2013

Review of adherence to malaria rapid diagnostic testing in different health care settings

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Boston University

http://hdl.handle.net/2144/12040

Boston University
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

REVIEW OF ADHERENCE TO MALARIA RAPID DIAGNOSTIC TESTING IN DIFFERENT HEALTH CARE SETTINGS

by

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Submitted in partial fulfillment of the requirements for the degree of Master of Arts 2013
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ACKNOWLEDGEMENTS

I would like to thank Dr. Davidson Hamer (Center for Global Health at Boston University School of Public Health) and Dr. Christopher Gill (Director of Boston University School of Public Health Pharmaceuticals Program) for giving me the idea for this thesis project. I would also like to thank my thesis readers, Dr. Caroline Attardo Genco, PhD and Dr. Michael Simberkoff, my principal investigator at my full-time research position (Executive Chief of Staff of the New York VA Harbor Healthcare System and a Professor of Infectious Diseases at NYU School of Medicine).

Furthermore, I would like to thank my parents for their insight into this project. They attended medical school in Nigeria during the 1980s, practiced in the United Kingdom in the 1990s, and then practiced in the United States from the 2000s on. Their comparisons among the different healthcare systems forever fascinate me.
REVIEW OF ADHERENCE TO MALARIA RAPID DIAGNOSTIC TESTING IN DIFFERENT HEALTH CARE SETTINGS

CYNTHIA O. AKAGBOSU
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ABSTRACT

Background: The antimalarial prescription response that community health workers (CHWs) and hospital workers in Africa give when faced with the new rapid diagnostic testing technologies for malaria.

Objectives: To understand why health workers subsequent treatment patterns are not always in alignment with the diagnostic result, especially when faced with negative test results- they frequently prescribe anti-malaria drugs despite these negative results.

Data Sources: Articles stemming from PubMed, the WHO, and the CDC. In reference to the PubMed articles used for the presentation of published results, the articles range from 2007-2012 and were found via PubMed using the MeSH search terms Africa, malaria, rapid, Malaria/diagnosis, health, community, residence characteristics, hospital, and hospitals.

Eligibility Criteria: The searches only looked at clinical trials and reviews. Then articles were narrowed down to ones that discussed rapid diagnostic testing
along with treatment given for both RDT positive and RDT negative results, the results, and the treatment that they were given by a caregiver after knowing the results of the test. In the end, 6 clinical trials involving community health workers and 11 clinical trials involving hospital workers underwent evaluation.

**Conclusions:** There is a discrepancy of perceived and actual malaria cases. While health care providers give antimalarial prescriptions in response to positive RDT results in essentially a 1:1 ratio, it is only when faced with a negative RDT result that adherence begins to falter. Trained clinicians and health care workers are more reluctant to adopt the changed protocols that RDT brings because of the ingrained attitude that fever equates to malaria even when presented with evidence to the contrary. On the other hand, there is high adherence in community health workers since they have less medical background knowledge to overcome. In order to remedy this, improved training regimens need to be enacted such as providing alternate diagnoses when presented with a negative rapid diagnostic testing result, especially in the format of a pictorial cascade diagram.
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INTRODUCTION

Prevalence of Malaria

According to the Centers for Disease Control and Prevention (CDC), malaria is found in areas where Anopheles mosquitoes can survive and multiply and where malaria parasites can complete their growth cycle of extrinsic incubation period in mosquitoes. At temperatures below 20°C (68°F), the most severe malaria parasite cannot complete its growth cycle in the Anopheles mosquito and cannot be transmitted. Subsequently, transmission is more intense and year-round in tropical areas such as Sub-Saharan Africa and parts of Oceania. Despite sufficiently high temperatures, transmission will not occur at high altitudes or in deserts, excluding desert oases (CDC-Centers for Disease Control and Prevention, 2010a). The reason malaria cannot thrive in deserts is because mosquitos lay their eggs in water and therefore malaria will be more prevalent in a given area during the rainy season.

From the World Malaria Report 2012 by the World Health Organization (WHO), it is estimated that there were 219 million cases of malaria (estimate ranges from 154-289 million) with an estimated 660,000 deaths (estimate ranges from 610,000-971,000) in 2010. Up to 3.3 billion people live in areas at risk of malaria transmission in 106 countries and territories. In 2010, 80% of those estimated cases occurred in 17 countries with the Democratic Republic of the Congo, India, and Nigeria accounting for 40% of all estimated malaria cases.
80% of malaria deaths in 2010 occurred in just 14 countries with the Democratic Republic of the Congo and Nigeria accounting for 40% of all estimated deaths due to malaria (see Figure 1). Overall, 80% of malaria cases and 90% of deaths are estimated to occur in the WHO Africa Region with children under five and pregnant women being most severely affected (WHO. Global Malaria Programme, 2012). The reason for the prevalence of malaria deaths in these areas is that malaria mortality rates are highest in countries with a lower Gross National Income per capita, countries that have a larger proportion of the population living in poverty, as defined by living on less than US $1.25 per person per day, and countries with large populations in rural areas. (WHO. Global Malaria Programme, 2012).

