CASE STUDY

Malaria Rapid Diagnostic Tests in the Peruvian Amazon: A Promising Start and an Uncertain Future

Submitted to:
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Case Study

Malaria Rapid Diagnostic Tests in the Peruvian Amazon: A Promising Start and an Uncertain Future

Prepared for the Bill & Melinda Gates Foundation
Seattle, Washington

Steven A. Harvey, PhD

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Center for Human Services: The CHS mission is to help clients meet today’s challenges and take advantage of tomorrow’s opportunities by providing a comprehensive array of education, training, advocacy, and health-related programs and services.


Acknowledgements: I am especially grateful for the tremendous assistance and thoughtful comments provided by Dr. Angel Rosas and Dr. Hugo Rodriguez of PAMAFRO and Dr. Jaime Chang of USAID. Without their help this case study would not have been possible. However, I take full responsibility for any errors of analysis or interpretation. SAH

For more information on this report, please contact Steven A. Harvey at sharvey@urc-chs.com.
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<th>Description</th>
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<tr>
<td>AMI</td>
<td>Amazon Malaria Initiative</td>
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<tr>
<td>CDC</td>
<td>United States Centers for Disease Control and Prevention</td>
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<tr>
<td>DIRESA</td>
<td>Regional Directorate of Health</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
</tr>
<tr>
<td>HRP2</td>
<td>Histidine-rich protein 2, an antigen useful as a marker for <em>P. falciparum</em> infection</td>
</tr>
<tr>
<td>INS</td>
<td><em>Instituto Nacional de Salud</em>, the Peruvian National Institute of Health</td>
</tr>
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<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>NMCP</td>
<td>National Malaria Control Program</td>
</tr>
<tr>
<td>NMRCRD</td>
<td>Naval Medical Research Center Detachment in Lima, Peru</td>
</tr>
<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
</tr>
<tr>
<td>PAMAFRO</td>
<td>Global Fund project to control malaria in the border areas of the Andean region (Spanish acronym)</td>
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<tr>
<td>pLDH</td>
<td>Protein lactate dehydrogenase, an antigen useful as a marker for <em>Plasmodium spp.</em> infection</td>
</tr>
<tr>
<td>RAVREDA</td>
<td><em>Red Amazónica de Vigilancia de la Resistencia a los Antimaláricos</em> (Amazon network for surveillance of antimalarial drug resistance)</td>
</tr>
<tr>
<td>RDT</td>
<td>Rapid diagnostic test</td>
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<tr>
<td>SP</td>
<td>Sulfadoxine-pyrimethamine</td>
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<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<td>WHO</td>
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ABSTRACT

Malaria was nearly eliminated from the Peruvian Amazon during the global eradication campaign of the 1960s and 70s. When significant transmission returned in the mid-1990s, the Peruvian Ministry of Health (MOH) established a network of volunteer community health workers ("promotores de salud") to provide diagnostic and treatment services in communities with limited access to health facilities. The promotores were trained to prepare blood slides in the community, then send or bring these slides to the nearest health facility with the capacity to read them. This system provided better diagnostic access to remote villages, but due to the distances between these villages and health facilities with the capacity to read the slides, febrile patients suspected of having malaria still had to wait as much as a week for their results. When malaria rapid diagnostic tests (RDTs) became available, the Ministry, with support from bilateral and multilateral donors, pilot tested their use by promotores as a strategy for reducing the time between diagnosis and result. Between 1998 and 2003, the MOH – in collaboration with the Peruvian National Institute of Health (INS), the U.S. Agency for International Development (USAID), and others – carried out four studies to confirm the efficacy, effectiveness, acceptability, and effects on time from onset of symptoms to treatment. Over this period of time, proponents of community-based RDT use were able to win the support of key decision-makers within the MOH. As a result, the MOH decided to implement the program in 2004 with little to no opposition. Funding for procurement of RDTs during testing stages was provided first by Proyecto Vigía, a collaborative project between USAID and the MOH. The MOH made an initial procurement of RDTs in 2004–2005. PAMAFRO (a multilateral Global Fund project to control malaria in the border areas of the Andean region), made an additional procurement in 2007. However, the program has experienced many operating difficulties since being officially implemented in 2004. Among the issues that threaten sustainability are lack of a dedicated funding stream, problems with logistics, and the absence of policies to guide RDT selection, procurement, transport, use, and quality control. Lack of official guidance on training and case management for patients diagnosed with rapid tests is an additional problem. This case study demonstrates that in addition to effective technology and political will, a key factor in the successful uptake of a new diagnostic test is a health system with the mechanical and managerial infrastructure to support sustainable routine implementation.
FOREWORD

The spread of infectious diseases is a critical global health concern. Despite recent progress in the availability of powerful drugs, many treatable infectious diseases continue to exact a terrible toll worldwide, particularly in developing countries. The World Health Organization (WHO) estimates respiratory disease to be a leading cause of infant death in countries with high childhood mortality rates. Malaria is estimated to cause 1–3 million deaths and 500 million–5 billion episodes of clinical illness, mostly in Africa. In 2005, an estimated 2.3 million children worldwide were living with HIV/AIDS, 2 million of them in sub-Saharan Africa. About a third of the world’s population is infected with the tuberculosis (TB) bacillus, and as many as 2 million people die of the disease each year. Among people with HIV/AIDS, TB is the leading cause of death. The highest rates of TB are in some of the world’s poorest countries, exacting an enormous economic toll. Likewise, sexually transmitted infections (STIs), such as gonorrhea and chlamydia, pose significant health risks, with prevalence rates as high as 40% even in low risk populations in Africa. Syphilis remains a major health problem during pregnancy, with an estimated prevalence rate as high as 18% among pregnant women attending antenatal centers in Africa. Diarrheal diseases affect an estimated 1–4 billion children under age five in developing countries, resulting in about 2.5 million deaths (85% of which occur in the poorest parts of the world); in some countries these diseases account for more than 20% of all deaths in children under age five.

