CHAPTER 5

MALARIA RAPID DIAGNOSTIC TESTS:
Access to Diagnostics
An estimated 40% of the world population today is at risk of malaria infection.¹ The disease, a parasitic infection spread from person to person by the bite of the female *Anopheles* mosquito, affects people in approximately a hundred nations. The World Health Organization (WHO) estimates that each year there are more than 300 million episodes of acute illness and at least a million deaths due to malaria worldwide.² In addition, more than 90% of the global burden is in sub-Saharan Africa. Children under five years of age are at greatest risk of death from malaria. Pregnant women and their unborn children are also vulnerable to the disease, which can lead to perinatal mortality, low birth weight, and maternal anemia. There are four types of human malaria: *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*. Of these, *P. falciparum* is the most deadly and the most common in sub-Saharan Africa.

The symptoms of malaria usually appear nine to fourteen days after the infectious bite of the mosquito, though this varies with the different *Plasmodium* species. Typical symptoms are fever, headache, vomiting, and other flu-like symptoms. Without effective treatment, malaria infection can lead to death by infecting and damaging red blood cells (anemia) and by blocking the capillaries that carry blood to the brain (cerebral malaria) or other essential organs.³ Malaria treatment is complicated due to the widespread resistance of *P. falciparum* to common antimalarial drugs such as chloroquine, sulfadoxine-pyrimethamine (SP), and amodiaquine. Today, WHO recommends that all countries experiencing resistance to these common monotherapies use combination therapies for *P. falciparum* malaria, preferably those containing artemisinin derivatives (known as artemisinin-based combination therapies, or ACTs).⁴ An artemether/lumefantrine combination therapy called Coartem, manufactured by Novartis, was the first fixed-dose ACT prequalified by WHO.

A major challenge for malaria treatment is the prompt and correct diagnosis of malaria infection. Diagnosis is critical because early treatment helps reduce morbidity and mortality. Malaria diagnosis has also become increasingly important due to the high price of ACTs. In 2008, governments could purchase Coartem for $0.80 per treatment for use in the public sector (where it is usually provided free to the end-user). End-users purchasing Coartem in the private sector pay a much higher price whereas they can purchase older treatments for $0.10–$0.20. Unfortunately, malaria diagnosis is often problematic and therefore presents a significant barrier to effective control of the disease.

The “gold standard” for malaria diagnosis is conventional light microscopy based on careful examination of a blood film by an expert microscopist. Microscopy is sensitive (it can detect densities as low as 5–10 parasites per microliter of
blood), informative, and relatively inexpensive ($0.12–$0.40 per slide, though these figures do not reflect the full costs, which are higher).\(^5\) Furthermore, as a general diagnostic technique, microscopy can be shared with other disease control programs and provides a permanent record of diagnostic findings. The method, however, is labor-intensive and time consuming (an estimated 20 to 60 minutes from specimen collection to result, depending on the available lab equipment). In practice, delays often occur in providing microscopy results to the clinician, so treatment decisions are commonly made before diagnostic results arrive. Finally, microscopy depends on good techniques, reagents, microscopes, and well-trained and well-supervised technicians. These conditions are often lacking at the lower levels of health systems in poor countries because microscopy has not been prioritized or supported by sustained financing.\(^6\)

In settings where microscopy is unavailable or unreliable, health professionals typically use clinical judgment to diagnose malaria. Clinical diagnosis is inexpensive, requires no special equipment or supplies, and is often the only option in health units without laboratory support at the periphery of a health system. It is the most widely used approach to malaria diagnosis. The symptoms of malaria, however, are nonspecific and overlap with symptoms of other febrile illnesses, so patients with fever are often treated presumptively and include many persons who do not have malaria.\(^7\)

Rapid diagnostic tests for malaria (RDTs) offer a new diagnostic alternative for health professionals and result from advances in molecular biology. These rapid tests are based on the detection of antigens, or proteins, derived from malaria parasites in lysed blood, using immunochromatographic methods. RDTs are relatively new products, and efforts to provide access to them are ongoing. This chapter traces the history of RDTs, beginning in the mid-1990s with the initial testing and commercial introduction of the first products and following through current efforts to scale up the technology. The case study highlights challenges of providing access to a new technology in an environment where external funding for procurement provokes rapid product uptake but where financing is lacking for other aspects of the access process, including information on product availability and quality. It also illustrates the important roles of a global coordinating body to arrange the architecture and promote the adoption and use of a new technology.

**Product Development (Phase 1)**

For many years, the World Health Organization and other global health agencies called for better diagnostic tools for settings with limited health infrastructure in developing countries. The goal was to develop simple and rapid diagnostic tests
that could be used to guide treatment in these settings for various infectious diseases, including malaria, AIDS, and syphilis. These tests became known as point-of-care (POC) tests, and most of them used immunochromatography to identify antigens (proteins) or antibodies in dipstick or lateral-flow formats. (For definitions of antigens and antibodies, see the Glossary.) Immunochromatography relies on the migration of liquid across the surface of a nitrocellulose membrane and became a popular platform for rapid tests since its introduction in the late 1980s. POC tests have the advantages of being inexpensive to make, simple to use, and quick to produce visual findings. In addition, they often require no additional equipment.8

