

Helpdesk Report: Malaria and Rapid Diagnostic Tests

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Query: What is the latest evidence on the efficacy of Rapid Diagnostic Tests (RDTs) for malaria? What are their reliability, validity, predictive values? Do they work at all times of the malaria cycle in the body? Is their effectiveness affected by temperature, transport, storage or other external conditions? Is there a difference between the different types of RDT?

Enquirer: DFID Ghana

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1. Overview

Rapid Diagnostic Tests (RDTs) do not require a laboratory or any special equipment; they are simple to use and can give results as a simple positive/negative result within 15 minutes. According to the World Health Organization (WHO), RDTs are adequate to diagnose malaria in febrile patients. RDTs have better sensitivity and specificity than routine microscopy and might be critical in improving the overall quality of malaria diagnostic capacity in routine settings. Demonstration of the presence of malaria parasites is advised before treatment with antimalarial medicines, because diagnosis based solely on clinical symptoms is of poor accuracy and leads to overdiagnosis of malaria, waste of antimalarial medicines, an increased frequency of adverse side effects and increased drug pressure on resistant parasites.

Health workers need to be trained and prepared for comprehensive case management, as well as given specific guidance for managing febrile patients with negative test outcomes, alongside providing RDTs. Evidence indicates occasional human errors leading to false positive or negative results from RDTs. These errors could be reduced with periodic performance appraisals for the workers involved. For RDTs to be effective, there needs to be

confidence in the results, which must then be acted upon. Health providers and patients may be reluctant to believe negative RDT results, which can lead to unnecessary prescribing of antimalarials for negative cases.

To be a useful diagnostic, RDTs must achieve greater than 95 per cent sensitivity. Most RDTs today have achieved this goal for *P. falciparum* malaria, but not for non-*P. falciparum* malaria. The high sensitivity and specificity of RDTs means they can replace or augment microscopy for diagnosing *P. falciparum* malaria. RDTs for malaria work by detecting specific proteins (HRP2, pLDH and aldolase) which are produced during the parasite's development cycle in the human host. During the malarial cycle in the human host, increasing amounts of HRP2, pLDH and aldolase antigens are produced and released into the bloodstream. HRP2-based RDTs should be able to detect parasites on the first day of symptoms and the persistence of the antigen will cause the tests to remain positive for at least seven days post-treatment.

It is estimated that currently about 60 manufacturers worldwide produce over 200 different commercially available RDTs. Decisions on which RDTs to procure are subject to a number of factors, for instance, if the RDT is vulnerable to high temperatures, it should be used only in areas with a temperate climate and transported under controlled temperature.

In most areas of sub-Saharan Africa and lowland Papua New Guinea the prevalent parasites are predominantly *P. falciparum*, with non-*falciparum* infections being rare. Therefore, RDTs that detect only *P. falciparum* are generally preferable in sub-Saharan Africa with Hrp2 and pLDH-pf as the target antigens. Type 1 tests were falsely negative in about five per cent of *P. falciparum* cases and were falsely positive in about five per cent of people without *P. falciparum*. No important differences in accuracy between different RDT brands within the same type have been identified. The performance of RDT types varied, though not significantly. The quality of RDTs provided by the private sector in malaria endemic countries may be questionable; regulation and monitoring may need to improve.

Most manufacturers recommend storage and distribution at temperatures between two degrees Celsius and 45 degrees Celsius. Exposure to high temperatures may reduce sensitivity or result in failure of RDTs and freezing may destroy diagnostic performance, both of which may reduce its diagnostic performance, especially at low parasite densities. Development of a 'cool chain' for RDTs is essential. Temperature control of central storage facilities should be a basic requirement if storage is prolonged. Simple measures during transport from manufacturer and within countries can help avoid exposure of RDTs to high temperatures. Careful planning of distribution and storage, purchasing policies that take product stability and intended conditions of use into account, and consideration of staggered procurement to minimise post-purchase storage time is needed to limit exposure to high temperatures. Quality control and quality assessment measures are important to ensure that the purchased products meet performance expectations and that product quality is maintained through the delivery process to the periphery of the healthcare system.

In the majority of African settings RDTs would be considered cost-effective. The cost-effectiveness of RDTs mainly reflected improved treatment and health outcomes for non-malarial febrile illness, plus savings in antimalarial drug costs.

2. Background to Malaria

Malaria is caused by the asexual form of the parasitic protozoan *Plasmodium*. Most cases of malaria are uncomplicated, commonly presenting with fever and sometimes with other non-specific symptoms including headache, and aches and pains elsewhere in the body. A few people develop severe malaria, with confusion, weakness, coma and other life-threatening complications. Malaria is curable and early, prompt and accurate diagnosis followed by

appropriate treatment helps to reduce illness and death. This is central to current malaria control policy. The two most common species of malaria parasite are *Plasmodium falciparum* and *Plasmodium vivax*. *P. falciparum* malaria is by far the most common type of malaria in Africa and it is also endemic in parts of Asia and South America. It is the most common cause of severe malaria, responsible for almost all malaria deaths and can cause other complications, such as anaemia and, in pregnancy, low birth-weight babies. *Vivax* malaria is a relapsing form, which is rarely fatal, but can cause serious anaemia in children. Less common human malaria parasite species include *P. malariae* and *P. ovale*.