To make treatment accessible, it is essential to identify those who require treatment; to administer and monitor appropriate treatment; and, importantly, to prevent overtreatment, which can cause the spread of drug-resistant microbes. At present, the diagnostic tools used in developing countries have many limitations and are largely inadequate for addressing health needs. There is a growing need to develop and test better and more accessible diagnostic tools for several infectious diseases, tools that would be particularly tailored to developing-country realities. In response, the Global Health Diagnostics Forum of the Bill and Melinda Gates Foundation recognized in 2004 the importance of access to appropriate and accurate diagnostic tools to evaluate and improve global health. The forum recommended focusing on six diseases or syndromes that cause among the highest disease burdens in the developing world: acute lower respiratory infections (ALRI), HIV/AIDS, diarrheal diseases, malaria, TB, and sexually transmitted infections.

In 2007 the Gates Foundation awarded a grant to the Center for Human Services (CHS) to research potential demand for rapid diagnostic tests (RDTs) for five of these disease areas: ALRI, HIV, malaria, TB, and STIs. Research on potential demand for diarrheal disease diagnostics was deferred pending further technical and clinical discussion. CHS is advancing the Gates Foundation’s vision of accelerating access to existing vaccines, drugs, and other tools to fight diseases that disproportionately affect developing countries and of identifying new health technologies that would be effective, affordable, and practical in resource-poor settings in the developing world.

As one part of this grant, CHS developed four case studies examining past experiences with the introduction of new diagnostic technologies. These studies explore factors that have helped facilitate or hamper the uptake of new diagnostic tests in specific settings. They offer lessons that may help smooth the way for introducing new diagnostics in the future. This study examines introduction of malaria rapid diagnostic tests at the community level in the Peruvian Amazon. The other three case studies in this series include:

- Discussion about the adoption of rapid syphilis tests in Tanzania,
- Development and introduction of microscopic drug susceptibility testing to diagnose TB and test for multi-drug resistant TB in Peru,
- Use of STI diagnostics in the private sector in India.

CHS also conducted research to evaluate potential demand for new diagnostic tests and identify factors that might affect that demand among consumers and within the public, private for-profit, and private non-profit health sectors. The research objectives were to:
The research includes six willingness to pay reports, one for each diagnostic in the study:

- A test to screen for syphilis in pregnant women as a routine part of antenatal care;
- A test for gonorrhea and chlamydia in high risk asymptomatic populations;
- A test for (HIV) in children under 18 months of age;
- A test for active TB in HIV-positive and HIV-negative patients;
- A test for malaria in children under age five; and
- A test for bacterial ALRI in children under age five.

The study addressed syphilis separately from gonorrhea and chlamydia because the target population for syphilis screening (pregnant women) was different from that for gonorrhea and chlamydia (high-risk asymptomatic populations such as commercial sex workers).

The project covers four countries: Benin, India, Peru, and Tanzania. Results for Benin, Peru, and Tanzania are presented as part of the report for each diagnostic. Each report provides country demographic and epidemiological profiles along with information on the current standard of diagnosis. Information for the study comes from health worker interviews and consumer surveys and focus groups, as well as from literature. The interviews provide data on the degree to which health professionals at different management and service-provider levels are satisfied with the current diagnostic standard or see a need for a newer technology. The surveys and focus groups offer perspectives on consumer willingness to pay, factors that influence willingness to pay, and consumer preferences about different types of diagnostic samples (e.g., blood, urine, sputum, etc.). CHS is conducting additional research in India and will publish those results separately.

For more information on the project and for copies of other reports, please contact the Bill & Melinda Gates Foundation or visit its Web site: http://www.gatesfoundation.org.
Figure 1: Malaria Transmission in Peru

INTRODUCTION

An estimated 3 billion people worldwide are at risk of malaria, and about 250 million are infected annually. For decades, the gold standard for parasite-based diagnosis of malaria has been examination of a blood slide by conventional light microscopy. Unfortunately, many developing countries lack both the physical and human resources to support microscopy, particularly in rural areas where access to formal health facilities is difficult. Since their appearance in the mid-1990s, malaria rapid diagnostic tests (RDTs) have offered an increasingly attractive alternative. RDTs detect one of three parasite antigens found in the blood of an infected individual: For falciparum malaria only there is histidine-rich protein 2 (HRP2); for both falciparum and non-falciparum malaria there is plasmodium lactate dehydrogenase (pLDH) or aldolase. All work in a similar fashion: A drop of blood is collected from the febrile patient and deposited at one end of a nitrocellulose strip. A small quantity of buffer is added to wash the blood up the strip past a line of dye-labeled antibody. If malaria antigens are present in the patient’s blood, they bind to the dye-labeled antibody, turning it a color (usually red), thus indicating a positive result. If malaria antigens are not present, the blood washes past the antibody line leaving it white and indicating a negative result. Figure 2 illustrates that process.

Figure 2: Schematic of a lateral flow malaria rapid diagnostic test

1. Blood, then buffer are added to one end of the strip and begin to wick their way towards the two pre-imprinted lines. The first line, marked “T,” contains the dyed antibody that will turn red if the patient has malaria. The second line, marked “C,” is a quality control line that will turn red if the test is functioning correctly.

2. At about 3 minutes, blood and buffer continue to wick their way toward the test and control lines.

3. At about 10-12 minutes, blood crosses the test line, “T,” which turns red, indicating a positive result (patient has malaria).