The POC tests developed for malaria became known as malaria rapid diagnostic tests (RDTs); they are also sometimes called “malaria dipsticks” or “malaria rapid diagnostic devices.” Malaria RDTs use a dipstick or test strip carrying monoclonal antibodies to detect specific antigens produced by malaria parasites that are present in the blood of infected people. Health professionals are the end-users of malaria RDTs. The health worker obtains a patient’s blood from a finger-prick and then places the blood sample on the RDT, as described in a WHO document.9 Although variations exist among different malaria RDT products, the principles of the tests are similar. The test follow three basic steps, as presented in the WHO document (see Figure 5.1):

1) Dye-labeled antibody (Ab), specific for the target antigen, is present on the lower end of the nitrocellulose strip or in a well provided with the strip. Antibody, also specific for the target antigen, is bound to the strip in a thin (test) line, and either antibody specific for the labeled antibody or antigen is bound at the control line.

2) Blood and buffer, which have been placed on the strip or in the well, are mixed with the labeled antibody and are drawn up the strip across the lines of bound antibody.

3) If the antigen is present, some labeled antibody will be trapped on the test line. Other labeled antibody is trapped on the control line.

Products vary by format and are available as a dipstick (placed in wells containing blood and/or buffer), cassette (dipstick in a plastic holder), or in a card format. Cassettes are generally easier to use.10 RDT tests for malaria typically use between two and six steps of test procedures and take five to thirty minutes.11

RDTs also vary by the kind of antigen (protein) detected by the product. Some products detect histidine-rich protein-2 (HRP2), others detect parasite-specific lactate dehydrogenase (pLDH), and still others react with pan-specific aldolase.12 All tests detect proteins specific to *P. falciparum*, either HRP2 or
pLDH. Some tests also detect pan-specific aldolase or pLDH; these can distinguish a non-\textit{P. falciparum} infection from \textit{P. falciparum} or mixed-species infections. One problem with the HRP2 tests is the persistence of the HRP2 protein following treatment—an estimated 14 days in a large proportion of people.\textsuperscript{13} This characteristic means that HRP2 tests can show positive results even after clinical symptoms have subsided and parasitemia has disappeared in the host.\textsuperscript{14} Emerging evidence also suggests broad antigenic variation in HRP2 from \textit{P. falciparum} iso-
lates within and between nations, likely influencing the accuracy of HRP2 tests at parasite densities below 500 per microliter blood.\textsuperscript{15}

The ideal malaria diagnostic would always correctly identify whether patients have the disease. In practice, however, all diagnostic methods have some level of false-negative results (negative results in patients with malaria parasites) or false-positive results (positive results in patients without malaria parasites). Under good conditions, RDT products can achieve a low level of false-negative results, similar to levels commonly achieved by microscopy. This is important because false-negative results can lead to failure to treat a potentially fatal disease. To limit malaria treatment costs for governments and patients, RDTs also need to achieve a low level of false-positive results so health workers prescribe expensive ACT treatment only to patients with the disease. The measures of sensitivity (high sensitivity means there is a low level of false-negative results) and specificity (high specificity means there is a low level of false-positive results) are the two most widely used statistics to assess the accuracy of diagnostic tests (for definitions of these measures, see the Glossary). WHO recommends sensitivity of greater than 95\% at parasite densities of 100 per microliter and specificity close to 90\%.\textsuperscript{16} Early field trials of the first commercially available RDT, the ParaSight-F test (Becton Dickinson), found sensitivity of 99\% and specificity of 94\%.\textsuperscript{17}

Environmental conditions can affect the performance of RDTs.\textsuperscript{18} The proteins identified by the tests are denatured by heat, causing some of their original properties to be diminished or eliminated. Exposure to low temperatures, 0\degree C and below, can also cause damage. Finally, high humidity can damage RDTs through the disruption of the nitrocellulose strip. Most manufacturers recommend RDT storage between 4\degree C and 30\degree C, requiring the maintenance of a “cool chain” for storage and distribution.\textsuperscript{19} A cool chain for RDTs has a wider temperature range than a cold chain (the temperature-controlled supply chain for vaccines, ranging from 2\degree to 8\degree C). A major challenge with the cool chain for RDTs is that temperature control is required for extended periods at peripheral units in the health system.\textsuperscript{20} If RDTs are stored at temperatures higher than the recommended limits, their shelf life and diagnostic accuracy will likely be affected. Packaging can help address temperature concerns, and some RDT manufacturers pay more attention to how their products are packaged than others. According to WHO, all tests should be individually packaged in sachets with two layers of foil and should remain sealed until use.\textsuperscript{21} Careful attention to distribution procedures (including temperature-controlled transport and storage) and packaging characteristics of RDT brands is therefore important in ensuring the proper performance of RDTs.
Manufacturers’ prices of RDT products depend in part on the quality of materials used (such as the nitrocellulose strip), internal quality control within the company, and an assessment of what the market can bear. On the international market, the price of most RDT brands in 2006 was between US$0.65 and US$2.50 per test.²² Pan-specific tests are usually about 40% more expensive than products detecting *P. falciparum* only.²³