Rapid diagnostic tests (RDTs) detect parasite-specific antigens in a drop of fresh blood through lateral flow immunochromatograph. RDTs do not require a laboratory or any special equipment; they are simple to use and can give results as a simple positive/negative result within 15 minutes. Although many products are available on the market, some can detect only one species (e.g. only *P. falciparum*), while others also detect further species of the parasite (i.e. *P. vivax*, *P. malariae* and *P. ovale*), in different combinations; nevertheless, the principles of these diagnostic tests are similar. Most RDTs detect malaria species-specific antigens produced by parasites present in the blood of infected individuals; enough blood for the diagnostic test can usually be obtained from a finger-prick. As the RDTs detect an antigen of the parasite and not the antibodies due to the human immunological response, the result is not affected by impaired immunity (due to e.g. HIV infection or malnutrition).

According to the World Health Organization (WHO), RDTs are adequate to diagnose malaria in febrile patients. Demonstration of the presence of malaria parasites is advised before treatment with antimalarial medicines, as diagnosis based solely on clinical symptoms is of poor accuracy and leads to overdiagnosis of malaria, waste of antimalarial medicines, an increased frequency of adverse side effects and increased drug pressure on resistant parasites. Early exclusion of malaria can enhance early diagnosis and appropriate management of other, potentially severe causes of fever. Parasitological diagnosis improves malaria case detection and surveillance systems (WHO, 2011).

3. Efficacy of RDTs

Results from a cross-sectional health facility survey in Tanzania (Masanja *et al.* 2012), found that the implementation of RDTs reduced over-treatment of malaria with artemisinin combination therapy (ACT) during high malaria transmission season in one area in Tanzania. Further research is needed to assess whether this reduction can be sustainable over time. Also, additional measures (such as refresher trainings, closer supervisions, etc.) may be needed to improve ACT targeting during low transmission seasons.

The study compared a post-RDT implementation area to a pre-RDT implementation area. The post-RDT implementation area had much higher availability of malaria diagnostic testing capacity; 74 per cent of patients were seen in a health facility that had either RDTs or microscopy available compared to 32.6 per cent of patients seen on the pre-RDT implementation area. However, availability of diagnostics alone does not improve malaria case management. It should be noted that more patients were correctly tested for malaria in the post-RDT implementation area (62.1 per cent) than the pre-RDT implementation area (46.5 per cent). Over-testing in the post implementation area was high. Over-testing can be associated with wasting resources; patients who do not meet clinical criteria for malaria should not be tested. This can be achieved by improving people's understanding of how RDTs work and what they should be used for (Masanja *et al.* 2012).

RDTs appear to have better sensitivity and specificity than routine microscopy and might be critical in improving the overall quality of malaria diagnostic capacity in routine settings. In addition, this study suggests that adherence to RDT results is reasonably high with 83.2 per cent of RDT-positive patients receiving ACT and only 7.8 per cent of RDT-negative patients

receiving ACT. Adherence to diagnostic test results is critical, if the implementation of RDTs is expected to reduce over-treatment. Results suggest that health workers do adhere to RDT results, even after routine implementation of RDTs. Evidence suggests that RDT introduction can lower anti-malarial drug consumption and may help reduce the problem of anti-malarial drug stock-outs (Masanja *et al.* 2012).

Only about a third of fever patients actually received ACT in the post RDT implementation area, despite the fact that most of the patients (94 per cent) were seen in a facility with ACT in stock. It is important to become conscious of the possibility for over-estimation of positivity rate that might result from use of RDTs. In particular, this is likely to be a problem with the use of histidine rich protein-2 (HRP-2) based RDT devices for detecting *Plasmodium falciparum* infection, as they may continue to test positive weeks after parasite clearance. In this case, training on RDTs should stress the need for assessing other disease conditions despite a positive test for malaria, and referral to higher level of care for a microscopic examination of malaria. It also supports present efforts to obtain accurate information about the disease burden in the population (Masanja *et al.* 2012).

Research by Counihan *et al.* (2012) focused on Community Health Workers using RDTs in Zambia recorded a consistently high diagnostic performance over a 12 month period. However, the results suggest that some difficulty was evident for reading faint positive test lines, possibly leading to false negative results. Despite this, it was concluded that with a well designed job aid and half day training, community health workers can diagnose malaria safely and accurately using RDTs. Occasional errors were found to occur, suggesting periodic performance appraisals for the workers being necessary (Counihan *et al.* 2012).

Data collected from 21 health centres in Uganda, found it acceptable for RDTs to be used by the target users, provided clear policy guidelines exist, ancillary tools are easy to use and health supplies beyond the diagnostic tools are met. Health workers need to be trained and prepared for comprehensive case management as well as given specific guidance for managing febrile patients with negative test outcomes alongside providing the new health technology. The effectiveness of the health system in providing the enabling environment and the integration of the diagnostic tool into routine service delivery is critical to the success of RDTs. For RDTs to be successful, they need to be perceived as medically useful (Asiimwe *et al.* 2012).

Microscopy is generally considered the gold standard in malaria diagnosis, but quality in routine service delivery varies and availability is restricted by the requirement for laboratory equipment and expertise. RDTs present a solution due to their ease of use and adequate sensitivity in detecting even sub-microscopic infections. Polymerase chain reaction (PCR) is an even more sensitive test, but it is mainly used for research purposes. Minja *et al.* (2012) focused on the diagnosis of pregnancy-associated malaria (PAM) assessing the accuracy and reliability of RDTs in diagnosing PAM by comparing the technique to microscopy and PCR.

