue, since false-negative results can result in the non-treatment of a potentially fatal disease. RDTs should be able to detect all four species of malaria parasite that infect humans, and at least to differentiate *P. falciparum* from the other species. Overall sensitivity (using expert microscopy as the “gold standard”) should be above 95%. Parasite densities above 100 asexual parasites per  $\mu\text{l}$  blood should be detected reliably, with a sensitivity close to 100%. The sensitivities obtained by the currently available kits for detecting *P. falciparum* are generally felt to be adequate. Those for detecting the other species (most experience to date being with *P. vivax*), however, have not all reached that level of sensitivity and need to be improved. In some situations, such as malaria in travellers, the current sensitivities are inadequate to exclude infection reliably; while RDTs may play a useful supporting role, a negative RDT result should always be confirmed by microscopy. Another sensitivity issue derives from reports of isolates of *P. falciparum* that do not express HRP-II. In view of their obvious impli-

cations for the diagnostic values of the tests, investigations should be conducted to ascertain the existence of such isolates, and of isolates that do not express other antigens targeted by the RDTs.

### 6.1.2. Detection of gametocytes

Gametocytes are not associated with clinical disease, and those of *P. falciparum* are not affected by most schizontocidal drugs. For the purpose of disease management, the diagnostic test does not need to detect pure gametocytaemias. A limited number of tests may be desired for epidemiologic studies to determine the prevalence of gametocyte parasitaemia (gametocyte index).

### 6.1.3. Specificity

Specificity should be at least 90% for all malaria species.

### 6.1.4. Persistence of antigenaemia

Persistence of antigenaemia despite parasite clearance following treatment has been observed for some target antigens, such as HRP-II. Persistence of HRP-II has not been consistently observed and its meaning remains unclear. It has been postulated that the phenomenon might occur variably, depending on the drug used to clear parasitaemia and possibly even the geographical location (49-51). As the persistent presence of antigen in successfully treated patients does not correlate with microscopy or with symptoms, these RDT results are considered false positives. Since treatment should not be based on laboratory results alone, the occurrence of this type of false positive should not lead to large numbers of unnecessary treatments.

However, the persistence of HRP-II decreases the utility, in terms of monitoring response to treatment, of tests targeting this antigen, and may cause some confusion in the evaluation of treated patients. Tests targeting other antigens will be useful for the monitoring of therapy only if they are able to differentiate between responding and non-responding patients with close to 95% accuracy. This goal may be difficult to achieve with the qualitative format of the current RDTs.

### 6.1.5. Additional diagnostic capability

Additional diagnostic properties that would prove useful, especially if they were available in RDT format, include:



- the provision of quantitative or semi-quantitative information on parasite densities in circulating blood (or, even better, total loads that include sequestered parasites); this would be valuable for prognostic assessments and drug resistance studies;
- tests that discriminate between the presence of viable parasites and that of parasite products (such as antigens and nucleic acids) that are not necessarily associated with living organisms;
- tests targeting putative markers that predict the development of complications, treatment outcomes and/or resistance to the commonly used antimalarial drugs; and
- a practical combination on the same test strip of diagnostic signals for multiple diseases that overlap epidemiologically and symptomatically (e.g. malaria and dengue).

### 6.2. "GOLD STANDARD"

The definition of a "gold standard" for malaria diagnosis is an issue that needs to be addressed. To date, RDTs have practically always been assessed against expert microscopy, with occasional backup by PCR. Microscopy, however, even when performed by an expert, has its limitations. It would be useful to determine whether this imperfect yardstick might not be replaced by some other, more accurate standard that could be derived by one measurement or a combination of measurements using other methodologies.

### 6.3. PACKAGING AND EASE OF USE

To ensure reliable performance by health care providers within the health services and the community, the test kits should possess certain characteristics. These include:

- clear, illustrated instructions adapted to local conditions;
- components that are easy to manipulate (e.g. larger pipettes or elimination of pipettes altogether; larger area on the strip for blood collection);

- a minimal number of steps (especially those that are time-critical) and a minimal number of reagents; and
- results that are easy to interpret (e.g. increased readability).

In some situations only a limited number of test strips are needed. Such cases might benefit from the availability of complete kits containing all the supplies necessary for blood collection as well as test performance, and of kits containing a smaller number of tests to reduce costs and avoid wastage.