In most developing countries, governments do not require regulatory approval for diagnostics like malaria RDTs, as they do for drugs and vaccines. Most manufacturers, therefore, choose not to enter the regulatory process for diagnostics. Of the multiple manufacturers producing RDTs in March 2008, only one company had approval from the U.S. Food and Drug Administration (FDA) or European regulatory agencies. This company is Binax, Inc., which worked in partnership with the U.S. Walter Reed Army Institute. Walter Reed wanted an RDT to use for its U.S. military personnel overseas, and since the product would be for purchase within the United States, it required FDA approval. Finding a company that was willing to seek FDA approval was difficult. It took years for Walter Reed to identify an appropriate partner, the American biotechnology firm Binax, a midsized company based in Maine. In looking for a commercial partner, Walter Reed staff learned that most diagnostic companies are small “mom-and-pop” businesses that do not possess the resources, know-how, or experience to navigate the FDA process.²⁴ They also discovered that larger companies were not interested in partnering because the technologies were not viewed as profitable enough for them.

By the early 1990s, laboratory and field trials showing high accuracy of malaria RDT products indicated that the technology could make an important contribution to malaria diagnosis. The RDTs could be particularly valuable for health workers in remote areas without reliable access to microscopy. In the next section, we examine how the technology was introduced globally and the challenges that arose.

**Introduction of Rapid Diagnostic Tests (Phase 2)**

Introduction of malaria RDTs began in the mid-1990s, when the first RDT, ParaSight-F (Becton Dickinson), became commercially available. The first RDT kits detected HRP2 proteins and therefore could only diagnose *P. falciparum* malaria. RDTs detecting other proteins were still being tested in clinical and field studies and were not yet commercially available. The first-to-market HRP2 RDT kits were primarily purchased for national malaria control programs. Government
agencies and non-governmental organizations and others also purchased RDTs for special situations such as complex emergencies, epidemics, and the diagnosis of malaria in returning travelers. The total number of RDT tests sold in the mid- to late 1990s is unknown, but one manufacturer reported selling 3 to 6 million tests in this period.

The early introduction of RDTs was not coordinated by any global organization and was driven by demand from developing-country governments and non-governmental organizations. Manufacturers introduced their products on the market as they became available, with little coordination among producers, potential purchasers, and global actors. In October 1999, a joint WHO/U.S. Agency for International Development (USAID) informal consultation in Geneva began to bring some global coordination to RDT introduction. At this meeting, developers, manufacturers, and potential users of malaria RDTs discussed the current status of the tests as well as future actions, research needs, and standards to ensure widespread access.

Participants in the meeting identified three priority areas for action. First, some of the technical characteristics of RDTs needed improvement, such as reducing false-negative and false-positive results, assistance to end-users (such as clear instructions in appropriate languages), and temperature stability. Second, the meeting called for the establishment of a system of international quality control and quality assurance outside the commercial sector. Participants agreed that the WHO or another agency should act as the global coordinating body for RDTs on quality assurance issues. Quality assurance for RDTs includes all processes for ensuring and sustaining high quality performance, from the manufacture of diagnostic components to their use and interpretation by RDT end-users, health workers in developing countries. The third area for action was the need for multidisciplinary analysis on such issues as the cost of deploying RDTs, the potential for RDTs to reduce malaria mortality and morbidity and delay drug resistance, and the use of diagnostic results by health workers.

Participants also discussed the affordability of RDTs. Many believed that national and global actors perceived product price as the most important obstacle to widespread use. The price was higher for RDTs ($0.65–2.50 per test) than for microscopy ($0.12–0.40 per slide). Participants discussed possible ways to decrease the cost of RDTs for governments, such as reducing distribution costs, import fees, and local taxes through government intervention; promoting technology transfer or local production; and encouraging bulk purchasing. Overall, participants agreed that even at a reduced purchase price of $0.30–0.50 per test,
widespread use of RDTs was unlikely to occur or continue without substantial and sustained external assistance.

In the early 2000s, the use of RDTs increased rapidly as did the number of products available. WHO estimates that procurement nearly doubled from 2000 to 2004. Reported procurement of RDTs in 2005 was 12 million units. WHO notes that these procurement figures are incomplete because of a lack of private-sector data and incomplete reporting by procurement agencies. Global RDT production figures are perhaps a more accurate measure of uptake because manufacturers usually only produce RDTs when they receive procurement orders. Figure 5.2 shows that global RDT production in 2005 was 28 million units. Increased funding for malaria control programs through the Global Fund to Fight AIDS, TB, and Malaria (Global Fund) fueled the rising procurement of RDTs. The number of countries adopting RDT use and budgeting for them in malaria control activities rose from 1 country in 2000 to 32 countries in 2005. In particular, the public sector in countries of South America, Southern Africa, and

Figure 5.2 | Country RDT procurement and manufacturer production data

Note. WHO calculated RDT procurement data from Global Fund to Fight AIDS, Tuberculosis and Malaria documents, the WHO World Malaria Report, UNICEF and MSF procurement information, and the WHO Global Atlas Query. These estimates are incomplete because they lack private-sector data and complete reporting by procurement agencies. RDT production figures may provide a better measure of RDTs obtained in developing countries, as manufacturers usually only produce RDTs when they receive orders. WHO calculated RDT production by taking the total amount of anti-HRP2 antibody supplied to manufacturers and dividing by 0.7 micrograms (the average amount of antibody used per RDT). WHO then calculated total annual RDT production assuming that HRP2 RDTs represent 8% of the RDT market. Data from “Forecasting Global Procurement of Malaria Rapid Diagnostic Tests: Estimates and Uncertainties,” by World Health Organization, available at http://www.wpro.who.int/sites/rdt.
Southeast Asia purchased RDTs on a large scale. The non-governmental organization Médecins Sans Frontières (MSF) also increasingly used RDTs in its operational programs.