The methodology saw a cohort of pregnant women in north-eastern Tanzania being followed throughout pregnancy for detection of plasmodial infection using venous and placental blood samples evaluated by histidine rich protein 2 (HRP-2) and parasite lactate dehydrogenase (pLDH) based RDTs (Parascreen™) or HRP-2 only (Paracheck Pf® and ParaHIT®f), microscopy and nested *Plasmodium* species diagnostic PCR. From a cohort of 924 pregnant women who completed the follow up, complete RDT and microscopy data was available for 5,555 blood samples and of these 442 samples were analysed by PCR. Of the 5,555 blood samples, 49 ((proportion and 95 per cent confidence interval) 0.9 per cent [0.7 - 1.1]) samples were positive by microscopy and 91 (1.6 per cent [1.3-2.0]) by RDT. Forty-six (50.5 per cent [40.5 - 60.6]) and 45 (49.5 per cent [39.4 – 59.5]) of the RDT positive samples were positive and negative by microscopy, respectively, whereas 19 (42.2 per cent [29.0 - 56.7]) of the microscopy negative, but RDT positive, samples were positive by PCR. Three (0.05 per cent

[0.02 - 0.2]) samples were positive by microscopy but negative by RDT. 351 of the 5,461 samples negative by both RDT and microscopy were tested by PCR and found negative. There was no statistically significant difference between the performances of the different RDTs (Minja *et al.* 2012).

The evidence suggests that microscopy underestimated the real burden of malaria during pregnancy and RDTs performed better than microscopy in diagnosing PAM. In areas where intermittent preventive treatment during pregnancy may be abandoned due to low and decreasing malaria risk and instead replaced with active case management, screening with RDT is likely to identify most infections in pregnant women and out-performs microscopy as a diagnostic tool (Minja *et al.* 2012).

Further research is required on effective implementation of RDTs, as they can only influence clinical practice if the results are believed and acted upon. There may be reluctance on the part of both health providers and patients to believe negative RDT results, leading to unnecessary prescribing of antimalarials for negative cases (Abba *et al.* 2011).

In Senegal, the national malaria control programme introduced universal parasite-based diagnosis using RDTs from 2007 in all public health facilities. Between 2007 and 2009 the prescription of ACT dropped from 72.9 per cent of malaria-like febrile illness to 31.5 per cent, reaching close equivalence to confirmed malaria (29.9 per cent of 584,873 suspect fever cases). An estimated 516,576 courses of inappropriate ACT prescription were averted. While more detailed information on management of parasite-negative cases is required at point of care level to assess overall cost-benefits to the health sector, considerable cost-savings were achieved in ACT procurement (Thiam *et al.* 2011).

D'Acremont *et al.* (2011) argue that presumptive treatment of all febrile patients with antimalarials leads to massive over-treatment. The results of their study in Tanzania indicate that programmatic implementation of RDTs in a moderately endemic area reduced drastically overtreatment with antimalarials. Properly trained clinicians with adequate support complied with the recommendation of not treating patients with negative results. They suggest that the implementation of Rapid Diagnostic Testing should be integrated with training on the management of other causes of fever to prevent irrational use of antibiotics.

A cross-over validation clinical trial conducted in four primary health care units in Zanzibar found RDTs resulted in improved adequate treatment and health outcomes without increased cost per patient (Msellem *et al.* 2009). Patients of all ages with reported fever in the previous 48 hours were eligible for the study and allocated alternate weeks to RDT-aided malaria diagnosis or symptom-based clinical diagnosis (CD) alone. ACT was to be prescribed to patients diagnosed with malaria in both groups. 1,887 patients were enrolled. RDT was associated with lower prescription rates of antimalarial treatment than CD alone, 361/1005 (36 per cent) compared with 752/882 (85 per cent) (odds ratio [OR] 0.04, 95 per cent confidence interval [CI] 0.03–0.05, $p < 0.001$). Prescriptions of antibiotics were higher after RDT than CD alone, i.e., 372/1005 (37 per cent) and 235/882 (27 per cent) (OR 1.8, 95 per cent CI 1.5–2.2, $p < 0.001$) respectively. Reattendance due to perceived unsuccessful clinical cure was lower after RDT 25/1005 (2.5 per cent), than CD alone 43/882 (4.9 per cent) (OR 0.5, 95 per cent CI 0.3–0.9, $p = 0.005$). Total average cost per patient was similar: USD 2.47 and 2.37 after RDT and CD alone, respectively. The findings indicate that RDTs resulted in improved adequate treatment and health outcomes without increased cost per patient. Therefore RDTs may represent a tool for improved management of patients with fever in peripheral health care settings (Msellem *et al.* 2009).

4. Reliability, validity and predictive values of RDTs

For detecting *P. falciparum* in areas of low and moderate transmission the World Health Organization state it is highly advisable to select RDTs with a *P. falciparum* panel detection score well above 50 per cent at 200 parasites per microlitre (e.g. > 75 per cent). In areas of high transmission this should be at least 50 per cent at 200 parasites per microlitre. High transmission areas are defined as hyperendemic and holoendemic areas in which the prevalence rate of malaria is over 50 per cent during most of the year among children aged 2–9 years. In these areas, practically all individuals are infected by late infancy or early childhood. As the extent of high transmission areas is likely to decrease with effective malaria control, a panel detection score well above this level should become the basis for product selection in the future. For all RDTs false positive rate should be less than ten per cent and invalid rate less than five per cent (WHO, 2011).