The total international and domestic funding committed towards malaria control is estimated to be US $2.3 billion in 2011. However, that number is substantially less than the US $5.1 billion necessary per year to achieve universal access to malaria interventions across the world. Fortunately, there has been an increase in international spending towards malaria regions every year, rising from less than US$100 million in 2000 to US $1.66 billion in 2011, and US $1.84 billion in 2012 (see Figure 2) (WHO. Global Malaria Programme, 2012). Much of the increased international funding was driven by the priority that the Bush administration in the US placed on health care and development in international relations, especially Africa (Tierney, 2011).
Figure 1: Cumulative Proportion of Global Estimated Deaths in Endemic Countries. Taken from Global Malarial Programme 2012 by the WHO.
The Malaria Parasite and Life Cycle

Malaria in humans is caused by five species of parasites from the genus *Plasmodium*; the species include *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*. Of these, malaria caused by *P. falciparum* is the most deadly and predominates in Africa, *P. vivax* remains less dangerous but exists on a more global scale, and the latter three infect humans much less frequently (WHO. Global Malaria Programme, 2012). The *Plasmodium* malaria parasite has female *Anopheles* mosquitoes and humans as hosts and has a distinct cycle of growth and multiplication in each (Neptune, 2011).

In *Anopheles* mosquitoes, the mosquitoes pick up blood stage parasites ("gametocytes") during a blood meal and after 10-18 days the infectious parasites ("sporozoites") are found in the salivary glands of the mosquito. The mosquito does not suffer from the presence of the malaria parasites (CDC-Centers for Disease Control and Prevention, 2010b). The mosquito acts as a vector since it carries the disease from one human to another. In humans, *Anopheline* mosquitoes transmit sporozoites from infected to uninfected humans.
through their bite with saliva via the human’s dermis so that the sporozoites rapidly infect the hepatocytes (CDC-Centers for Disease Control and Prevention, 2010b). After the parasite multiplies, the hepatocytes rupture to release scores of parasites that then infect erythrocytes and induce the blood stage. The blood stage causes the clinical symptoms associated with malaria since the parasite also multiplies within the erythrocyte causing them to hemolyse and release daughter parasites (“merozoites”), inducing cytokine release (Taylor et. al 2010). A more detailed description of the malaria cycle and growth in humans and mosquitos is available in Figure 3.

Clinical Presentation of Malaria

Clinical symptoms occur 7 to 14 days after a bite from an infected mosquito due to the need for the parasite to transit through the liver. Anemia and pallor is caused by hemolysis, dyserythropoiesis, and extra splenic clearance of both damaged and uninfected erythrocytes. Fevers and rigors occur due to the cytokine release due to hemolysis, symptoms that prove flu-like in nature. Splenomegaly and hepatomegaly are caused by damaged erythrocytes and cellular debris that enlarge the sinusoids of the liver and spleen. Nausea, vomiting, headache, acidosis, renal failure, hypoglycemia, and thrombocytopenia also develop from multifactorial causes (Taylor et al., 2010).
Figure 3: Malaria Parasite Life Cycle in Humans and Mosquitoes. A female malaria-infected *Anopheles* mosquito inoculates sporozoites into the human host during a blood meal (1). In the liver stage, sporozoites infect hepatocytes (2) and mature into schizonts (3) that rupture to release merozoites (4). After replication in the liver, called exo-erythrocytic schizogony (A), there is multiplication in the erythrocytes, called erythrocytic schizogony (B). In the blood stage, the merozoites infect red blood cells (5) then the immature ring stage trophozoites mature into schizonts that release merozoites (6). Some parasites then go on to differentiate into sexual erythrocytic stages as gametocytes (7). *Anopheles* mosquitoes ingest these gametocytes, both male (microgametocytes) and female (macrogametocytes), during a blood meal (8) and the parasites’ multiplication in the mosquito is known as the sporogonic cycle (C). Inside the stomach of the mosquito the microgametes penetrate the macrogametes to produce zygotes (9), those zygotes develop into ookinetes after becoming motile and elongated (10) in order to invade the midgut wall of the mosquito where they develop into oocysts (11). The oocysts grow, rupture, and release sporozoites which enter the mosquito’s salivary glands which allow the cycle to begin again when the mosquito bites a human. Taken from the CDC Malaria section on biology (CDC-Centers for Disease Control and Prevention, 2010b).

The clinical syndrome that evolves depends on the interplay among the infecting parasite species, the immune status of the host, and the timeliness of the use of antimalarial drugs. Non-immune patients such as children and
travelers manifest with an undifferentiated febrile illness with fluctuating paroxysms of fevers and rigors, malaise, headache, myalgias, arthralgias, pallor, mild jaundice, tender hepatosplenomegaly, anemia, and thrombocytopenia. If infected with *P. falciparum* these non-immune patients may manifest life-threatening syndromes such as cerebral malaria, which is preceded by altered consciousness, seizures, or non-focal dysfunction of the central nervous system. Other severe disease manifestations include severe anemia, hypoglycemia, acidosis, respiratory distress, shock, and acute renal fire. On the other hand, adult patients in endemic areas who have developed partial immunity to malaria parasites due to repeated infection have reduced intensity and severity of the disease (Taylor et al., 2010).

**Diagnosis**

The diagnosis of malaria is necessary to allow people to detect malaria when suspected due to patients’ symptoms in order to treat the malaria or to delve into other causes of their symptoms such as pneumonia. It is imperative that malaria is recognized promptly and treated to restore the health of the patient and to limit the spread of malaria via mosquitos in the area. Additionally, one must know that there is a slight tendency for over diagnosis of malaria in people who live in malaria endemic regions: a person may have the malaria parasite in their system due to recently getting over an infection or because they may have enough immunity to protect them from the full-blown malaria illness.
even if they are infected. Therefore, the presence of malaria parasites in endemic regions does not definitely mean that their symptoms are caused by malaria, it could be another disease.