### 6.4. ROBUSTNESS OF TEST KITS

RDTs will arguably be most useful in communities and health facilities in remote areas with extreme environmental conditions and no electricity. For this reason, the kits should not require refrigeration and should be able to tolerate temperatures of at least 40°C and preferably peaks of up to 50°C, which may occur during storage under tropical conditions. The addition of a colour strip on the box to monitor heat exposure might increase test reliability. The shelf-life should be at least one year and preferably two following arrival in the country. Since the greatest delays may occur between shipment and arrival at the location where the RDTs will be used, reducing this delay will result in a longer useful shelf-life at the diagnostic facility.

### 6.5. QUALITY CONTROL AND QUALITY ASSURANCE

To guarantee inter-batch reproducibility and optimal performance of marketed RDT kits, production standards (good manufacturing practices) should be provided and followed. Standard reagents, such as positive controls, should be made available for quality control. The provision of standards for quality control and the management of a reference reagent bank are functions best performed by an agency such as WHO. An additional role for such a coordinating body would be to co-ordinate the production and distribution of antigen or antibody reagents. This could facilitate test development and decrease costs since 40-50% of the cost of manufacturing RDT kits may be attributable to the monoclonal antibodies. Such an arrangement, however, would need to be carried out under agreements that do not inhibit the development of improved assays.

### 6.6. NEW TEST EVALUATION

The evaluation of new candidate assays should follow published guidelines for diagnostic trials to avoid common errors and to satisfy defined criteria, such as choice of control groups and uniform case definitions (52). For such evaluations, the development of a network of field test sites and a series of standardised protocols would be scientifically valuable and might prove cost-effective. Experience gathered in such field sites, if shared with the manufacturers, could guide them in their future development work. When new test kits are developed, they should be screened in the populations in which they will be used before they are introduced on a wide scale.

Similar standards of quality control and quality assurance should also be provided for microscopy.

### 6.7. ECONOMIC CONSIDERATIONS

Cost considerations are often perceived as being the most important obstacle to the widespread introduction of RDTs. The cost per test is higher for RDTs than for microscopy, except at low levels of utilization. Nevertheless, this is balanced by the fact that the costs for organization, supervision, quality control and skilled personnel, as well as the cost to patients, are likely to be lower for RDTs than for microscopy.

Overall, it is unlikely that the introduction of RDTs would result in net savings in areas of high transmission where relatively inexpensive first-line antimalarial drugs are still used. Cost savings from the use of RDTs are more likely to occur in areas of low to moderate transmission, where microscopic diagnosis is unavailable or of low quality and where multidrug resistance dictates the use of more expensive therapy.

Policy decisions on diagnostic approaches will rely on quantitative data such as the cost-effectiveness of the different approaches. Assessing cost-effectiveness through theoretical models, though necessary, will be difficult because the potential effects on health of diagnostic tests (e.g. improved disease management or inhibition of the development of drug resistance) are ambiguous, difficult to quantify and measured by a range of non-comparable intermediate outcome indicators.

Affordability will be a major consideration for the widespread use of RDTs in low-income countries. The cost of RDTs includes not only the manufacturer's costs (research and development and production) but also distribution costs, import fees and local taxes. The latter can be substantial, but could be reduced through government intervention. Other approaches to reducing costs include technology transfer and local production, bulk purchase and technical improvements. The prices of RDTs should drop when their patents expire. Even at a cost of US\$ 0.30–0.50 per test, however, wide use in most developing countries is unlikely to be affordable without substantial and sustained external assistance.

Affordability issues might be addressed in two ways. One could be to target those patients for whom the tests would be most beneficial. This would reduce net costs to the health system and would improve individual case management. Another approach might consist of a multi-tier system whereby tests that are of higher performance and more costly (e.g. that identify specific species or are of very high sensitivity) would be made available only to reference facilities and should be marketed to a different population than the more basic tests intended for use at the periphery of the health care system.

### 6.8. DEPLOYMENT

While RDTs are unlikely to be of great benefit in areas with high rates of transmission, they could justifiably be used in areas with low to moderate rates, and in special situations such as complex emergencies. Under these conditions, however, determining which populations to target or who should perform the tests requires information that is only partly available. A practical issue deserving immediate attention is that of assessing the potential benefits and risks of RDTs being performed by private health practitioners, pharmacists, shopkeepers, community volunteers or even the patients themselves.