Results from a study into RDTs provided by the private sector in malaria endemic countries found the quality of the tests available to be questionable. Of the 14 RDTs available for purchase, nine passed the quality control testing at both 200 and 2000 Plasmodium falciparum parasites per microlitre, one RDT (malaria RDT Pf Pan type) failed quality control testing at both 200 and 2000 *P. falciparum* parasites per microlitre, and four RDTs (malaria Pf RDT types) failed to detect a dilution of 200 *P. falciparum* parasites per microlitre. Although this investigation is limited by sample size, it found some RDTs available through private outlets had inadequate sensitivity, suggesting regulation and monitoring may need to improve (Albertini *et al.* 2012).

Research from Tanzania assessed the accuracy of RDTs (when used at different community settings), the impact of using RDTs on anti-malarial dispensing by community-owned resource persons (CORPs) and adherence of CORPs to treatment guidelines by providing treatment based on RDT results. Data were obtained from a longitudinal study of passive case detection of fevers using CORPs and cross-sectional surveys (CSS). Performance of RDTs was compared with microscopy as a gold standard, and factors affecting their accuracy were explored using a multivariate logistic regression model. Overall sensitivity and specificity of RDTs in the longitudinal study (of 23,793 febrile cases; 18,154 with microscopy and RDTs results) were 88.6 per cent and 88.2 per cent, respectively. In the CSS, the sensitivity was significantly lower (63.4 per cent; $c^2 = 367.7$, $p < 0.001$), while the specificity was significantly higher (94.3 per cent; $c^2 = 143.1$, $p < 0.001$) when compared to the longitudinal study. As determinants of sensitivity of RDTs in both studies, parasite density of <200 asexual parasites/ μ l was significantly associated with high risk of false negative RDTs ($OR \geq 16.60$, $p < 0.001$), while the risk of false negative test was significantly lower among cases with fever (axillary temperature $\geq 37.5^\circ C$) ($OR \leq 0.63$, $p \leq 0.027$). The risk of false positive RDT (as a determinant of specificity) was significantly higher in cases with fever compared to afebrile cases ($OR \geq 2.40$, $p < 0.001$). Using RDTs reduced antimalarials dispensing from 98.9 per cent to 32.1 per cent in cases aged ≥ 5 years. The results indicate that although RDTs have low sensitivity and specificity, which varied widely depending on fever and parasite density, using RDTs can reduce over-treatment with antimalarials significantly. RDTs can potentially identify the majority of malarial febrile cases and lead to improved management of malaria and non-malaria fevers (Ishengoma, D. *et al.* 2011).

To be a useful diagnostic, RDTs must achieve greater than 95 per cent sensitivity. Most RDTs today have achieved this goal for *P. falciparum*, but not for non-*P. falciparum* (Wongsrichanalai *et al.* 2007).

The high sensitivity and specificity of RDTs means they can replace or augment microscopy for diagnosing *P. falciparum* malaria (Abba *et al.* 2011).

A study in Burkina Faso (Bisoffi *et al.* 2009) aimed to assess the if the clinical outcome of patients treated after performing RDT is at least equivalent to that of controls (treated presumptively without test) and to determine the impact of the introduction of a malaria RDT on clinical decisions. A total of 852 febrile patients were recruited in the dry season and 1317

febrile patients in the rainy season, and randomized either to be submitted to RDT or to be managed presumptively. The study was inconclusive on RDT safety, because of an exceedingly and unexpectedly low compliance with the negative test result. However, it does raise concerns about the potential harm affects RDTs, including false positive patients. For example, in endemic areas the presence of malaria parasites in blood may not reflect a clinical malaria episode. Some febrile, RDT positive patients may be carriers of malaria parasites, with another (potentially severe) disease. The harm from a missed treatment, under the influence of a positive malaria test, might not be negligible. In one case in the dry season, a child with a false positive RDT result was treated for malaria only and subsequently died (presumably of pneumonia) (Bisoffi et al. 2009).

A study conducted in rural Ghana (Baiden *et al.* 2012) evaluated the performance of CareStart, a HRP-2 based RDT, using microscopy as reference. ACT was restricted to RDT-positive children and followed-up both RDT-positive (malaria) and RDT-negative (non-malaria) cases over 28 days. A total of 436 children were enrolled in the RDT evaluation and 391 were followed-up to assess treatment outcomes. It was found that the RDT had good sensitivity and specificity. The results suggests that it is possible for children who do not receive ACT based on RDT results to develop clinical malaria within a short period in high transmission settings. This could undermine caregivers' and health workers' confidence in RDTs and approved guidelines. The findings include the suggestion that improving the quality of management of non-malarial febrile illnesses should be a priority (Baiden *et al.* 2012).