**Clinical Diagnosis**

Clinical diagnosis is based on the patient’s symptoms during a physical examination. Clinical findings should receive confirmation through a laboratory test for malaria, especially since the first symptoms of malaria such as elevated temperature, perspiration, and tiredness are nonspecific. Additionally, the associated first symptoms of fever, chills, sweats, nausea and vomiting, headaches, and muscle pains are found in many other diseases like influenza and common viral infections. The more severe symptoms are more indicative of malaria such as coma, severe anemia, respiratory difficulties, and confusion. A health-care provider should perform a complete blood count and a routine chemistry panel to determine if the malaria is uncomplicated or severe based on the tests ability to detect severe anemia, hypoglycemia, hyperbilirubinemia, renal failure, and acid-base disturbances (CDC-Centers for Disease Control and Prevention, 2012). Despite the inconclusive results of this form of diagnosis alone, this has been the main way that developing countries have diagnosed malaria cases throughout the years. This method of diagnosis leads to massive over-treatment of malaria.
Rapid Diagnostic Testing

A rapid diagnostic test (RDT) involves immunologic (immunochromatographic) test kits that detect antigens derived from malaria parasites. A blood specimen from the patient is applied to a sample pad on the test card along with some reagents. An immunochromatographic strip assay involves blood being applied to one end of the nitrocellulose strip to allow the specimen to mix with lysing agents, a buffer solution, and labeled anti-
Plasmodium indicator antibody. Then, the liquid mixture migrates down the strip to an area where capture antibodies are already fixed in lines on the strip surface and which detect parasite antigens or indicator antibodies (Wilson, 2012).

Currently, RDTs can detect two antigens: an antigen specific to P. falciparum and another antigen that is common to all 4 human Plasmodium species. RDTs usually come in a dipstick or cassette format, return a result in 2-20 minutes, and indicate patient infection by looking at specific bands on the test card window. If infected, it determines whether it is P. falciparum or the other 3 species, see Figure 4 (CDC-Centers for Disease Control and Prevention, 2012).
Figure 4: A Guide to the Interpretation of RDT Test Results. Specifically, the Paracheck Pf Device Rapid Test that is the most popular of the RDT tests for *P. falciparum*. Image A represents the control line and *P. falciparum* (Pf) line, image B a negative result, image C two positive results (it is positive even if the Pf line is faint). Image D represents an invalid result where no control line appears and the test must be done again. Taken from the FIND Diagnostics webpage ("Paracheck Pf Device Rapid Test for Malaria (Ver. 3) (30301025)," 2012).

The use of RDTs is increasing (from 20% in 2005 to 27% in 2011) along with the overall percentage of suspected malaria cases that receive a parasitological test- that latter number increased from 68% globally in 2005 to 77% in 2011. In Africa specifically, it rose from 20% in 2005 to 47% in 2011, mainly because of the use of RDTs which accounted for 40% of all the cases tested in Africa in 2011 (WHO. Global Malaria Programme, 2012). In 2004, Zambia was the first sub-Saharan country to use RDTs, followed by Senegal in 2006; today several countries use it. The WHO recommends laboratory-confirmed diagnosis to treat malaria and different agencies are now trying to
steer away from presumptive treatment to using laboratory-based diagnosis, especially since there is a trend of malaria decline in Africa (D'Acremont et al., 2011). The implementation of RDTs requires rigorous procedures to train/supervise providers and to obtain RDTs while enacting quality assurance. Furthermore, the use of RDTs in different settings should ensure that RDTs reduce over-diagnosis, overconsumption of antimalarials, and prevent patient suffering (D'Acremont et al., 2011). On June 3rd, 2007 the U.S. Food and Drug Administration (FDA) approved BinaxNOW® Malaria as the first RDT for use in the United States to be used by hospital and commercial laboratories, but not by individual clinicians nor patients; it remains the only RDT approved for use in the United States (CDC-Centers for Disease Control and Prevention, 2012).

RDTs have a high sensitivity, low specificity, high positive predictive value, and high negative predictive value. The low specificity of RDTs can sometimes result in difficulty detecting very low levels of parasite and therefore can give a false negative, however, generally such a low level of parasite does not cause severe symptoms in people frequently exposed to malaria in malaria endemic areas. However, non-immune individuals may be symptomatic at very low parasitic densities (CDC-Centers for Disease Control and Prevention, 2010c).

In Mtove et. al (2011) the sensitivity (probability that a test will indicate a positive for the disease) for the RDT Paracheck™ was very high at 97.5% and the specificity (fraction of those without disease who will have a negative result) was poor at 65.3%. However, the sensitivity of Paracheck™ was lower in
detecting infections with <2,000 parasites/μl and especially infections with <200 parasites/μl. False positives were significantly associated with pre-admission use of antimalarial drug, absence of current fever, and non-typhi *Salmonella* bacteremia. Poor specificity is likely due to Histidine-Rich Protein II (HRP-2) persistence following a recent parasite clearance (Mtove et al., 2011). In Chinkhumba et al. (2010), the RDTs used had a high sensitivity: First response malaria (92%), Paracheck (91%), and ICT diagnostics (90%). However, the RDTs had a low specificity: First response malaria (42%), Paracheck (68%), and ICT diagnostics (54%) (Chinkhumba et al., 2010).

In Kahama-Maro et al. (2011), the RDTs used had a high sensitivity of 97%, high specificity of 96.8%, positive predictive value (proportion of people that test positive that have the disease) of 79.2% and negative predictive value (proportion that test negative that don’t have the disease) of 99.6%. The investigators recommended RDT use over microscopy due to microscopy’s poor positive predictive value of 2.8% (Kahama-Maro et al., 2011). In Ly et al. (2010), the sensitivity, specificity, positive predictive value, and negative predictive value of RDT Paracheck were respectively 100.0%, 98.3%, 80.0%, and 100.0%. This study involved 189 consultations of clinically suspected malaria cases in Senegal (Ly et al., 2010).
Microscopy Diagnosis

The use of blood smear patterns under light microscopy can indicate the presence of malaria. A clinician takes a drop of the patient’s blood, stains the specimen (usually with the Giemsa stain) to make the parasite look distinct, and then spreads it out onto a microscope slide. The quality of this technique depends on the quality of the reagents, the microscope, and the laboratory specialist (CDC-Centers for Disease Control and Prevention, 2012).