Another major issue relates to the respective use of RDTs and microscopy, two diagnostic approaches that offer complementary advantages. Identification of the circumstances that allow the best synergy between the two types of test will ensure their optimal utilization in terms of cost as well as health benefit.

A related issue is the potential effect of the use of RDTs on malaria surveillance. The adoption of RDTs as approved diagnostic tests in an area or a country may modify malaria case reporting, with resulting consequences for the surveillance system. Potential disruptions should be avoided by planning carefully the transition from one system to the other, as applicable.

### 6.9. IMPACT ASSESSMENT

As RDTs are introduced and used, it will be important to measure their impact on the diagnosis and treatment of malaria in the public and private sectors, and on the disease itself. Such assessments aim to identify parameters whose modification will maximize the benefits of RDTs, and will also provide information needed for a cost-effectiveness analysis of RDTs. Parameters to be assessed include: drug usage; treatment-seeking behaviour; access to RDTs; the time between diagnosis and treatment; management of patients; incidence of severe disease, morbidity and mortality; treatment failure; and drug resistance.

One parameter of interest is the utilization of diagnostic results. Experience indicates that some health care providers treating a patient with suspected malaria will ignore negative RDT results and give antimalarial drugs regardless. Similar observations have been made in the case of microscopic diagnosis (53). Such patterns of disease management negate the benefit offered by confirmatory diagnostic tests and strategies to understand and correct this behaviour should be investigated.

Delaying the emergence of drug resistance by reducing the number of unnecessary treatments has been postulated as one of the potential benefits of RDTs. Another strategy that aims to delay drug resistance is malaria combination therapy (e.g. mefloquine plus artemisinin derivatives in areas of multidrug resistance) (54). While studies on the potential impact of RDTs and combination therapy on the development of drug resistance might provide useful information for malaria control policies, it must be acknowledged that in practice such studies are complex.

# Research needs

# 7

### 7.1. RESEARCH ON THE DEVELOPMENT OF IMPROVED ASSAYS

- *Develop methods that permit quantification of parasite density with RDTs.*

The main research questions are the following.

- Can tests be developed or adapted that would permit a semi-quantitative or quantitative estimate of parasite density?
- Can tests be developed that can estimate the total parasite load in the patient's body?

- *Develop improved tests that reflect viable asexual parasitaemia only.*

The main research questions are as follows:

- Can tests be developed, or can existing tests be modified to reflect viable asexual parasitaemia, in an RDT format?
- Can tests be developed that better reflect the total parasite load including both circulating and sequestered parasites?
- Would such tests be better in terms of predicting disease outcome and/or treatment failure?

- *Identify potential markers that predict the development of complications, treatment outcomes and/or drug resistance.*

The main research questions are as follows:

- Are there biological products derived from the parasite or the host that can be used to develop such tests, possibly in an RDT format?
  - How well would such markers correlate with complications, treatment outcomes and drug resistance in a complex multifactorial host–parasite relationship?
- *Develop a bank of reagents and a network of testing sites in support of quality control and test development.*

A shared bank of reagents (antigens, parasite material, sera) and a common network of well equipped, geographically diverse sites where new tests can be assessed would greatly facilitate the adoption of uniform standards and the comparison of various tests, including RDTs.

- *Improve current test performance characteristics.*

The following improvements would greatly enhance the applicability of the tests and/or their reliability:

- an increase in sensitivity, aiming at 100% sensitivity for densities of >100 parasites per  $\mu\text{l}$  blood in all four species;
- reduction or suppression of time-critical steps, or development of methods for self-timing;
- improvement in stability at high temperatures and against short temperature surges;
- improvement in the robustness of the test kits;
- reduction in the number of steps and test components;
- improvement in the readability of the tests (applies to better signal intensity as well as to the avoidance of mix-ups);
- development of safer methods of blood handling; and
- development of non-blood-based tests (e.g. saliva).

- *Identify the “gold standard” against which malaria diagnostic tests should be assessed.*

While microscopy is acknowledged to be an imperfect diagnostic tool, it has practically always been used as the standard against which other tests such as RDTs are assessed. Tests such as PCR are more sensitive and specific, but may not reflect accurately the presence of live parasites. The identification of a better “gold standard” would not only provide an improved tool for the development of new diagnostic tests, but might also offer a better understanding of the biology of malaria in the human host. The main research questions are as follows.