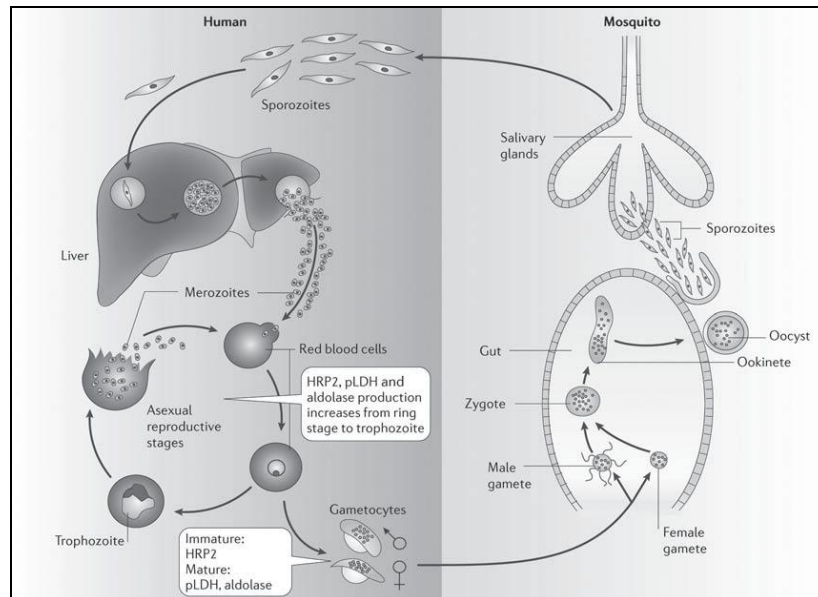
English *et al.* (2009) argue against abandoning presumptive treatment for under-fives arguing that important evidence gaps remain about alternative approaches including the sensitivity and reliability of using RDTs. They also argue that health system capacity to implement a shift towards RDTs has not been demonstrated. In addition, they argue that while rapid diagnostic tests (RDTs) perform relatively well in research studies, limited data on performance in routine settings suggest relatively poor sensitivity overall (65 per cent) and worrying variability between sites (19 to 86 per cent sensitivity). Limited data suggest that the risk of failure to detect true malaria in febrile children is very low. However, these studies are based on active follow-up, and do not measure the risks of serious morbidity and mortality from a failed diagnostic process in real-life settings where there are considerable barriers to accessing (re-)treatment.

5. RDT and the malaria cycle in the body

RDTs for malaria are lateral-flow immunochromatographic devices for detecting specific proteins (HRP2, pLDH and aldolase), that are produced during the parasite's development cycle in the human host. The malaria parasite's life cycle depends on two hosts: the female anopheline mosquito and the human being. Mosquitoes become infected with the parasite when they feed on a person whose blood contains gametocytes, the sexual forms of the parasite. Gametocytes develop in a number of steps in the mosquito, until, on rupture of the oocyst form, sporozoites are released and migrate to the mosquito's salivary glands, from where they are injected into the human body by the bite of the mosquito. Sporozoites enter the human host's bloodstream and are carried to the liver, where they multiply and develop into schizonts, which, upon rupture, release merozoites into the bloodstream. Merozoites invade red blood cells and, nourished by the haemoglobin, develop from ring stages to trophozoites.

During this process, increasing amounts of HRP2, pLDH and aldolase antigens are produced and released into the bloodstream. Upon rupture of the infected red blood cells, further merozoites are liberated, which infect additional red blood cells. The cycle of red blood cell invasion continues, resulting in increasing levels of parasitaemia and antigen production. Some merozoites differentiate into micro- and macrogametocytes, the male and female forms of gametocytes, respectively, which produce HRP2 in their immature stage, while pLDH and

aldolase are generated in the mature stage. With the ingestion of the gametocytes by another female anopheline mosquito, the cycle of malaria transmission continues. HRP2 antigen may persist for a few weeks after elimination of viable malaria parasites from the blood, while pLDH and aldolase are generally cleared within 5–6 days (WHO, 2011).



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A mathematical model that focused on the dynamics of Plasmodium falciparum histidine-rich protein 2 in human malaria found that PfHRP2-based RDTs should be able to detect parasites on the first day of symptoms, and that the persistence of the antigen will cause the tests to remain positive for at least seven days post-treatment. The post-treatment duration of positive tests is dependent on the duration and density of parasitaemia prior to treatment, and possibility other factors such as anti-PfHRP2 antibodies. In chronic infections a steady state parasitaemia of only 4-65 parasites/ μ L is likely to be sufficient to maintain a positive RDT result (Marquart *et al.* 2012).

6. RDTs – temperature, transport, storage and other external conditions

Most manufacturers recommend storage and distribution at temperatures between 2°C and 28–45°C. Freezing may destroy diagnostic performance, and exposure to temperatures above the range specified by the manufacturer may accelerate degradation of the RDT, affecting the reliability of the test and reducing its diagnostic performance, especially at low parasite densities. The importance of the thermal stability of an RDT varies with the ambient conditions under which it is expected to be transported and stored. Thus, stability at high temperatures is vital if an RDT is to be stored in clinics in a country in which the ambient temperature can reach 45°C, but it is less critical at high altitudes or in cooler tropical environments where the temperature rarely rises above 35°C. It is important to consider the implications of these requirements for maintaining RDT product quality throughout the supply chain, particularly during steps such as transport to the country of receipt, trans-shipment and customs clearance, when the risk may be greatest. Control measures might include both preventive steps to avoid undue delays and the use of temperature-monitoring devices (WHO, 2011).

The World Health Organization recommends the following is taken into account when procuring RDTs:

- Stability requirements at temperatures of intended storage, transport and use: RDTs submitted for WHO product testing were evaluated for positivity against 200 parasites per microlitre of cultured *P. falciparum* after 60 days' incubation at 35°C and 45°C. RDTs with high thermal stability should be selected for areas with high ambient temperatures.
- Ease of use and training requirements for health workers: RDTs submitted for WHO product testing were also evaluated for blood safety, quality of instructions, number of steps, time to results, blood transfer device, format and kit completeness. Cassettes and cards are easier to use than dipsticks. For reasons of blood safety, kits that include lancets and alcohol swabs are preferred over kits that do not contain these items. Dipsticks are more suitable for settings with a laboratory facility.
- Price: After having considered all the above factors, good procurement practice requires that the price be taken into account (WHO, 2011).