An illustration of the potential erythrocyte stages that one may see when looking at a blood smear of *P. falciparum* is available in Figure 5; the other human infecting strains of *Plasmodium* look different but have the same general progression of the malaria parasite (CDC-Centers for Disease Control and Prevention, 2012). Although microscopy results under a highly trained diagnostician frequently proves better than RDT results and should be used in combination with RDTs, the quality needed to efficiently utilize this diagnostic tool proves difficult in most areas of Africa due to lack of constant electricity, lack of reagents, lack of skilled manpower, and high cost. In fact, many clinicians are aware of the fact that operational conditions of microscopy are low (Reyburn et al., 2007). Under the best of conditions sensitivity is no better than 75-90% and can be as low as 50% in some settings (Wilson, 2012).
Molecular Diagnosis

An alternative method that is slightly more sensitive than smear microscopy is detecting parasite nucleic acids with polymerase chain reaction (PCR). Unfortunately, PCR takes more time and is frequently not available quickly enough to establish diagnosis of malaria for timely treatment. It is best used to confirm malaria positive results generated by microscopy or RDT (CDC-Centers for Disease Control and Prevention, 2012).

Figure 5: *Plasmodium falciparum* Blood Stage Parasites in Thin Blood Smears with Microscopy. Normal red blood cell (1), ring-stage trophozoites (2-10), trophozoites (11-18), schizonts (19-25), ruptured schizont (26), mature macrogametocytes (27, 28), mature microgametocytes (29, 30). An illustration from the book *The Primate Malarias* seen via the CDC website section called DPDx (GR Coatney et. al, 1971).
Serology

Serology involves detecting antibodies against malaria parasites using indirect immunofluorescence or enzyme-linked immunosorbent assay. Therefore, serology is used to detect past malaria exposure and not current infection for clinical purposes since one has to wait weeks for antibodies to develop (CDC-Centers for Disease Control and Prevention, 2012).

Prevention

Effective prevention methods include vector control using insecticide-treated nets, indoor residual spraying, larval control, chemoprevention for the most vulnerable populations of pregnant women and infants, confirmation of malaria diagnosis for every suspected case, and timely disease management with the appropriate anti-malarial medication. Unfortunately, many malaria strains are becoming resistant to insecticide use. The malaria vectors can be resistant to some insecticides as evidenced by Figure 6 and are also becoming resistant to the anti-malarial drugs themselves. (WHO. Global Malaria Programme, 2012). Another way to help limit the severity of malarial illness in infants is by breastfeeding: the mother is able to pass on antimalarial antibodies to their child through the breast milk.
Treatment

Malaria control necessitates prompt diagnosis and treatment; treatment should occur within 24 hours of onset in order to help stymy the potential progression of malaria from an uncomplicated case to a severe case of malaria.

Artemisinin-based combination therapies (ACTs) were endorsed by the World Health Assembly in 2007 as the first-line treatment for malaria caused by *P. falciparum* over oral artemisinin-based monotherapies since the monotherapies foster the spread of resistance to artemisinin. Since this recommendation in recent years, treatment courses of ACT have been increasing in the region, growing from 11 million in 2005, go 76 million in 2006, and 278 million in 2011. Artemether-lumefantrine (AL) accounted for the largest percentage of ACTs given (77%) with artesunate + amodiaquine being the second most used ACT. 77% of the ACTs were used in Africa. On the other
hand, *P. vivax* malaria should be treated with chloroquine or again with ACTs if that *P. vivax* strain is resistant to chloroquine. Additionally, *P. vivax* should be combined with a 14-day course of primaquine in order to prevent relapse (WHO. Global Malaria Programme, 2012).

Other treatments that are active against the parasite forms in the blood include atovaquone-proguanil (Malarone®), mefloquine (Larium®), quinine, quinidine, doxycycline (in combination with quinine), clindamycin (in combination with quinine), and primaquine (active against the dormant parasite liver forms and prevents malaria relapse). If a person has a severe form of malaria where they can no longer take oral medications, they should receive the treatment via continuous intravenous infusion (CDC-Centers for Disease Control and Prevention, 2010c). Additionally, some countries in Africa have national guidelines indicating sulphadoxine-pyrimethamine as the antimalarial drug of choice (Ishengoma et al., 2011).

A reason for rampant presumptive treatment when seeing febrile patients despite new guidelines is due to the old WHO guideline from the 1980s involving the Integrated Management of Childhood Illness (IMCI) decision chart which was implemented as a method to improve the survival rate of children under five with fever when fewer diagnostics tools were available. Unfortunately, presumptive treatment started to spread beyond the group of high-risk children to children over five and adults, to low endemicity areas, and to facilities where diagnostic tools were actually available. Therefore, almost all fevers were treated with
antimalarial leading to massive over diagnosis of malaria (D'Acremont et al.,
2011). Since then, parasite prevalence has gone down, with presence of
*Plasmodium falciparum* in sub-Saharan Africa in children between the ages of
two and ten decreasing from 37% in 1985-1999 to 17% in 2000-2007
(D'Acremont et al., 2009). This may be partly due to effective chemoprophylaxis
for children in malaria endemic areas who received an antimalarial but did not
have malaria by reducing the human infectious reservoir, however, this idea may
no longer be viable since malaria transmission rates are lower (Bastiaens et al.,
2011).
SPECIFIC AIMS

As per the guidance of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009), this review decided to provide details throughout including context, objectives, data sources, study selection with participants and interventions, study appraisal and synthesis methods, results, and limitations.