4. At about 15 minutes, the blood has collected at the far end of the strip. The red line marked “T” indicates that the patient has malaria. The red line marked “C” indicates that the test is functioning correctly.

Peru took an early interest in malaria RDTs. Initial field test results for Becton Dickinson’s ParaSight® F – one of the first commercially available malaria rapid tests – were published between 1993 and 1995.
By 1998, the Peruvian Ministry of Health (MOH) and the Peruvian National Institute of Health (INS) were conducting efficacy tests of both ParaSight® and OptiMAL® with support from the U.S. Agency for International Development (USAID), the U.S. Naval Medical Research Center Detachment, Lima (NMRCRD), Walter Reed Army Medical Center, and the U.S. Centers for Disease Control and Prevention (CDC).9,10,11

Over the next five years, these same partners carried out a carefully developed series of studies that, taken together, built a solid evidence base for the introduction and scale-up of community-based RDT use in the Peruvian Amazon. The partners worked strategically to build support by involving key Ministry of Health decision-makers in planning the research and by ensuring them early access to results. Thus those responsible for malaria control in Peru’s Amazon region were able to implement community-based RDT use with little political opposition. The program made impressive strides toward achieving its objective: improving malaria case management in remote areas by providing opportune diagnosis that dramatically reduces the time elapsed from onset of symptoms to initiation of treatment. Despite its popularity and success, however, the program has suffered a number of setbacks due to problems with procurement, logistics, and finance. As external donor support dries up, the program is struggling to find a way forward. Peru’s RDT experience is the story of a new technology that offers a significant public health benefit, has attracted widespread evidence-based support, but now faces an uncertain future. This case study tells that story.

METHODS

This study is based on in-depth interviews with key informants, a review of project and government documents, and a review of appropriate literature in English and Spanish. The appendix includes the list of people interviewed, along with their titles, institutional affiliations, and interview dates. However, due to the sensitive nature of some comments, interviewees are not quoted by name.

BACKGROUND

Malaria was nearly eliminated from the Peruvian Amazon during the global eradication campaign of the 1960s and ’70s. While a handful of cases occurred in the 1980s and early ’90s, the disease did not return as a major health problem until around 1994. In that year, Loreto, the largest and most populous department in the Peruvian Amazon, reported a total of 16,332 cases, 49.6% of them Plasmodium vivax and 50.4% Plasmodium falciparum. An epidemic outbreak occurred in 1997 with 121,224 cases reported (55.2% P. vivax, 44.8% P. falciparum).12 Malaria transmission is unstable in the region, both over the course of a single year and from one year to another. In most years, vivax malaria accounts for 65–75% of cases, but occasionally falciparum cases equal or even slightly exceed vivax, as occurred in 1994. Malaria-related mortality is low. Unlike Africa, where most deaths occur among children under five, those most at risk of dying are the immunocompromised, the elderly, and unexposed visitors from outside the region. Because case fatality rates are low, malaria transmission in Peru (and in Latin America generally) receives less global attention than it does in Africa. But Peru’s government and population consider it one of their most serious health problems, and studies show that malaria has a major economic impact on those affected and on public expenditures.13 Both vivax and falciparum malaria have developed resistance to chloroquine and sulfadoxine-pyrimethamine (SP) in certain zones within the region, and in these areas the MOH has changed first-line treatment to mefloquine plus artesunate.

Prompt malaria diagnosis is essential to both successful treatment and effective control. The World Health Organization (WHO) and the Roll Back Malaria Partnership recommend that treatment based on parasitological diagnosis be provided within one day of the onset of symptoms.14 Parasitological diagnosis in Peru is important since a relatively small percentage of febrile patients actually have malaria. MOH surveillance statistics from 1998 show a total of 247,229 confirmed cases nationwide out of about 2 million patients tested.9 In Loreto, about 18% of febrile patients were confirmed to have malaria during the same period. Presumptive treatment would result in a tremendous overuse of antimalarials,
representing an enormous unnecessary expense to the Ministry. Such overuse might also speed
development of antimalarial resistance. As early as 1999, up to 30% of *P. falciparum* cases in some areas
of Loreto were resistant to both chloroquine and SP. Moreover, transmission of both *P. vivax* and *P. falciparum* makes parasite-based diagnosis necessary to ensure correct treatment.

**COMMUNITY-BASED MALARIA DIAGNOSIS**

Since the re-emergence of significant malaria transmission, the Peruvian health system has relied upon microscopy for diagnosis. Because the population in Peru’s Amazon region is widely dispersed and transportation is often difficult, access to microscopy-capable health facilities is limited. For residents of some villages, the nearest health center may be hours or even days away by canoe or on foot. To provide the most opportune diagnosis and treatment possible at the community level, the MOH began recruiting a network of volunteer community health workers (*promotores de salud*) as early as 1994. *Promotores* are village residents who receive basic training in malaria prevention and control. They organize activities such as bed net promotion, clearing of larval breeding sites, and health education campaigns for other residents on reducing exposure to malaria and seeking appropriate attention for fevers. By 2001, the network had grown to 850 *promotores* linked to 329 health facilities.