In this period of rapid uptake, three challenges associated with RDTs emerged: (1) varying performance of RDT products in field use and study findings, (2) confusing range of products on the market, and (3) limited health worker and patient adoption of malaria diagnostic results. We discuss these challenges next.

**Varying Performance of RDT Products**

Health workers in developing countries using RDT products reported performance problems with some products. In particular, a high level of false-negative results appeared with a range of products and sometimes necessitated product lot replacement.\(^3^3\) The specific reasons for these problems remain unclear. One explanation could be poor quality of product manufacturing, possibly related to overly rapid expansion of production. Poor quality of manufacturing can also result when procurement orders have short delivery times and require manufacturers to increase production at short notice, placing pressure on quality assurance processes.\(^3^4\)

A second reason for performance problems could be that products were exposed to temperatures exceeding the recommended 4°C to 30°C range during transport and storage. One study that assessed temperatures in the distribution chain from manufacturer to villages in Cambodia and the Philippines found that the RDTs were frequently exposed to conditions outside the recommended limits.\(^3^5\) The authors suggested that health workers use cheap and simple evaporative cooling boxes for long-term storage in villages. They also recommended a study of whether vaccine vial monitors (see chapter 7) could be used to indicate product damage due to temperature.

Problems with product performance could also arise from how health workers use RDTs. Often, the absence of clocks and timers in health clinics makes it difficult for health workers to know when to read the test results.\(^3^6\) Reading the test results too late can result in back-flow of blood and buffer appearing as a positive line, leading to false-positive results on previously negative strips.\(^3^7\) Furthermore, using too much blood for an RDT can result in a false-negative result because it becomes difficult to read the positive line on the test.\(^3^8\) Operational difficulties such as these can decrease RDT performance. Health worker use is closely linked to the technical characteristics of the RDT product. Improving product characteristics (such as providing clear instructions and including timers) can improve health worker performance. Better training of health workers...
can also improve product performance and appropriate use of RDTs, as shown in various field trials.\textsuperscript{39}

These problems with product performance created considerable uncertainty among local, national, and global actors about whether and where RDTs should be used in health systems in developing countries. For example, when is it appropriate to use RDTs instead of improving microscopy in a particular setting? In what situations are RDTs cost-effective? Should RDTs be used in both the public and private sectors? Are RDTs effective for self-diagnosis by individuals (such as travelers)?

The publication of a wide range of field and laboratory studies on RDT products, often with conflicting or inconsistent results, added to the uncertainty. Some published studies report diagnostic accuracy for \textit{P. falciparum} well below that required for operational use. The studies also report results on individual products with widely divergent findings.\textsuperscript{40} Publications have not suggested methods for improving RDT performance; rather they have created confusion for potential purchasers and have not provided evidence needed for guiding scaling up. With no global coordinating body in place during early introduction to help make sense of the confusing range of field experiences and research findings, potential purchasers’ decisions about whether and what kind of RDTs to procure were difficult.

\textbf{Confusing Range of Products}

The growing range of commercial products also created confusion among purchasers of malaria RDTs. In the late 1990s, only three tests were available commercially: ParaSight-F (Becton Dickinson), ICT Malaria Pf (ICT Diagnostics), and OptiMAL (Flow, Inc.). By early 2008, 40 branded products could be purchased commercially.\textsuperscript{41} Two of the three original tests, ParaSight-F and ICT Malaria Pf, were no longer available, and many other manufacturers had taken their products off the market. This shifting range of products is not surprising since RDTs are a new technology with a low profit margin. This situation, however, makes the assessment of products by buyers (developing-country governments and non-governmental organizations) both confusing and difficult.

\textbf{Limited Health Worker and Patient Adoption}

Even in contexts where RDTs are available and used, some health workers do not base their malaria treatment decisions on RDT results. As reported by WHO, “Experience indicates that some health care providers treating a patient
with suspected malaria will ignore negative RDT results and give antimalarial drugs regardless.” The same phenomenon occurs with malaria diagnosis by microscopy. A study in Zambia found that results from microscopy had little influence on how clinicians treated patients with fever; from 20 to 54% of patients with negative blood slides were prescribed antimalarial drugs. In this study, despite the availability and use of microscopy for diagnosis, many health workers continued to rely on their personal experience and intuition about clinical diagnosis in making decisions about patient management.