- Which of the currently available methods should be used as the “gold standard”?
- Is there a combination of diagnostic findings that might yield a better approach to a “gold standard”?
- Can the same “gold standard” be used for all epidemiological situations?

## 7.2. OPERATIONAL FIELD STUDIES USING EXISTING DIAGNOSTICS

- *Obtain, in several areas, qualitative and quantitative information that could be used to develop a model for the appropriate introduction or expansion of the use of diagnostic tests (especially RDTs) at the peripheral level, aiming at their optimal deployment.*

The model could allow the identification of specific situations in which interventions might be concentrated to derive the maximum benefit. Research questions include the following:

- In a given situation, what are the current practices and perceptions about the diagnosis and treatment of malaria?
- Are there particular decision-making nodes (e.g. in treatment-seeking behaviour) where certain interventions (e.g. RDTs) might alter outcomes (e.g. drug use or morbidity/mortality) in diagnosis and treatment?
- What is the cost–effectiveness of each intervention?

- *Assess the feasibility and acceptability of introducing RDTs in selected situations, such as use in isolated communities, use by private health providers, and diagnosis of malaria in travellers.*

Such studies should be multidisciplinary and include economic analysis, behavioural studies, monitoring and quality control, and measurement of outcome.

- *Assess the potential role of RDTs in the detection of treatment failures.*

Research questions include the following:

- Compared to microscopy, do RDTs offer any advantages (e.g. outcomes, logistics, economics) that would make them preferable for monitoring of treatment?
- What should be done to achieve a rate of patient follow-up that would make this a usable tool?
- What are the potential implications of persistent antigenaemia after parasite clearance from peripheral blood?

- *Assess the potential relationships between inappropriate drug use and the development of resistance.*

If such a relationship is proved, it could strengthen the rationale for using confirmatory diagnosis – including RDTs – to avoid unnecessary drug use. This assessment will include situation analysis and operational studies, the principal research questions being the following:

- Are there data that demonstrate a direct causal link between drug use and the development of resistance?
  - If such a link exists, can it be quantified?
  - Are the situations similar in areas with high and low levels of transmission?
- *Develop a model of the introduction of RDTs and other approaches (e.g. combination therapy) and their potential effect on the development of drug resistance.*

Research questions include the following:

- Can the development of drug resistance be delayed by improving disease management through the use of RDTs and/or combination therapy?
  - If yes, how should RDTs and/or combination therapy be used to achieve the maximum impact?
  - Would there be an additive or synergistic effect between use of RDTs and combination therapy?
- *Investigate whether the persistence of some antigens (such as HRP-II) in circulating blood following parasite clearance is associated with persistence of a low-level (subpatent) parasite load, and is thus a predictor of drug resistance.*

The main research questions are the following:

- Does such an association exist?
  - If yes, does it occur for all drugs, or is it dependent on drug characteristics such as rapidity of action, mode of action or pharmacokinetics?
- *Assess the occurrence of HRP-II deletions in parasite populations.*

The discovery of such deletions would influence the interpretation of RDTs that detect HRP-II.

- *Conduct longitudinal investigations of untreated patients with clinically suspected malaria but with negative blood smears and/or RDTs.*

The main research questions are the following:

- Without treatment, do these patients develop patent parasitaemia or detectable antigenaemia?
- If they do not, what is their clinical outcome, and what is (are) the disease(s) causing the symptoms?

## Conclusion

# 8

RDTs have introduced a new dimension to the diagnosis and treatment of malaria. They now permit, among other things, on-the-spot confirmatory diagnosis of malaria at the periphery of the health care system, by health workers with minimal training. The rational use of RDTs as a complement to microscopy might give substantial health benefits (*a*) through earlier treatment and a consequent reduction in morbidity and mortality, (*b*) by targeting expensive drugs and drug combinations to high risk populations in multidrug resistant areas and (*c*) through a more rational use of drugs that might effectively reduce drug pressure and possibly delay the progress of drug resistance. Nevertheless, RDTs are unlikely to be widely adopted until their detection capacities have been improved, their potential benefits have been confirmed, and their cost has come closer to what most national malaria programmes can afford.

Addressing these issues, and ensuring the optimal use of RDTs as a key tool in malaria control, will require a coordinated effort among users, control programmes, manufacturers and international agencies.

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# 9

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