**MICROSCOPY AT THE COMMUNITY LEVEL**

From the program’s inception, *promotores* were trained to prepare blood slides for malaria diagnosis and treat malaria patients. But only 137 of the 329 health facilities in the regional malaria network had a working microscope; even fewer had a trained microscopist. Thus, while preparing blood slides at the village level facilitated opportune diagnosis in theory, transporting them to be read became a significant barrier. Transportation options were limited and much less than ideal. The patient or a family member could take the slide to a health center, the *promotor* could take it to a health center, or the *promotor* or patient could send it via some form of public transportation: a passing boat if the village was near a river or a passing bus or car if the village was near a road. Having a patient transport his or her own slide would defeat the purpose of village-based diagnosis since the patient might just as well have gone directly to the facility. *Promotores* are volunteers, elected by the village or recruited by the doctor in charge of the nearest health center. Like other village residents, most are subsistence farmers. Carrying a slide to the nearest microscopy-capable facility often means losing many hours of work in the fields. This is not an undue hardship for a *promotor* dealing with an occasional patient, but in high transmission season when a *promotor* might see multiple patients per day and many in a week, leaving the fields daily to transport slides would quickly jeopardize the economic well-being of the *promotor* and his or her family. On the other hand, allowing slides to accumulate for some time and transporting them periodically – perhaps weekly – would also defeat the purpose of village-based diagnosis.

The experience described by one *promotor* interviewed about the program provides a concrete illustration. This *promotor* lives in San Carlos, a village of about 100 people located on the banks of the Itaya River about 20 or 25 km from Iquitos, the region’s largest city. There are two forms of access to San Carlos: A cargo boat passes by the village twice daily, bringing goods up-river from the city in the morning and returning with agricultural products in the afternoon. The boat trip takes three to four hours. The second form of access involves walking out to the nearest road, about 1½ hours away. From this road public vans pass every 15 or 20 minutes during daylight hours en route to the city. The van ride takes another 30 to 45 minutes. There are two health centers about an hour from San Carlos, one down river in the village of Munich, accessible by canoe, the other in the village of Varillal, about a 10-minute van ride from where the footpath meets the road. Munich has no microscope. Varillal has a microscope, but at the time of this interview had not had a microscopist for some time and had little prospect of finding one. Thus the closest facility with capacity to read a thick smear was the San Juan Health Center, about a half hour from the entrance to the road.
The *promotor* related the story of a villager who had come to see him one Friday evening. The villager had begun to feel feverish the previous night. Thinking it might be due to overexertion or a passing virus, he did not seek immediate attention. But by morning, the villager began to suspect he might have malaria and that evening went to see the *promotor*. The *promotor* prepared a thick smear, but the afternoon boat had already passed, and it was too dark to walk out to the road. The San Juan Health Center is open on Saturdays, but the microscopist does not work over the weekend. When the *promotor* arrived with the slide on Monday, there was a backlog of slides to be read, so he was told to return the following day for results. He was able to obtain results Tuesday afternoon and arrived back in the village in the early evening with the diagnosis. Five days had passed from the time the patient noticed the first signs of fever to the time he received a diagnosis. The remarkable fact about this story is that San Carlos is relatively close to Iquitos. Many villages in the region are much more isolated and thus have much greater difficulty accessing services.

**Figure 3: Transporting slides to a microscopy-capable health facility can be difficult.**

Research by the MOH and USAID confirms the diagnostic delays illustrated by this story. In a September 2001 study, the MOH collected data on 200 villagers who had experienced fever and sought malaria diagnosis during the four previous weeks. The villagers were residents of eight communities drawn from among the 61 with the region’s highest malaria incidence. The study measured a total of three time intervals: from onset of symptoms to exam by the *promotor*, from exam by the *promotor* to receipt of the diagnostic result, and from receipt of the diagnostic result to initiation of treatment. The villages were located one-half to three hours from the nearest health center capable of reading a blood slide, assuming transport was immediately available. As in San Carlos, however, motorboats and minibuses pass infrequently. Results demonstrated that the average time between preparation of the
blood slide and receipt of the diagnosis was three days.\textsuperscript{15,16} In more distant villages, the time elapsed could be much greater.

**Rapid Diagnostic Tests**

Given the difficulties in achieving opportune diagnosis via microscopy, officials within the national malaria control program (NMCP), the Loreto Regional Directorate of Health (DIRESA Loreto), INS, USAID, and NMRCD began discussing alternatives as early as 1997 or 1998. A catalyst for these discussions was *Proyecto Vigía*, a joint initiative of the MOH and USAID established to support control of emerging and re-emerging infectious diseases.

**Choosing a test**

There are currently some 60 different RDT brands on the market, and about 200 different tests, at a wide range of prices. This has led to confusion among potential RDT buyers who have difficulty sorting out the best combination of test characteristics, including price, sensitivity and specificity, stability in high heat and humidity, and shelf-life. WHO does not yet have a prequalification program for RDTs, but recently released the report from its first round of product testing, carried out in 2008.\textsuperscript{17}

There were only a few choices when Peru began looking at RDTs in the late 1990s, and these were limited to HRP2 and pLDH: The first field trial of an aldolase test was reported in 1999.\textsuperscript{18,19} After weighing the pros and cons of HRP2 and pLDH, the program opted for the latter. The HRP2 test available at the time had a slightly higher sensitivity (95% versus 85–90%), but the program preferred pLDH for two reasons. First, it offered the advantage of being able to both detect and distinguish between falciparum and non-falciparum malaria. Given the high disease burden caused by vivax malaria in the region, differentiating *P. vivax* from *P. falciparum* was an important characteristic. Second, the HRP2 antigen persists in the blood of a treated patient for up to two weeks after parasite clearance.\textsuperscript{6} This makes HRP2 ineffective for measuring treatment failure – also an important characteristic in an area of growing antimalarial resistance. By contrast, pLDH clears more rapidly, meaning that a positive result indicates a current rather than past infection.\textsuperscript{20,21} Thus the INS and its partners selected OptiMAL\textsuperscript{®}, the pLDH test available at the time, for their 1999 efficacy trial.\textsuperscript{9,10} The program continues to use later generations of that test to this day.