Health workers resist RDT results for multiple reasons, including the varying quality of available products and inconsistent evidence about their accuracy. In addition, RDTs are heat- and humidity-sensitive, and health workers at the clinic level have no way to know about the environmental exposure of kits during transport and storage. Also, when resupply systems are not in place at the national level, stock-outs may occur at health clinics, creating further frustration for health workers. Another explanation is that many health workers have always relied on clinical diagnosis of malaria and find it difficult to change their diagnostic habits. A study in Malawi that assessed two RDTs found that providers were unwilling to believe negative RDT results when their clinical diagnosis was positive for malaria. In this instance, they wished to run a second test to confirm the different result from clinical diagnosis. Finally, health workers may not adopt RDT results because of patient expectations about treatment when presenting with fever. The Malawi study found that patients were happy with RDT diagnostic results when the test confirmed they had malaria; if the results were negative, they were not happy with the product. Public education about the benefits of test-based treatment, whether using microscopy or RDTs, could help health workers use these diagnostic methods in their patient management decisions.

**Emergence of WHO as Coordinating Entity for Scaling Up (Phase 3)**

High product demand and a sufficient number of manufacturers characterized the market for malaria RDTs in the early 2000s. Unlike other technologies analyzed in this book, product champions were not faced with the need to stimulate demand and encourage the entry of new manufacturers. Instead the challenges involved information, product performance, and adoption. Building a global architecture for RDT access—specifically, identifying a global coordinator to provide information, set up quality assurance systems, and bring together partner organizations—was required to address these access barriers.
The WHO/USAID meeting in 1999 recommended that WHO take on a global coordinating role for RDTs. Two years later, in 2001, WHO began an initiative to develop policies defining the place of RDTs in malaria management. The initiative also sought to address the uncertainties that had arisen about the technology and their impacts on adoption and availability. These uncertainties included the role of RDTs in health systems, quality problems, product delivery problems, and perceptions of health workers and patients. Three groups in WHO became involved in this initiative: the Roll Back Malaria Partnership (RBM) and the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), both in Geneva, and the Western Pacific Regional Office (WPRO) of WHO in Manila. In early 2002, WPRO hired David Bell as the “global focal point” for malaria RDTs and charged him with heading the preparation of WHO guidelines on the use of this technology. He sat in WPRO’s office in Manila because at the time this region had the highest use of RDTs.47 By 2006, however, sub-Saharan Africa had become the leading user of RDTs, while Bell remained in Manila.

Early on, Bell and his WHO colleagues planned a large field trial to assess the performance of RDTs. But this field trial never occurred because of its expense (and the lack of budget) and the rapidly changing RDT products. The rapid turnover of products in the global market meant that those tested in the field trial would probably be irrelevant by the end of the trial.48 Bell decided to shift his focus to quality assurance issues because of increasing reports about complications in field use. A meeting on Field Trials and Quality Assurance on Malaria Rapid Diagnostics Tests (funded by USAID, the U.K. Department for International Development, and Australian AID) was held at WHO’s WPRO office in Manila in January 2003 to assess progress since the 1999 meeting and consider ways forward. In the meeting, participants emphasized that quality assurance processes enhance the value of RDTs because they provide “the evidence necessary to permit greater reliance on RDT results as a guide to treatment.”49

Participants at the 2003 meeting recognized the “limited progress” in addressing the priorities identified in 1999 and “some confusion as to WHO’s position in addressing them.”50 To focus WHO’s position, Bell and his WHO colleagues moved forward on three strategies.

- **Policy development**: Specify policy for when and where RDTs should be used
- **Information dissemination**: Provide information about RDT products and suppliers
- **Quality assurance**: Establish quality assurance mechanisms to ensure performance of RDT products
Below we discuss these strategies and progress on them.

**Policy Development**

WHO efforts at policy development helped shape global consensus on RDT adoption by specifying when and where RDTs should be used. The policy states that the tests should be used as a guide for decisions on the presence of clinically significant malaria infection, particularly when microscopy is not available. According to the policy, RDTs can improve malaria management if: (1) a clear plan of action has been prepared to deal with the test results (i.e., drug treatment or appropriate further investigation), (2) a clear benefit is demonstrated in health outcomes, (3) the RDTs are affordable, and (4) adequate systems exist to ensure RDTs are in good condition and are used correctly. Global experts also recognized that microscopy must remain an important tool for patient management because of its many diagnostic applications and that microscopy should be supported where possible. WHO policy therefore specifies that RDTs should be used in areas where good quality microscopy does not exist or cannot be maintained.

WHO staff and other technical experts also sought consensus on the role of RDTs in areas of high malaria transmission. In these areas, people acquire immunity to malaria after continued exposure to malaria parasites over time. This immunity protects most people from the severe effects of the disease, though not complete protection from malaria parasites. As a result, in high-transmission areas, children under five years are most at risk of malaria mortality and acute morbidity, while individuals over five years are relatively protected against the disease. Consequently, WHO policy states that in high transmission areas, all children under five years with a clinical suspicion of malaria (i.e., with fever) should be treated presumptively rather than tested with RDTs or microscopy. This policy recognizes that the mortality risk of misdiagnosis with RDTs (from a false-negative result) exceeds the costs and risks of overtreatment (from a false-positive result) that can occur in clinical diagnosis. For children over five and adults, however, WHO recommends that treatment only be provided following parasitological diagnosis, either from microscopy or RDTs, in order to reduce the wastage of malaria treatments.