As noted above, exposure to high temperatures may reduce sensitivity or result in failure of RDTs. Refrigeration and air-conditioning is commonly unavailable in malaria endemic areas where RDTs are intended for use. Research from Cambodia and the Philippines indicated that RDTs are frequently exposed to conditions outside the 4–30°C limits recommended by most manufacturers both while in transit and in storage. Development of a “cool chain” for RDTs is essential to ensure the RDTs arrive in the required condition. Temperature control of central storage facilities should be a basic requirement if storage is prolonged. In remote health facilities, simple and inexpensive evaporative cooling boxes may offer a solution to the problem of high temperatures during long-term storage, and thatch roofs are likely to be cooler than iron roofs. Simple measures during transport from manufacturer and within countries can help avoid exposure of RDTs to high temperatures. These include notifying the shipper/air carrier of storage requirements, notification of arrival, avoid leaving RDTs inside a vehicle in the sun or on an airport tarmac, and transporting the RDTs in vehicles with air-conditioning whenever possible. Transport of RDTs in insulated containers could further reduce large temperature fluctuations. Clear temperature specifications should be displayed on packaging. Careful planning of distribution and storage, purchasing policies that take product stability and intended conditions of use into account, and consideration of staggered procurement to minimise post-purchase storage time should be part of a national policy for malaria (Jorgensen *et al.* 2006).

As well as environmental conditions, several factors in the manufacturing process may affect RDT performance. Quality control and quality assessment measures are important to ensure that the purchased products meet performance expectations and that product quality is maintained through the delivery process to the periphery of the healthcare system (Wongsrichanalai *et al.* 2007).

TDR, a Special Programme for Research and Training in Tropical Diseases, is a global programme of scientific collaboration that helps coordinate, support and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged. It was established in 1975, and is based at and executed by the World Health Organization (WHO), and is sponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and WHO. TRR provide a Procurement Selection Algorithm, which assists with selecting the most appropriate product to use is available here:

http://www2.wpro.who.int/sites/rdt/using_rdt/selecting_rdt/procurement_selection_algorithm.htm

The Foundation for Innovative New Diagnostics (FIND) interactive guide is designed to help select malaria RDTs with the specific performance characteristics required by national

malaria control programmes, based on the results of the WHO-FIND malaria RDT product testing programme Round 1 (2008), Round 2 (2009) and Round 3 (2010). It is available here: http://www.finndiagnostics.org/programs/malaria-afs/malaria/rdt_quality_control/product_testing/malaria-rdt-product-testing/index.jsp?resubmit=Y&format=chart&sel=&pageWidth=1600&NPF=%2525&d1=on&DRPV=&FPR=&ITR=&fmt=

A list of manufacturers and products accepted into Round 4 of WHO Malaria RDT Product Testing Programme is available here: http://www.finndiagnostics.org/export/sites/default/programs/malaria-afs/docs/manufacturers-RDTproducts_round4.pdf

7. Different types of RDT

RDTs use antibodies to detect one or several antigens. The most commonly used antibodies react to histidine-rich protein-2 (HRP-2), aldolase and plasmodium lactate dehydrogenase (pLDH). HRP-2 is a marker for *P. falciparum*, while pLDH can be specific for *P. falciparum*, or *P. vivax*, or may detect all species (including *P. ovale* and *P. malariae*) or other combinations of these species. Aldolase antibodies are pan-specific, detecting all types of malaria parasite but not differentiating between them. Until recently, there were seven main types of commercially available test that use different antigen combinations (detailed below). Choice of RDT will depend on several factors, including prevalence of malaria. Policy makers will also take into account factors relating to cost and test stability as discussed in the previous section (Abba *et al.* 2011).

It is estimated that currently about 60 manufacturers worldwide produce over 200 different commercially available RDTs; an estimated 50–70 million tests were procured in 2008 and 90 million in 2009. As the quality of the products varies widely and regulatory control of diagnostic devices in malaria-endemic countries is often weak, procurement agencies face problems in selecting quality-assured RDTs with high diagnostic performance.

The diagnostic performance of RDTs is influenced in particular by the:

- quality of the manufacturing process,
- antigen threshold the RDT is designed to detect,
- species of parasite,
- density and strain of parasites present,
- concentration of target antigen,
- exposure of the test to extreme temperatures and relative humidity,
- technique used in performing the test, and
- correct interpretation of the results.

Several components of RDTs that are essential to good diagnostic performance are subject to vulnerability, which, depending on the situation, requires risk management (as detailed in the previous section). If, for instance, the RDT is vulnerable to high temperatures, it should be used only in areas with a temperate climate and be shipped under controlled temperature. Depending on the level of risk, systems such as product and lot testing can minimise the intrinsic vulnerability of the RDT and the risks related to procurement.

In most areas of sub-Saharan Africa and lowland Papua New Guinea the prevalent parasites are predominantly *P. falciparum*, with non-falciparum infections being rare. The majority of non-falciparum infections occur as mixed *P. falciparum* infections, rarely as single-species infections. Therefore RDTs that detect only *P. falciparum* are generally preferable in sub-Saharan Africa with Hrp2 and pldH-pf as the target antigens. Hrp2-detecting RDTs in general are likely to be more sensitive than pldH- and aldolase-detecting RDTs for *P. falciparum* infections in most environments (WHO, 2011).