**Laying the groundwork**

The 1999 efficacy trial was the first in a series of studies conducted as a partnership among *Proyecto Vigía*, the INS, the NMCP, NMRCD, and the DIRESA Loreto. It and subsequent studies laid the groundwork for evidence-based promotion of RDT use in Peru’s Amazon region. For the first study, the partners recruited 20 *promotores* from 20 communities along the upper Nanay, Momon, and Amazon River Basins. The study was conducted in two phases. First, each *promotor* prepared 30 rapid tests in the regional reference laboratory in Iquitos using blood samples with known parasite densities. Then each was assigned to one of four health facilities within the city of Iquitos and carried out rapid tests on approximately 20 febrile patients. In addition to the rapid test, *promotores* prepared two thick smears for each patient. One smear was read by a trained microscopist at the reference laboratory in Iquitos; the second was sent to Lima to be read by an expert microscopist at the INS. For the first phase of the study, *promotores* achieved a sensitivity of 88.5% and a specificity of 90.1% compared to tests on the same samples carried out by laboratory technicians. In the second phase, performance improved: the *promotores* achieved a sensitivity of 94.4% and a specificity of 96.5% compared to tests on the same patients carried out by the technicians.\textsuperscript{9} Results of the study were published in the same year as a report by *Proyecto Vigía*, then published as a journal article in 2004.\textsuperscript{9,10}

The 1999 report was followed by the previously cited September 2001 study documenting delays between preparation of a thick smear and receipt of microscopy results. That study demonstrated not only that diagnostic delays were common, but also that these delays were the most important contributor to the total
time elapsed between onset of symptoms and initiation of treatment. To address the issue of long delays between the patient’s initial visit to the *promotor* and receipt of the microscopic diagnosis, the MOH, INS, USAID, and NMRCD conducted a longitudinal study from September 2001 to May 2003 in 50 communities in the Nanay River Basin and along the Iquitos-Nauta highway. Communities were selected based on their high incidence of malaria. From the study’s launch through July 2002, the MOH and partners trained and equipped *promotores* in RDT use and carried out information, education, and communication (IEC) activities aimed at winning community acceptance of the approach. Then from August 2002 to May 2003, the study team carried out a community trial of RDT use by *promotores*. One objective of this 10-month surveillance was to track time elapsed in hours from onset of symptoms to initiation of treatment. Table 1, adapted from reports by *Proyecto Vigía*, compares the results to the earlier measure of time elapsed during diagnosis by microscopy. The study results do not present statistical tests of significance, but the median time between initial visit to the *promotor* and receipt of diagnostic results dropped from 68 hours to 20 minutes. As shown in Table 2, use of rapid tests led to significant increases in the percentage of confirmed malaria cases treated within two days from the onset of symptoms, the percentage of patients receiving treatment appropriate to the parasite species (*P. falciparum* or *P. vivax*) and the number of *P. falciparum* patients receiving correct treatment. RDT use also led to a significant decrease in the percentage of patients receiving treatment without a confirmed diagnosis.

**Table 1. Elapsed time in hours from onset of symptoms to initiation of treatment (by stage and type of diagnostic)**

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<td></td>
<td>Mean</td>
<td>Median</td>
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<tr>
<td>1. From onset of symptoms to contact with <em>promotor</em></td>
<td>32</td>
<td>41</td>
</tr>
<tr>
<td>2. From contact with <em>promotor</em> to receipt of diagnostic result</td>
<td>89</td>
<td>68</td>
</tr>
<tr>
<td>3. From obtaining result to start of treatment</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>4. From onset of symptoms to start of treatment</td>
<td>110</td>
<td>69</td>
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*Adapted from *Proyecto Vigía* reports.*

At an evaluative workshop held in July 2003, 30 local health workers involved in various aspects of the trial spent two days reviewing results and discussing what factors facilitated or served as obstacles to effective community-based RDT use. Factors identified by the group as playing a favorable role in reducing time between initial visit and diagnosis included the *promotor*’s geographical and social accessibility to other members of the community, the immediate availability of appropriate treatment, the *promotor*’s round-the-clock availability, and the rapidity of the test itself. Factors identified as obstacles included supply stock-outs, some level of community distrust generated by false negative results, the test’s inability to detect low levels of parasitemia, and the *promotor*’s limited skill at taking finger stick blood samples and reading test results correctly. Participants also noted that even with RDTs, malaria diagnosis continued to create a conflict between the *promotor*’s community responsibilities and his or her income-earning activities. In addition, there were some quality control problems with tests, arrivals of test stock shortly before their expiration dates, and inadequate storage of test stock by *promotores*. 
Some political problems were also evident. Many *promotores* had limited experience working with community organizations and struggled to gain the trust of community leaders. Some community leaders and residents assumed – incorrectly – that the *promotores* were being paid for their efforts; this created jealousy. Evaluation participants recommended that the MOH avoid similar problems in the future by providing a more formal introduction of the *promotor* to the community and offering more frequent support and supervision. Unfortunately, the MOH had insufficient staff to provide such support.

### Table 2. Percentage of patients receiving appropriate treatment by type of diagnostic*

<table>
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<th>Indicator</th>
<th>Microscopy</th>
<th>Rapid test</th>
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<tbody>
<tr>
<td>Confirmed malaria cases treated within ≤ 2 days from onset of symptoms</td>
<td>15.5 (11/71)</td>
<td>54.9 (50/91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Febrile patients receiving antimalarials without confirmed parasite-based diagnosis</td>
<td>20.5 (41/200)</td>
<td>0.5 (1/205)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients receiving appropriate treatment for parasite species</td>
<td>26.7 (19/71)</td>
<td>83.5 (76/91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>P. falciparum</em> patients receiving appropriate treatment</td>
<td>5.3 (1/19)</td>
<td>73.1 (19/26)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adapted from *Proyecto Vigía* report.*

Evaluation participants recommended continued and expanded use of RDTs at the community level, but cautioned that such a program would be sustainable only if the MOH were able to overcome political, supervisory, and logistical obstacles. Specifically, participating health workers urged more attention to training and supervision, to ensuring a stable supply of both test kits and antimalarial medications, and to building community awareness of and confidence in the RDT program.