**Information**

To address the problem that potential RDT purchasers lack information about the range of products available, Bell and his WHO colleagues have undertaken several activities. First, they developed a website with information on trials, manufacturers, and large-scale users of RDTs (http://www.wpro.who.int/rdt). The
website improves information flows and communication among end-users of RDTs (health workers), researchers, purchasers, and manufacturers, and assists policy development.\(^55\)

WHO staff have also disseminated information to potential purchasers on the range of available RDT products and their manufacturers. WHO, in collaboration with UNICEF, Population Services International, and Management Sciences for Health made this list available in its first report of *Sources and Prices of Selected Products for the Prevention, Diagnosis and Treatment of Malaria*, which provides market information on malaria-related products from manufacturers worldwide.\(^56\) The report gives names, format, and contact details of all diagnostic manufacturers, but the authors do not endorse or evaluate any of the products. Activists from the MSF Access Campaign complained in a January 2005 online discussion forum, E-drug, that listing the RDTs makes it inevitable that readers will assume they are endorsed by WHO and that it is “irresponsible” not to give information on the quality or performance of these tests.\(^57\) In his reply the next day, Bell explained, “It is impossible for WHO to verify the quality of such data at present,” and “WHO is continuing to develop a transparent evidence-based product testing/prequalification system.”\(^58\)

In early 2007, the WHO RDT website began to post a list of products and manufacturers that was regularly updated. The list does not represent WHO endorsement of a specific product but is restricted to manufacturers with evidence of quality manufacturing standards. Also on the website was a report from August 2005 including “interim notes” for national malaria control programs on how to select an RDT in relation to the occurrence of different parasite species. Bell sees it as the organization’s role to advise countries on what kind of product would respond best to the country’s epidemiological situation.\(^59\) For instance, choosing the appropriate RDT depends on whether the purchaser’s region is a low-, moderate-, or high-transmission context and which malaria species (i.e., *P. falciparum* or *P. vivax*) is predominant. These information activities helped to fix some of the market failures that have affected global sales of malaria RDTs, especially as the market expanded rapidly in the past five years.

**Quality Assurance**

A main focus of WHO’s work as the RDT coordinating body has been the development of quality assurance methods for RDT products. WHO’s initiative on quality assurance began in 2002 and functions in collaboration with the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Dis-
eases (TDR) and the Foundation for Innovative New Diagnostics (FIND). These organizations are focusing their work in three areas: product testing, lot testing, and testing at the level of the end-user. In the early years, WHO had limited funding to implement these quality assurance activities; this changed with a December 2006 grant ($9.8 million) from the Bill & Melinda Gates Foundation (through FIND) and funding from Australian AID (through WPRO) and TDR.

WHO and its partners in the quality assurance initiative have prioritized activities that ensure high quality RDTs because they believe this is a precondition to addressing other elements of RDT use, such as health worker use and interpretation. Product testing has been a primary focus. Partners in the initiative have developed a global specimen bank of antigen and parasite samples (housed in the U.S. Centers for Disease Control and Prevention) to support product testing. The laboratory-based product assessment involves testing on sensitivity, specificity, stability, and ease of use. The goal of this product testing is to generate performance data on commercially available RDT products. The data can then be used to guide UN procurement and WHO recommendations to government procurement agencies, and will provide a basis for future WHO prequalification of RDT products. Lot testing (the testing of product conformity to expected standards at time of purchase) has also been conducted by the WHO quality assurance initiative through a network of laboratories around the world.

WHO and partner organizations have also begun quality assurance activities that address health worker use of RDTs. The Quality Assurance Project, funded by USAID, conducted quality-design research in the Philippines and the Lao People’s Democratic Republic. The project sought to develop a generic RDT “job aid” that could be used with different products and in varying cultural contexts. Job aids provide “simplified words and pictures on a card to explain each step in the correct application of the test,” helping to train health workers in contexts with limited resources. These job aids can improve health worker performance, particularly for procedures that involve concrete, predefined steps that must be followed each time the procedure is carried out, as is the case for RDTs.

**Conclusions**

The malaria RDT is a new diagnostic technology whose use has steadily increased since the early 2000s. WHO estimates that RDT procurement will continue to increase and that over 460 million RDTs will be purchased in the next 10 years. In this period of scaling up, the product has faced several challenges that have
affected availability and adoption, especially problems with product performance in field use, a confusing array of products, and resistance by health workers to use test results in patient management (see Table 5.1 for a summary of access barriers and strategies). Unlike most of the other health technologies discussed in this book, the global introduction phase for RDTs did not happen through product advocacy, a global architecture, or carefully planned access phases. Product introduction occurred mainly through commercial channels, beginning with the first malaria RDT product (from Becton Dickinson) in the mid-1990s. Other RDTs appeared in the global market as companies brought their new products forward. Commercial demand for this product was fueled by new external financing for purchasing malaria diagnostics—especially from the Global Fund—leading to a rapid expansion of the RDT market.

The provision of global financing for malaria control thus drove the technological innovation and global adoption of these rapid diagnostic tests. A major challenge for countries that have adopted malaria RDTs is future affordability. How will they build sustainable funding sources to purchase and use RDTs in the future if the external funds (from global aid) start to decline and dry up? As with many health technologies discussed in this book, the world’s poorest countries do not have the internal resources to purchase the product or would be unwilling to purchase the product given other competing demands on their limited national budgets.