In spite of over 100 published RDT trial reports, comparative assessment is difficult because (1) trials do not share common guidelines; (2) clinical and epidemiologic characteristics of the study populations, especially the parasitemia level vary; (3) reference standards are different; even among those using Giemsa microscopy, reading rules and microscopist skills vary; and (4) products of different lots may differ in quality or be damaged by extreme temperature or humidity during transportation and storage (Wongsrichanalai *et al.* 2007).

Types of malaria RDTs by antibody combination and parasite species detected

Type of Test	Antibody Combinations	Possible Results
Type 1	HRP-2 (<i>P. falciparum</i> specific)	No Pf; Pf; invalid
Type 2	HRP-2 (<i>P. falciparum</i> specific) and aldolase (pan-specific)	No malaria; Pf or mixed; Pv, Pf and/or Pm; invalid
Type 3	HRP-2 (<i>P. falciparum</i> specific) and pLDH (pan-specific)	No malaria; Pf or mixed; Pv, Pf and/or Pm; invalid
Type 4	pLDH (<i>P. falciparum</i> specific) and pLDH (pan-specific)	No malaria; Pf or mixed; Pv, Pf and/or Pm; invalid
Type 5	pLDH (<i>P. falciparum</i> specific) and pLDH (<i>P. vivax</i> -specific)	No malaria; Pf; Pv; Pf and Pv; invalid
Type 6	HRP-2 (<i>P. falciparum</i> specific), pLDH (pan-specific) and pLDH (<i>P. vivax</i> specific)	No malaria; Pf and Pv +/- Po and/or Pm; Pf +/- Po and/or Pm; Pv +/- Po and/or Pm; Po and/or Pm; invalid
Type 7	Aldolase (pan-specific)	No malaria; Pf, Pv, Po and/or Pm; invalid

Pf P. falciparum; Pv P. vivax; Pm P. malariae; Po P. ovale

Malaria 'zones' by endemic parasite species and RDT type appropriate for each

Zone	Endemic malaria parasites	Geographic area	Appropriate test type
1	<i>P. falciparum</i> only or other species almost always as a mixed infection	Most of sub-Saharan Africa; lowland Papua New Guinea	Tests using HRP-2 to detect <i>P. falciparum</i> only (Type 1)
2	Both <i>P. falciparum</i> and <i>P. vivax</i> , most commonly as a single species	Asia and the Americas; Ethiopian highlands	Combination RDTs which detect all species and distinguish between <i>P. falciparum</i> and <i>P. vivax</i> (Types 2 to 6)
3	Non-falciparum only	<i>Vivax</i> only areas of East Asia and Central Asia; some highland areas elsewhere	Pan-specific or vivax-specific RDTs (Type 7; Pan-pLDH only; vivax-pLDH only)

RDT type 1 brands (suitable for most of sub-Saharan Africa) verified with microscopy

RDT type 1 brands	Study (n)	Patients (n)	<i>P. falciparum</i>	Pooled sensitivity	Pooled specificity	Test
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	Cohorts		cases (n)	(95% CI)	(95% CI)	
Paracheck-Pf	27	22,319	6,929	93.2 (89.7, 95.6)	95.6 (92.8, 97.3)	P = 0.15
ParaSight-F	17	12,521	3,261	94.1 (89.9, 96.6)	94.6 (90.4, 96.8)	
ICT Malaria-Pf	16	2,955	1,200	97.6 (95.5, 98.8)	94.5 (90.5, 96.9)	
ParaHIT-F	4	1,119	192	92.3 (74.9, 98.0)	98.9 (94.9, 99.8)	
Determine Malaria-Pf	1	526	262	98.2 (85.4, 99.8)	86.8 (35.1, 98.8)	
PATH	2	378	180	96.6 (83.8, 99.3)	93.3 (68.6, 98.9)	
Rapid Test Malaria	1	306	36	97.8 (70.1, 100.0)	96.1 (65.6, 99.7)	
DiaSpot Malaria	1	153	63	71.8 (23.1, 95.6)	82.6 (27.3, 98.4)	
Hexagon Malaria	1	119	32	100.0 (.)	65.7 (13.4, 96.0)	
New Pf-1 mini	1	10	6	100.0 (0, 100.0)	100.0 (.)	

(Abba *et al.* 2011)

In diagnosing *P. falciparum* malaria, all tests above performed reasonably well. Type 1 tests were falsely negative in about five per cent of *P. falciparum* cases and were falsely positive in about five per cent of people without *P. falciparum*. There is a trade-off between sensitivity and specificity. Studies of Type 1 tests conducted in Africa reported slightly lower estimates of sensitivity and specificity than those conducted in Asia. The reasons for this are unclear, and may relate to the relative quality of the studies conducted in different locations, but are most likely due to higher rates of transmission and persistent antigenaemia in Africa. The results indicate no important differences in accuracy between different RDT brands within the same type were found. Type 1 RDTs were found to be more sensitive than Type 4, and HRP-2 antibody-based tests to be more sensitive than pLDH antibody-based tests, although the differences were not statistically significant. The performance of RDT types varied but the differences were not large (Abba *et al.* 2011).