### Implementation

By 2003, RDT proponents had amassed considerable evidence supporting the value of community-based malaria diagnosis using rapid tests. Their series of studies had confirmed the efficacy of the diagnostic for use with local parasite strains, documented the delays caused by microscopy and the time saved by RDT use, and demonstrated that *promotores* – volunteer community agents with limited training – could use the tests safely and effectively. An analysis of risk factors for severe malaria highlighted delayed diagnosis as a key contributor; RDT use could significantly reduce that risk. Finally, a study modeling cost-effectiveness of different diagnostic approaches under different scenarios strongly suggested that RDT use would generate savings for the MOH by greatly reducing overtreatment. Additional savings would come from reducing complicated cases since RDT-based treatment would be more rapid and more likely to be correct for the parasite species. Based on this evidence, the MOH decided to implement community-based RDT use as a norm in communities with limited access to microscopy. In 2004 and 2005, the MOH purchased approximately 40,000 OptiMAL tests for use in six Amazonian departments including Loreto as well as sites along the northern Pacific coast.

Despite the years of careful preparation by RDT proponents, the roll-out did not go particularly smoothly. The INS carried out training and supervision of health workers and *promotores*, but no evaluation was completed, so there is no summary of this initial experience that could inform further scale-up. Procurement took longer than expected. One official interviewed for this study explained that, like many producers of lateral flow rapid tests, OptiMAL’s manufacturer does not maintain an inventory of tests but produces them to order. This makes sense from the perspective of maximizing product viability: Once assembled the test has a shelf life of only about 24 months. But the made-to-order manufacturing led to several months of delay from the signing of the contract to arrival of the tests in country. Once in country, the tests have to be cleared through customs, undergo quality testing, and then await transport from Lima to Iquitos. Since there are no roads connecting the
two cities, transport is via air or river. As shown in Table 3, a year or more can elapse between the time the order is placed and the time RDTs arrive in the hands of the promotor. Beyond the issue of moving tests from the manufacturer to the port and from the port to the end user, allocation of appropriate quantities to different end users was also a problem. In the words of one program manager, “distribution through the Ministry of Health was a disaster. It’s important for sustainability [to set up distribution that way], but it didn’t work well at all: Tests got to where they weren’t needed and didn’t get to where they were needed.”

Table 3. Time and routing of malaria RDTs: From signing of contract to use by promotor

<table>
<thead>
<tr>
<th>Step</th>
<th>Time elapsed</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>From the time the order is placed to the time it is shipped</td>
<td>3–6 months</td>
<td></td>
</tr>
<tr>
<td>From the time order is shipped to arrival at the Port of Callao</td>
<td>2–3 months</td>
<td></td>
</tr>
<tr>
<td>Customs clearance after arrival</td>
<td>2 weeks</td>
<td></td>
</tr>
<tr>
<td>Transported to Lima warehouse for quality testing</td>
<td>1 month</td>
<td></td>
</tr>
<tr>
<td>Transport from Lima warehouse to Iquitos</td>
<td>2–3 weeks to obtain cargo space if shipped by air</td>
<td>Air shipment is expensive, but rapid, and provides adequate storage conditions (controlled temperature and humidity). River transport is cheaper, but storage and arrival time can be problematic. The NMCP lost 100 boxes of tests in one shipment due to water and temperature damage.</td>
</tr>
<tr>
<td></td>
<td>A month or more if shipped by river</td>
<td></td>
</tr>
<tr>
<td>Arrival and storage in Iquitos central medical stores</td>
<td>1 month</td>
<td>Temperature and humidity can cause damage; the study recorded storage temperatures up to 37.6°C (99.7°F)</td>
</tr>
<tr>
<td>Distribution from central medical stores to health centers</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Distribution from health centers to communities</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6 months–1 year</strong></td>
<td></td>
</tr>
</tbody>
</table>

Supply-chain instability was fed by certain problems and contributed to others. Professional health workers were reluctant to trust promotores with the technology and therefore reluctant to keep them supplied with RDTs and antimalarials. “How is some promotor going to know how to treat a case of falciparum?” is the way one key informant summarized the feeling. The same informant noted that lack of access to RDTs then had a negative effect on performance: “You overcome the acceptability barrier, and the tests run out.” Finally, insufficient training caused some difficulties: “You leave, and they forget how to use them because there are so many different steps. Rapid tests are more difficult to use than a thick smear.”

**Seeking a more affordable alternative**

By 2004, there were many more RDTs on the market. OptiMAL® – the test of choice in Peru since discussion of RDT use began in 1998 or 1999 – is relatively expensive, so interest in identifying a cheaper alternative was growing. A meeting of regional experts convened in Guayaquil by the Pan American Health Organization (PAHO), the Amazon Malaria Initiative (AMI), and the Amazon Network
for Surveillance of Antimalarial Drug Resistance (RAVREDA) acknowledged the desirability of identifying a cheaper test and established consensus guidelines for evaluating potential candidates.* Among these were the ability to distinguish falciparum from vivax infections, a unit cost below US $1.50, sensitivity and specificity as good as tests previously evaluated in the region, and availability in individual packaging.

Figure 4: A promotor uses an RDT to test a child for malaria in a remote village of the Peruvian Amazon.