Market expansion of malaria RDTs thus occurred before a global-level architecture existed to support the scaling up of the new technology. It took WHO two years after a formal recommendation in 1999 to establish a “global focal point” for RDTs to address the challenges of making the diagnostic widely available. Moreover, the “global focal point” took the form of an individual, David Bell of the WHO regional office in Manila. Product champions for diagnostics within WHO usually consist of a single person, as the diagnostic field tends to be underfunded compared to other types of health technologies. Though Bell is doing an excellent job as the global focal point for RDTs, he initially operated with extremely limited resources. This stands in stark contrast to the increased funding for RDT procurement through the Global Fund, which is expected to continue rising in the near future. This case study emphasizes that for new health technologies for poor countries, well-financed, effective global coordinating bodies are important for addressing market failures (such as information and quality problems) that arise in attempts to provide access. Furthermore, these global coordinating bodies are more effective if they are in place early, before rapid market expansion occurs.
This case study also demonstrates the importance of ensuring a good quality product from manufacturers. This availability issue arises in particular for diagnostics because most developing countries do not require regulatory approval for diagnostics, as is required for drugs and vaccines. As of March 2008, only one malaria RDT product had U.S. FDA approval. Alternative methods to assess quality—through quality assurance and prequalification systems—required time to put in place for malaria RDTs so that purchasers often had little guidance or independent information on the quality or appropriateness of products they considered. The development of assessment systems for product quality thus enables adoption at the global and national levels, as well as by end-users (in this case, health workers), since it helps create knowledge and trust about the diagnostic's performance during field use.

Finding a good partner for production in the private sector was not easy for one product developer of malaria RDTs, the Walter Reed Army institute, because the developer needed to find a company that would take the product to the FDA. After several years, Walter Reed located an appropriate partner in Binax, Inc., a midsized company. This experience shows that many diagnostic companies are unable to work through the FDA process because they do not possess the resources, know-how, or experience. Furthermore, large diagnostic companies may not be interested in partnering for the production of certain health technologies if the technologies are not viewed as sufficiently profitable.

The RDT access story emphasizes the importance of health systems in affecting adoption and use, even for relatively simple technologies such as rapid diagnostics. The operational use of RDTs requires good compliance with certain procedures and, depending on the product, appropriate infrastructure (such as a clock or timer) for producing accurate results. Suitable training, supervision, and clear instructions in the correct languages all influence the quality of RDT use by health workers. Health systems in poor countries thus require various kinds of targeted support if malaria RDTs are to produce the intended result of improved treatment of malaria cases.

Even if high-quality RDTs reach remote clinics and health workers have sufficient training to use the tests appropriately, other problems can affect whether the diagnostic is used in clinical decision-making. Some health workers have been hesitant to accept RDT results because of variable product quality, as well as their own diagnostic habits. Better product information and improved product quality will help address these challenges. But sometimes the problem arises from patient expectations of malaria treatment when presenting with fever. This case study
highlights the importance of in-depth understanding by product developers of the challenges that end-users face. For malaria diagnostic products (and many other health technologies), this may require a paradigm shift in product development to involve people who understand operational realities at the field level in developing countries.65

The story of RDT access is still unfolding in malaria endemic countries around the world. Efforts to promote the product show that just developing a promising new technology is not enough to ensure access. Financing, global coordinating bodies, sufficient information flow, and quality assurance mechanisms all are important factors in promoting the adoption at global, national, and local levels, in assuring the high quality availability of the technology, and in securing the continued financing and affordability that can together ensure ongoing access to new malaria diagnostics. Even if RDTs reach health workers in the periphery of health systems in poor countries, the technology’s influence on malaria mortality and morbidity ultimately depends on how end-users use test results in patient management decisions and on the availability and appropriate use of antimalarial medication. Future access efforts for this product will need to include contextually relevant strategies to address these ongoing challenges.
Table 5.1 | Malaria rapid diagnostic tests access table

<table>
<thead>
<tr>
<th>BARRIER</th>
<th>STRATEGY</th>
<th>SPECIFIC ACTION</th>
</tr>
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<tbody>
<tr>
<td>ARCHITECTURE</td>
<td></td>
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<tr>
<td>Lack of effective global architecture for access in developing countries</td>
<td>Create global coordinator to promote the technology</td>
<td>Global focal point for malaria RDTs established in WHO regional office in Manila; the focal point consists of one individual who has limited funding for access activities</td>
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<tr>
<td>ADOPTION</td>
<td></td>
<td></td>
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<tr>
<td>Lack of global consensus about when and where RDTs should be used (affecting national and end-user adoption)</td>
<td>Promote global dialogue on appropriate policy and develop global policy guidelines</td>
<td>WHO held global meetings to discuss and develop guidelines on when and where RDTs should be used in health systems</td>
</tr>
<tr>
<td></td>
<td>Promote global dialogue on appropriate policy and develop global policy guidelines</td>
<td>WHO collaborated with the Foundation for Innovative New Diagnostics to develop a quality assurance system for malaria RDTs</td>
</tr>
<tr>
<td></td>
<td>Facilitate international agreement on quality assurance system and supply stability</td>
<td>WHO developed “job aids” for health workers to provide simplified and effective training that can be implemented in resource-poor health systems</td>
</tr>
<tr>
<td></td>
<td>Improve training for health workers on RDT use</td>
<td>WHO developed “job aids” for health workers to provide simplified and effective training that can be implemented in resource-poor health systems</td>
</tr>
<tr>
<td></td>
<td>Limited health worker use of RDT results in decisions about patient management and treatment</td>
<td>WHO held global meetings to discuss and develop guidelines on when and where RDTs should be used in health systems</td>
</tr>
<tr>
<td>AFFORDABILITY</td>
<td></td>
<td></td>
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<tr>
<td>High product price (affecting government affordability), especially compared to microscopy</td>
<td>Promote international financing to support government purchases of malaria RDTs</td>
<td>The Global Fund to Fight AIDS, TB and Malaria provided ample funds to countries to support increased procurement of malaria RDTs, thereby fueling market expansion</td>
</tr>
<tr>
<td></td>
<td>Improve forecasting to take advantage of potential economies of scale</td>
<td>WHO has proposed a coordinated procurement and staggered delivery scheme but this is still in planning stages</td>
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</table>
Table 5.1 | Malaria rapid diagnostic tests access table (continued)