Context

The response that community health workers (CHWs) and hospital workers have towards the new rapid diagnostic testing technologies.

Objectives

To understand why health workers subsequent treatment patterns are not always in alignment with the diagnostic result, especially when faced with negative test results- they frequently prescribe anti-malaria drugs.

The overall purpose of this paper is to examine the interpretation of rapid diagnostic testing results by CHWs and hospital workers and the subsequent treatment that they give in relation to that test result.

This paper goes one step further from determining the ability of RDTs to detect malaria and to examine the actions taken by CHWs and hospital workers in response to the RDTs, especially when those persons decide to prescribe
antimalarials in the absence of positive diagnostic results. This paper’s main goal is not to determine the efficacy of RDTs over other malaria diagnostic kits or to evaluate the efficacy among specific RDT brands.

Data Sources

Articles stemming from PubMed, the WHO, and the CDC. In reference to the PubMed articles used for the presentation of published results, the articles range from 2007-2012 and were found via PubMed using MeSH search terms Africa, malaria, rapid, Malaria/diagnosis, health, community, residence characteristics, hospital, and hospitals.

Study Selection

These searches also only looked at clinical trials and reviews. Then articles were narrowed down to ones that discussed rapid diagnostic testing along with treatment given for both RDT positive and RDT negative results, the results, and the treatment that they were given by a caregiver after knowing the results of the test. The study was narrowed down to articles referring to people living in Africa (not travelers in Africa), the RDT interpretations by trained health care providers and not by i.e. families, and the restriction on age was that this study eliminated articles talking mainly about RDTs in relation to prenatal fetuses in pregnant mothers. In the end, 6 clinical trials involving CHWs and 11 clinical trials involving hospital workers underwent evaluation.
POTENTIAL PROBLEMS DUE TO OVER PRESCRIPTION

One should test all suspected cases of malaria and only those with confirmed malaria cases should be treated with antimalarial medicines. Compared to today’s actual practice, the need for malaria treatment would be dramatically reduced (WHO. Global Malaria Programme, 2012). Improving malaria diagnosis with RDTs is a proposed approach to reducing the overtreatment of malaria, especially with the new implementation of ACTs (Hamer et al., 2007). Use of antimalarials alone leads to adverse drug reactions and mistrust of ACTs may develop if ACTs are used inappropriately for viral or bacterial diseases and then don’t work (D’Acremont et al., 2009).

Resistance

The parasite has a relatively quick reproductive period and resistance has developed to early and commonly prescribed drugs like chloroquine and antifolates, along with resistance to newer generations of drugs (Tierney, 2011). Parasite resistance to artemisinin has been detected in many countries to multiple ACTs, therefore, studies have been enacted to observe treatment using non-artemisinin-based combination of atovaquone-proguanil (WHO. Global Malaria Programme, 2012).

There is a concern for the reduced susceptibility of *P. falciparum* parasites to ACTs, especially from studies that report allelic selection of malaria parasites
after AL overuse (Bastiaens et al., 2011). There has been a growth of resistance to older antimalarial drugs and newer ACTs have been developed to help combat that, but ACTs cost 10 times that of the previous set of antimalarial drugs (Reyburn et al., 2007).

**Missed Diagnosis of Other Febrile Causing Diseases**

Over diagnosis of malaria in febrile cases causes clinicians to miss diagnosing other febrile causing disease. Malaria and pneumonia account for 40% of mortality among children less than five years of age in sub-Saharan Africa and have much symptom overlap (Ukwaja et. al, 2011). Therefore, it is imperative to try to distinguish the two diseases because one requires antimalarials while the other generally requires an antibiotic and an antipyretic.

Fevers not attributable to malaria in malaria endemic regions are 56% acute respiratory infections, 10% gastroenteritis, 6% urinary infections, 3% typhoid, 3% other documented infections, and 22% fever of unknown origin (D’Acremont et al., 2010). Additionally, 68% of the acute respiratory infections and 31% of the gastroenteritis cases are associated with viruses that will not respond to antibiotics (D’Acremont et al., 2010). Therefore, they will persist longer than malaria cases treated with an antimalarial drug.
Side Effects

The most commonly encountered side effects to antimalarials are mild. Most antimalarial can cause gastrointestinal disturbances including nausea, vomiting, diarrhea, loss of appetite, and mild weight loss. They can affect the brain by causing lightheadedness, dizziness, and headaches. Other general side effects include rashes, coughs, and general weakness (Herriman, 2010).

Doxycycline is a weak antimalarial that can also cause an increased sensitivity to sun and increased vaginal yeast infections. Contraindications exist in children because doxycycline forms deposits in growing bones and teeth (Weld, 2010).