Participants considered individual packaging important because in low-transmission areas, promotores may be unable to use an entire box of tests by the lot expiration date. In these areas, RDT proponents and the MOH estimated the number of tests to be distributed to each promotor based on the number of recently reported cases from each area. Individually packaged tests include buffer, a lancet, a blood collection device, and the test itself in a single envelope. In contrast, non-individually packaged tests come with one bottle of buffer per box, making it impossible to distribute tests from a single box among several promotores.

Candidate RDTs were to be evaluated in the laboratory by the CDC, then field tested by one AMI member country. Participants agreed that multiple field tests in various countries would be unnecessary.26

In October of 2005, PAMAFRO, a Global Fund project to control malaria in the cross-border areas of Colombia, Ecuador, Peru, and Venezuela, launched operations. A five-year US $26.5 million initiative, PAMAFRO encompasses a broad range of malaria prevention and control activities, including use of

* RAVREDA is a network of Amazon-region countries (Bolivia, Brazil, Colombia, Ecuador, Guyana, Peru, Suriname, and Venezuela) organized in 2001 to track antimalarial resistance throughout the region and coordinated through the Pan American Health Organization.
RDTs in remote communities. Parallel to or shortly after the Guayaquil meeting, a PAMAFRO procurement committee with representatives from Columbia, Ecuador, Peru, and Venezuela called for opening the RDT solicitation process to all manufacturers in the hopes of identifying a cheaper alternative to OptiMAL®. While the objective of this decision was in keeping with the consensus developed in Guayaquil, the process – at least according to some observers – was not:

This decision was obviously not consistent with the agreement at the 2005 Guayaquil meeting, since it increased the possibility that a test not previously evaluated in the countries (quality evaluation by an independent laboratory and evaluation of sensitivity and specificity under both ideal and real conditions) could be chosen. And that is exactly what happened, a test was selected that was new to the region, Parascreen®, whose ease of use made people think that it would have additional advantages over OptiMAL IT® and ICT NOW® (emphasis original).17

Parascreen® had not been previously tested or used in Latin America. Its selection seems to have generated significant controversy among Peruvian RDT proponents. Procurement was conditioned on the manufacturer demonstrating that the test had a sensitivity and specificity at least equal to OptiMAL® in field conditions. However, a multicenter study carried out in Columbia, Ecuador, Peru, and Venezuela found Parascreen® to be only 72% sensitive for *P. falciparum* and 84% sensitive for *P. vivax*.17 Nevertheless, PAMAFRO expanded implementation in 2007 with the purchase and distribution of 124,000 Parascreen® tests plus another 40,000 units of OptiMAL®. The Parascreen® RDTs were prioritized for use in areas with mostly *P. vivax* transmission, while OptiMAL® tests were designated for areas with a significant percentage of *P. falciparum* cases. Since that 2007 procurement, RDT use seems to have stalled. Neither PAMAFRO nor the MOH has procured additional tests. UNICEF has been donating a small quantity of RDTs to trained promotores in Amazonas, the department to the immediate west of Loreto, but there is no national or regional program providing an ongoing supply. With PAMAFRO set to end in 2010, there is no prospect of support for RDT procurement in the immediate future.

**DISCUSSION**

In retrospect, early proponents of malaria RDT use in Peru were able to develop a broad base of support for the new diagnostic technology by organizing a series of carefully planned studies, making results from those studies available to key decision-makers and program managers within a short period of time, and consciously focusing debate and decisions on empirical evidence. The group, according to one member involved from the beginning, had several advantages in its favor. First, though they represented different institutions, most of the group’s members had worked together on previous projects and had known one another since medical school. This made it possible to work within an existing atmosphere of trust and avoid getting side-tracked by personal or institutional political agendas. Second, the group agreed early on to operate within a common conceptual framework: Decisions would be made based solely on concrete technical criteria. As one group member put it:

You have to construct a culture of not working on the basis of personal convictions, but on the basis of reasoning. The trick is to try to avoid creating a situation in which people act purely based on [personal beliefs]. If you keep the discussion on technical grounds, and keep it transparent, it’s difficult for people to oppose you just because they want to be difficult. When someone says, “I don’t agree with that,” you have to say, “What is it exactly that you don’t agree with? What are your reasons for disagreeing?”

Third, there was a conjunction of interests between donors, technical staff, and political leadership. The recent re-emergence of malaria as a serious public health concern, the growing incidence of antimalarial resistance and the need for more expensive drugs, and the recognition that expanding microscopy would not be possible in the Amazon region helped keep those involved focused on the practical implications and applicability of their efforts. “There was good correspondence,” in the words of the previously quoted group member, “between what the donors were proposing and what the country needed.” There
was also a strong orientation toward collaborative work between both donors and implementers. Disseminating information widely and rapidly was also seen as crucial:

You have to provide decision-makers with information in the most open manner possible. It’s not just a question of bringing in international experts [to present the evidence]; you have to have meetings that are open to everyone: doctors, private parties… It’s not always necessary to publish your results in a peer-reviewed journal – you can publish them on a university web page or in other media more accessible to the stakeholders… [but] knowledge that doesn’t get diffused transforms itself into the patrimony of the few: The academic community, the public health community. You have to disseminate [the information] to everyone who plays a role – if you make it common knowledge, it becomes very difficult to oppose.