<table>
<thead>
<tr>
<th>BARRIER</th>
<th>STRATEGY</th>
<th>SPECIFIC ACTION</th>
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</thead>
<tbody>
<tr>
<td>Poor quality products, leading to performance problems of RDTs</td>
<td>Set up quality assurance system, improve forecasting, and ensure steady supply</td>
<td>WHO collaborated with the Foundation for Innovative New Diagnostics to develop a quality assurance system for malaria RDTs</td>
</tr>
<tr>
<td>Shifting array of products on the global market, creating information problems for purchasers</td>
<td>Create information system on available products and prices</td>
<td>WHO has proposed a coordinated procurement and staggered delivery scheme but this is still in planning stages</td>
</tr>
<tr>
<td>WHO has collaborated with the Foundation for Innovative New Diagnostics to develop a quality assurance system for malaria RDTs</td>
<td>WHO focal point in WPRO (Manila) created website with regularly updated information on products and suppliers</td>
<td></td>
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</tbody>
</table>

Endnotes


2 Roll Back Malaria Partnership.

3 Roll Back Malaria Partnership.


6 World Health Organization, *New Perspectives*.

7 World Health Organization, *New Perspectives*.

Chapter 5: Malaria RDTs

9 World Health Organization, The Use of MRDTs.


11 Kakkilaya; and World Health Organization, New Perspectives.

12 A water-soluble protein, HRP2 is produced by the asexual stages of young (but not mature) gametocytes of \( P. falciparum \). PLDH is a soluble glycolytic enzyme produced by the asexual and sexual stages (gametocytes) of the live parasites and has been found in all four human malaria species. Pan-specific aldolase is an enzyme expressed by the blood stages of \( P. falciparum \) as well as the non-\( P. falciparum \) malaria parasites. Kakkilaya, 2003; World Health Organization, The Role of Laboratory Diagnosis to Support Malaria Disease Management: Focus on the Use of Rapid Diagnostic Tests in Areas of High Transmission (Geneva: WHO, 2006), http://www.who.int/malaria/docs/ReportLABdiagnosis-web.pdf (retrieved February 9, 2007).

13 World Health Organization, The Role of Laboratory Diagnosis.

14 Moody.

15 World Health Organization, The Role of Laboratory Diagnosis.


18 World Health Organization, The Role of Laboratory Diagnosis.


20 Jorgensen.

21 World Health Organization, The Role of Laboratory Diagnosis.

22 World Health Organization, The Role of Laboratory Diagnosis.


24 Interview by author (Laura Frost) with anonymous official, March 31, 2006.

25 World Health Organization, New Perspectives.

26 World Health Organization, New Perspectives.

27 World Health Organization, New Perspectives.

29 World Health Organization, *New Perspectives*.

30 World Health Organization, *New Perspectives*.


32 World Health Organization, “Forecasting Global Procurement.”

33 World Health Organization, *Malaria Rapid Diagnosis*.

34 World Health Organization, “Forecasting Global Procurement.”

35 Jørgensen et al.

36 Interview by author (Laura Frost) with anonymous NGO official, November 15, 2005.

37 World Health Organization, *The Role of Laboratory Diagnosis*.

38 Interview with anonymous NGO official.


40 World Health Organization, *Malaria Rapid Diagnosis*.

41 World Health Organization, “Forecasting Global Procurement.”


44 World Health Organization, *The Role of Laboratory Diagnosis*.


46 Tavrow et al.

47 Interview by researcher (Jennifer Nanni) with anonymous official, October 28, 2005.

48 Interview with anonymous official, October 28, 2005.
50 World Health Organization, *Malaria Rapid Diagnosis*, 3.
51 World Health Organization, *The Use of MRDTs*.
52 World Health Organization, *The Use of MRDTs*.
53 World Health Organization, *The Role of Laboratory Diagnosis*.
54 World Health Organization, *The Role of Laboratory Diagnosis*.
59 Interview with anonymous official, October 28, 2005.
60 World Health Organization and TDR, *Towards Quality Testing of Malaria Rapid Diagnostic Tests*.
63 World Health Organization, “Forecasting Global Procurement.”
64 Interview by author (Laura Frost) with anonymous official, January 4, 2007.
65 Interview with anonymous NGO official.