Antimalarials also cause severe and life threatening side effects. Those psychiatric in nature most frequently arise from the drug mefloquine that commonly causes hallucinations, nightmares, seizures, feelings disconnected from oneself, thoughts of suicide, and other confused behavior. Therefore, people with psychiatric illness and epilepsy have contraindications from use of mefloquine; these psychiatric symptoms can even last after the drug course has ended. Chloroquine can also cause psychological symptoms from mild depression to severe psychiatric disturbances, create cardiac arrhythmias, and cause a severe drop in blood pressure. After chronic use, renal disease, disease of the bone, and disease of the heart muscle can occur from chloroquine (Sage Weld, 2010). Several antimalarials, such as quinine, cause hemolytic anemia when a patient has a Glucose-6-phosphate dehydrogenase deficiency. Quinine can also cause cardiac problems such as heart arrhythmia’s, weak pulse, and
EKG irregularities. Malarone can cause severe skin rashes, bleeding disorders, and uncontrolled diarrhea and vomiting. It can even cause the life threatening skin disease Stevens-Johnson syndrome where the epidermis separates from the dermis. Pregnant women have contraindications against most antimalarials due to the association with potential birth defects (Herriman, 2010). Quinidine can cause ringing in the ears, hearing loss, mild depression, EKG changes that can lead to fatal arrhythmias. After high doses, quinidine commonly causes hypoglycemia and less commonly causes blindness, deafness, paralysis, destruction of platelets, and hepatitis (Weld, 2010). Overall, antimalarials can be lethal if taken in high dosages, partially because the medication absorbs rapidly. There are few side effects associated with ACTs.

Costs

Excessive costs for malaria will ensue due to over prescription. Therefore, in 2010 the WHO said that due to over prescription of antimalarials, before malaria treatment there should first be a confirmation of malaria presence in a person. In addition, due to the high costs of the new ACTs, especially AL, in 2003 the Global Fund for HIV/AIDS, Tuberculosis, and Malaria decided that improved malaria diagnosis proved necessary to rationalize the use of ACTs in peripheral clinics (Hamer et al., 2007). Additionally, lower health status contributes to the economic burden that malaria can pose on society (Neptune, 2011).
Parasitological diagnosis and treatment with ACTs is cost-effective in all current malaria-endemic situations as long as the RDT test result is taken into account (D’Acremont et al., 2009). Therefore, if the RDT result does not receive consideration then the RDT diagnosis used to prescribe ACT treatment approach will not result in cost-effectiveness.

In the study Hamer et al. (2007), if 27% of RDT negative patients receive ACTs, as occurred in their study, the use of RDTs does not appear cost-effective. They utilized the estimate of US $0.5 per RDT and US $1 per course of AL, the cost savings is only US $0.33 per patient ($330 per 1,000 patients) (Hamer et al., 2007). Therefore, a greater adherence to RDTs and/or a lowered cost of AL need to occur.
COMMUNITY HEALTH WORKERS AND RAPID DIAGNOSTIC TESTS

Study Designs, Results, and How Training Affected Adherence

Hamer et. al (2012) performed a cluster-randomized controlled trial with specific guidelines on how to manage RDT results, involving community-based management of malaria and/or non-severe pneumonia in children under the age of 5 in rural Zambia. The intervention arm trained CHWs to treat RDT positive cases with AL and non-severe pneumonia with amoxicillin, and to refer severe cases of pneumonia to a health facility while the control CHWs group treated all febrile children with AL, and referred any form of pneumonia. 95.9% of the 1,017 children enrolled received RDTs, in the intervention arm 94-100% of the time the malaria or pneumonia was correctly identified and treated for with amoxicillin, AL, and an antipyretic (see table 1). 90% of febrile children with a negative RDT result recovered with only an antipyretic (Hamer et al., 2012).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Correct treatment</th>
<th>Appropriate treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All malaria</td>
<td>AL</td>
<td>267/272 (96.2%)</td>
</tr>
<tr>
<td>Malaria only</td>
<td>AL</td>
<td>170/170 (100%)</td>
</tr>
<tr>
<td>All pneumonia</td>
<td>Amoxicillin</td>
<td>358/362 (96.9%)</td>
</tr>
<tr>
<td>Pneumonia only</td>
<td>Amoxicillin</td>
<td>257/260 (96.8%)</td>
</tr>
<tr>
<td>Malaria and pneumonia</td>
<td>AL and amoxicillin</td>
<td>96/102 (94.1%)</td>
</tr>
<tr>
<td>RDT-negative fever</td>
<td>Analgesics or no treatment</td>
<td>464/485 (95.7%)</td>
</tr>
</tbody>
</table>

Table 1: Appropriate Prescription Given Based on CHW Diagnosis. Taken from Hamer et al., 2012.

That strong data point of 90% recovering without malarial treatment may help assuage the fears that hospital workers and CHWs have by not giving a
treatment to febrile children. A theory as to why CHWs are more likely adhere to the test results is because they do not have as much background knowledge and will more likely follow the guidelines that others provide for them in evaluating rapid diagnostic testing. In addition, in this particular case the training was novel in that few programs trained CHWs to help treat both pneumonia and malaria, both of which are the two leading causes of mortality in children under 5 worldwide. It helps to make CHWs adhere to not providing antimalarials to RDT negative patients since they still have tools to treat patients for the other diseases that they learned about in training.

Masaninga et. al (2012) was a retrospective study of community-level introduction of RDT use in Livingstone District, Zambia where RDT introduction in 2007 use led to a large decline in reported malaria cases and antimalarial consumption. Malaria declined by 96.6% from 30,723 cases in 2007 to just 1,022 total cases in 2009 (23 confirmed, 999 unconfirmed), mortality due to malaria declined from 60 cases in 2004 to zero cases in 2008, malaria-like fever declined, ACT use declined from 12,550 courses per quarter to 822 courses per quarter, and quinine consumption declined. The exact RDT positive rate was not well documented over the years of the study, but the authors sought trends by comparing data from the study period to more recent data. 2009 records show that 3,605 suspected cases were tested with RDTs or microscopies, garnering 119 positive results, while in 2011 2,926 suspected malaria cases were tested and 72 were positive.
The training in this program involved CHWs who received training to treat with ACT only if the patient had an RDT positive result and to refer patients with significant fever and RDT negative results. Prior to this, the region mainly used symptom-based diagnosis due to limited microscopy (only 12.5% of their 1,750 public health facilities) (Masaninga et al., 2012). Training helped adherence since it stated that most RDT results would result in negative results since malaria stands as a highly over diagnosed disease. However, there was still malaria treatment above the confirmed malaria rate in this study. The authors feel that full the potential of RDTs will only be achieved when better strategies to manage RDT-negative cases emerge.