8. Cost effectiveness of RDTs

Data from the WHO indicates that compared to RDTs, the costs of field microscopy per case are very high at low fever prevalence, mainly due to the high costs of maintaining equipment and a technician. At higher diagnostic throughput, the microscopy cost per case falls while the RDT cost per case remains fixed. Microscopy can also have other advantages including parasite quantitation and diagnosis of other diseases that increase its value. At a cost per ACT adult dose of \$1.70 we can be 95 per cent sure RDTs are cost-effective below a threshold of 64 per cent malaria prevalence and 99 per cent sure below 20 per cent

prevalence. RDTs become more cost-effective as the cost of ACT increases. At an ACT cost of \$2.70 we can be 95 per cent sure RDTs are cost effective below 72 per cent malaria prevalence and 99% sure below 43 per cent prevalence. This implies that in the majority of African settings RDTs would be considered cost-effective, as rates of over-diagnosis with Presumptive Treatment (PT) are frequently very high and the range of ACT and RDT costs used in the model reflects current prices. The cost-effectiveness of RDTs reflects mainly improved treatment and health outcomes for non-malarial febrile illnesses and anti-malarial drug cost savings. RDTs are also robustly cost-effective relative to field microscopy at this cost per test, reflecting the higher estimated accuracy of RDTs in peripheral health facilities, despite their generally higher cost. Sensitivity analysis shows that cost-effectiveness is most affected by malaria prevalence among febrile outpatients, the cost of the diagnostic test, the cost of ACT, and adherence to antibiotics for, and factors which influence the severity of, non-malarial febrile illnesses (WHO accessed 2012)

Shillcutt et al. (2008) found that RDTs have the potential to be cost-effective in most parts of sub-Saharan Africa but that appropriate management of malaria and non-malarial febrile illnesses is required to reap the full benefits of these tests. RDTs were found to be cost-effective compared with presumptive treatment up to high prevalences of *Plasmodium falciparum* parasitaemia. Decision-makers can be at least 50 per cent confident of this result below 81 per cent malaria prevalence, and 95 per cent confident below 62 per cent prevalence, a level seldom exceeded in practice. RDTs were more than 50 per cent likely to be cost-saving below 58 per cent prevalence. Relative to microscopy, RDTs were more than 85 per cent likely to be cost-effective across all prevalence levels, reflecting their expected better accuracy under real-life conditions. Results were robust to extensive sensitivity analysis. The cost-effectiveness of RDTs mainly reflected improved treatment and health outcomes for non-malarial febrile illness, plus savings in antimalarial drug costs. Results were dependent on the assumption that prescribers used test results to guide treatment decisions.

A study involving a random sample of 1,627 patients with fever in Uganda found that RDTs were cost effective in both low and high transmission settings. The results showed that RDTs were most cost-effective with a lowest Incremental Cost-Effectiveness Ratio (ICER) of US\$5.0 compared to US\$9.61 per case correctly diagnosed and treated for microscopy. In the high transmission setting, ICER was US\$4.38 for RDT and US\$12.98 for microscopy. The corresponding ICERs in the low transmission setting were US\$5.85 and US\$7.63 respectively. The difference in ICERs between RDT and microscopy was greater in the high transmission area (US\$8.9) than in low transmission setting (US\$1.78). At a willingness to pay of US\$2.8, RDT remained cost effective up to a threshold value of the cost of treatment of US\$4.7 (Batwala et al. 2011).

A study in Zambia found that Home Management of Malaria (HMM) which included the use of RDTs, was more cost effective than facility-based management of uncomplicated malaria. The cost per case correctly diagnosed and treated was USD 4.22 for HMM and USD 6.12 for facility level. Utilization and adherence to diagnostic and treatment guidelines was higher in HMM than at a health facility. HMM with RDTs is was found to be not only economical but also a method to potentially improve health outcomes (Chanda et al. 2011).

English *et al.* (2009) argue that in operational settings health workers frequently ignore diagnostic results and prescribe antimalarials to negative cases. This behaviour significantly impairs the cost-effectiveness of introducing confirmed diagnosis.

Mosha et al. (2010) carried out a study in rural Tanzania that aimed to estimate the rates of over diagnosis of malaria and examine the potential cost implications of improving the quality of diagnosis. The magnitude of over diagnosis of malaria was estimated by comparing the proportion of outpatient attendees of all ages clinically diagnosed as malaria to the proportion of attendees having a positive malaria rapid diagnostic test over a two month period. The results indicate over diagnosis of malaria by the routine outpatient care system compared to

RDT confirmed cases of malaria was highest among <5 year old children in the low transmission site (RR 17.9, 95 per cent CI 5.8–55.3) followed by the ≥5 year age group in the lower transmission site (RR 14.0 95 per cent CI 8.2–24.2). In the low transmission site the proportion of morbidity attributable to malaria was substantially lower in <2 year old cohort compared to children seen at routine care system (0.08 per cent vs. 28.2 per cent; p<0.001). The results suggest that using a RDT reduced overall drug and diagnostic costs by ten per cent in the high transmission site and by 15 per cent in the low transmission site compared to total diagnostic and drug costs of treatment based on clinical judgment in routine health care system. The implication of these results is that the introduction of RDTs is likely to lead to financial savings. It should be noted that improving diagnosis to one disease may lead to over diagnosis of another illness (Mosha et al. 2010).

9. Additional information

The Foundation for Innovative New Diagnostics (FIND) aims to address the urgent need for better diagnostic tests for poverty-related diseases. Their website has a section with several key resources on malaria and RDTs:

http://www.finddiagnostics.org/resource-centre/reports_brochures/?year=0&domain=Malaria

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