Unfortunately, as we have seen, this careful and deliberate planning was not enough to ensure successful implementation. The research orientation of the group promoting RDT use was definitely practical rather than theoretical or academic. Nevertheless, the needs for implementing and scaling up a new technology are different than those for confirming its effectiveness and forging political consensus around its use. Even during the longitudinal test of RDTs from 2001–2003, funding, procurement, logistics, and monitoring and evaluation were assured externally. To answer questions such as whether promotores can use RDTs safely and effectively over time, the research team could justify managing inputs and resources more carefully than would be possible under day-to-day operating conditions. To successfully implement the intervention, however, regular operating structures must be in place to manage procurement, logistics, training, and supervision within the existing health system. For instance, people at all levels of the supply chain from village health workers to health facility managers to district and national supply chain officials tend not to think about replenishing stock until it is almost exhausted. But if it takes up to a year from the time the MOH signs a contract to the time a diagnostic test reaches the village health worker, village health workers will spend a lot of time with no diagnostic tests unless there is a system in place to begin procurement well in advance. This can lead to what one key informant called “supply use trauma”: People at each level of the supply chain try to hoard supplies rather than use them for fear that once used they will not be replaced.

Similarly, while obtaining research funding is always a challenge and research budgets always tight, it is much easier to stretch a limited research budget a bit further for a limited time or convince a donor to provide a finite amount of additional funding to reach the next milestone than it is to ensure an ongoing source of funding for the indefinite future. Once it began to implement community-based RDT use, the MOH purchased rapid tests over a two-year period. This was followed by the PAMAFRO procurement in 2007. Now the lack of an ongoing dedicated source of funding could threaten the program’s long-term viability.

However, some key informants closely associated with the initiative argue that funding is a minor barrier compared to systemic and policy weaknesses. One weakness has been failure to develop guidelines for key aspects of implementation. Despite deciding that RDT use should be targeted to communities with “limited access” to microscopy, the MOH has never concretely defined limited access or developed a list of communities that meet the definition. This has made it difficult to forge consensus about where, exactly, the limited supply of RDTs should be used. Similarly, there are no agreed-upon criteria for test selection, procurement, quality control, transport, and storage at the regional and local levels. Guidance is similarly lacking on training, monitoring, evaluation, and even case management of patients diagnosed with RDTs.

Some would add that recent decentralization of management and health service delivery further complicates the situation. As one informant explains:

Peru has enough money to buy RDTs in the number needed nowadays; it even has the procurement mechanisms, but the malaria control program, at the national and sub-national levels, has lost strength. Regional health authorities are not effectively assuming their operational roles (planning, budgeting, procuring, etc.). RDT implementation is facing the
same problems as that of other more conventional tools. For example, right now there are stock-outs of lab supplies required for follow-up of [patients] receiving HAART [highly active antiretroviral therapy].

Finally, in addition to convincing program managers and key decision-makers – at which Peruvian RDT proponents were quite successful – it is also necessary to achieve buy-in from front-line health workers. The doctors and nurses who run individual health centers or health posts and serve as the day-to-day link between the formal health system and the promotores do not have access to the same communication channels as their more senior counterparts. They will not have read reports from initiatives like Proyecto Vigia and have few opportunities to attend seminars in Lima like those sponsored by the INS. Those working in facilities within an hour or two of Iquitos may be invited to attend regional workshops or trainings, but those posted many hours or days away will not. Their buy-in is important, because regardless of official policy, once regional officials or district supervisors make their occasional supervisory visit to or organize their occasional workshop for those on the periphery; it is the local health personnel who will ultimately determine whether promotores receive supplies of diagnostics and antimalarials.

The lesson of this case study may be that effective technology and political buy-in are necessary but not sufficient to ensure sustained uptake of a new diagnostic test. Successful adoption also depends upon development of policies that guide procurement, distribution, and use – including training, supervision, and quality control – on an ongoing basis. From a donor’s perspective, this suggests two principles: First, delivering a new technology is just as important as discovering and developing it. And second, delivery is not just about getting the new technology to the door. Instead, it is about ensuring that health systems have both the mechanical and the managerial infrastructure in place to implement the technology in a sustainable fashion.

“It’s not about the commodities themselves,” said one informant closely involved with the Peruvian RDT initiative for more than a decade. “The situation should not reverse to one in which commodities are bought or sold – unless a crisis occurs.” Instead, this informant concluded, “[donors] need to consider collaborating in the improvement of systems.”
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17 Ciclo de implementación del uso de pruebas rápidas de diagnóstico (PR) de la malaria en el Perú. (Lima, 2008).


26 Operations Research on the Use of Rapid Diagnostic Tests (RDTs) for Malaria. (Pan American Health Organization/Amazon Malaria Initiative, Guayaquil, Ecuador, 2005).

APPENDIX: PEOPLE INTERVIEWED FOR THIS CASE STUDY


Dr. Lenin del Cuadro, Director, Reference Laboratory, Iquitos Directorate of Health. Iquitos. 4/3/2009.


Dr. Lenka Kolevich, Infectologist, Hospital del Nino. Lima. 4/6/2009.

Dr. Carlos Manrique, Director, Regional Directorate of Health. Iquitos. 4/2/2009.

Captain Alejandro Mercado Noriega, Chief, Department of Infectious Diseases, Naval Hospital. Callao. 3/30/2009.


Dr. Willy Pozo, Pediatrician, Hospital del Nino. Lima. 4/7/2009.

Dr. Cesar Ramal Asayag, Chief of HAART (Highly Active Antiretroviral Therapy), Iquitos Regional Hospital. Iquitos. 4/2/2009.


Dr. Angel Rosas Aguirre, Regional Technical Coordinator, PAMAFRO (Malaria control project, Andean Health Organization). Lima. 3/31/2009.

Dr. Sixto Sanchez, Director of Epidemiological Investigation, National Institute of Health. Lima. 8/21/2007.

Dr. Karina Sebrian, Infectologist, Maria Auxiliadora Hospital. Lima. 4/8/2009.