Thiam et al. (2012) performed a study in remote villages of Senegal and attempted to demonstrate the feasibility of integrated use of RDTs for diagnosis and ACTs for treatment via a scale-up process from 2008 to 2010 using trained volunteer Home Care Providers (similar to CHWs). 93% of the 12,582 suspected cases were evaluated by Home Care Providers and 37% of patients had a positive RDT, so that 97% of those people were cured via antimalarials (Thiam et al., 2012).

The training stated that if a patient was RDT negative or a more sensitive case, home care providers referred patients to health care facilities: 6,486 RDT negative patients, 119 infants, 105 pregnant women, and 161 severe cases were referred. Overall, incidence of in-hospital deaths attributed to malaria decreased significantly by 62.5%, while the decrease in the comparison group was slight.
and not statistically significant (Thiam et al., 2012). Part of the reason for the success of this program in bringing effective malaria diagnosis to remote regions is that the Home Care Providers had an option to give a form of treatment to RDT negative patients, the option of referral. In Ishengoma et al. (2011), 23,739 febrile cases were examined and 18,217 of those cases were examined after RDT use had been implemented in an area of declining malaria prevalence in Tanzania by community-owned resource persons (similar to CHWs). These centers also had microscopy available. Only 27.8% of the 18,158 patients were tested for the malaria parasite with RDTs, however, of the RDT negative results 20.1% received AL treatment. Of the group that received antimalarials with negative RDT test results, 74.3% (3,154) were under the age of five and 3.4% (475) were over the age of 5. Despite this, RDTs greatly reduced the overtreatment using antimalarial dispensing from 98.9% of febrile cases to 32.1% of febrile cases in children under the age of 5 (Ishengoma et al., 2011).

A key component of the training was how to identify which patients to treat and which patients to refer to the nearby health facility. Therefore, adherence by the community-owned resource persons to treatment guidelines was over 95% in cases from all age groups (Ishengoma et al., 2011). Adherence was very high since they were just following Tanzanian protocol, which stated to treat all febrile children under 5 with antimalarials irrespective of diagnostic result.
In Chanda et al. (2011), they used CHWs for delivery of ACTs and RDTs in home management for malaria in two districts in Zambia from June 2008 until December 2009. There was excellent adherence: in the Chongwe district, 100% of RDT negative results were not prescribed an antimalarial and 99.4% in the Kalomo district. All RDT positive patients in both districts received an antimalarial. Most importantly, none of the negative RDT cases progressed to severe malaria and no deaths were recorded. Severe cases of malaria received referrals to a health facility for further management. Adherence in this trial is the best ever reported in Zambia. This was maintained even though there were large differences in malaria prevalence in the two districts: Chongwe district had 4.5% of its febrile cases diagnosed as malaria (257/5,648) while Kalomo had high malaria prevalence with 49.1% (2,061/4,199) of its febrile cases diagnosed as malaria.

Training included practical sessions on how to use RDTs for malaria testing and how to interpret the result, essence of stock management, essence of infection prevention, and an emphasis placed on using the diagnostic result to inform the decision to prescribe an anti-malarial or not with referral mechanisms for severe malaria and non-malaria febrile cases. Of those not needing referral, the most common prescriptions involved painkillers, multivitamins, and deworming tablets. In these Zambian districts, care givers were happy with the services provided by the CHWs and their committed attention to patients, partially because in these areas community members recommend certain
individuals to be trained by health center personnel to work as a CHW. Since CHWs were so effective in this trial, if and when their case loads get higher due to success these volunteers may need compensation to maintain keeping up with the workload (Chanda et. al, 2011). Part of the reason for success is also that researchers gave the CHWs alternate treatments that they could use to help aid the patient, helping to ease the anxiety of sending a febrile patient away with no treatment if they receive an RDT negative result. The fact that the community helps to recommend CHWs may have added to the adherence of the CHWs since they community has already seen them as hardworking, diligent, patient, and intelligent.

Elmardi et al. (2009) executed a study in 20 villages of Sudan: volunteers (similar to CHWs) were trained one per village on how to use RDT for diagnosis and to treat them using artesunate plus sulphadoxine-pyrimethamine or refer the severe malaria cases and non-malaria cases between May 2007 and January 2008. Their communities based on the study team’s important five characteristics chose these “Malaria Control Assistants”: availability in the area most of the time, acceptability by the community, reading ability, writing ability, and willingness to work as a volunteer. Pre- and post-intervention assessment involved household surveys, focus group discussions with community leaders, structured interview with the volunteers, and records and reports analysis (Elmardi et al., 2009).

Use of RDT improved accuracy and trust in diagnosis, but 30% of volunteers (6) did not rely on negative RDT results when treating fever cases but
instead relied on their clinical sense which equated fever with malaria. Therefore, those “Malaria Control Assistants” with experience in managing malaria or educated were less likely to rely on the RDT result. They treated 3,475 patients with 17.6% being under the age of 5 years and referred 0.9% of cases to the nearest hospital by diagnosing them as having another febrile condition and not malaria. There was no data regarding antimalarial prescriptions given to patients based on RDT results. Unfortunately, the project increased treatment-seeking behavior from 83.3% to 100% with the introduction of the CHWs (Elmardi et al., 2009). Even though some programs may assume that CHWs do not have much background knowledge on malaria, some do and therefore will need some training to overcome their old diagnostic habits.

**Effect of Children Patients on Adherence**

In Ishengoma et al. (2011), Tanzanian guidelines were part of the reason that adherence was not as high as it could have been in the CHWs. Their reason for providing antimalarials to children less than 5 years when faced with an RDT negative result is that the most recent Tanzanian guideline when the study occurred was made in January 2007 when Tanzania changed its malaria guidelines due to the new ACTs on the market. This change stated AL should be prescribed to all febrile children less than 5 years irrespective of laboratory results while treatment of people over 5 years has to be based on laboratory conformation.
Study Designs, Results, and How Training Affected Adherence

Reyburn et al. (2007) was the first randomized clinical trial to examine if RDTs changed prescribing practices and lasted from January to August 2005, during which time 2,416 patients received RDT or microscopy for malaria testing in northeastern Tanzania. There was a high rate of malaria treatment for negative results in both groups: 86% of the 1,030 patients randomized to the microscopy group had a negative result but 51% were treated with an antimalarial, 84% of the 1,193 patients randomized to the RDT group had a negative RDT result but 54% were treated for malaria. Overall, more than 90% of the prescriptions for antimalarial medicine in low-transmission areas were for patients that had a negative diagnostic test for malaria.

The training they received was basic and did not seem to help them adhere to the RDT results. The training included discussion of RDTs and their high sensitivity and specificity and reviewed Tanzanian national malaria treatment guidelines which stated that a negative malaria test should allow a provider to think of alternative diagnoses to be considered (Reyburn et al., 2007). However, they were only told that alternative diagnoses should be considered, perhaps the providers considered others but did not act on them. An additional reason for massive over diagnosis of malaria and the lack of adherence may be
because physicians would use different tests for different patients, as opposed to there being a whole health facility effort to use one type of diagnostic tool.

Hamer et. al, (2007) relates to a clinical trial in Zambia that surveyed 104 health facilities, most had microscopy, RDTs, or more than one diagnostic test present. However, 58.4% of patients with negative blood smears received an antimalarial drug as well as 35.5% of negative RDT results. The febrile patients that did not have a diagnostic test performed received an antimalarial 65.9% of the time. Almost all of the patients with a positive microscopy and positive RDT result received an antimalarial. Overall, RDTs remain underused and many patients with negative RDT results inappropriately receive antimalarials.

A few years later, Hamer et. al (2012) executed another clinical trial with an excellent training program. Training was given to 260 participants (clinical officers, nurses, environmental health technicians) in all 72 districts that included multi-language (English, Bemba, Nyanja) workshops, wall charts, and pictorial guides that gave participants knowledge on how to check RDT expiration dates, perform the test, and see if the test gave a positive, negative, or an invalid result. However, it did not provide recommendations on how to respond to a positive or negative result. The lack of giving the participants information on how to respond to conclusive results might have confused the participants. It is not that the workers do not understand the test, because the lowest rate they had in prescribing an antimalarial to a RDT positive case was 96.6%. Adherence to the
test result with RDT negative patients would have been higher if they had specific recommendations on how to respond to negative test results.

Masanja et al. (2010) exemplifies an instance of adherence in health workers in peripheral health facilities without microscopy. It involved 12 health facilities in Rufiji District, Tanzania where 30,195 patients were seen over an 11-month span, and 35.6% of those patients acquired diagnosis with an RDT. 51.5% patients received RDT positive results, of which 98.6% were treated. 48.5% of patients were RDT negative and only 4% of them were treated with antimalarial medication (Masanja et al., 2010).

The training, which involved local malaria epidemiology, the importance of RDTs, patient testing criteria, subsequent actions to follow with positive and negative RDT results, how to perform an RDT, practice reading and recording RDT results, and practice sessions on febrile patients and other health workers, can partially explain high adherence (Masanja et al., 2010). The guide on how to respond to RDT positive and negative results is most likely the training tool that most influenced the high adherence.

In the clinical study of Chinkhumba et al. (2010) in Blantyre, Malawi 2,576 patients were tested with RDTs, and 58% of patients with negative RDT results were treated with antimalarials in sites without local microscopy. Training stated that patients with mixed microscopy negative, RDT positive cases should not receive treatment with antimalarials but 54% of providers still prescribed an antimalarial to those patients. 98% of patients with positive microscopy and RDT
results received an antimalarial prescription. 7% of patients who were both microscopy negative and RDT negative were still prescribed an antimalarial (Chinkhumba et al., 2010).

All health workers received training—clinicians and nurses received one-day refresher training on malaria diagnosis and treatment according to the new national malaria treatment guidelines. At the time of the study, the WHO recommended malaria management based on parasite-based diagnosis in all cases and the Malawi National Malaria Control Programme therefore developed new malaria treatment algorithms incorporating the use of RDT in patients over 5 years for health facilities where malaria microscopy is not available (Chinkhumba et al., 2010).

The D'Acremont et al. (2011) RDT intervention involved a cluster-randomized control analysis from January 2006 until September 2008 in Dar es Salaam, Tanzania. Three hospitals and 6 health facilities underwent the RDT intervention and 3 health facilities were matched as RDT-free controls. The positivity rate of microscopy used before the intervention was 49% and after intervention, the RDT positivity rate reduced to only 8% that is more in line with Tanzanian parasite prevalence using expert microscopy. RDT use greatly reduced AL prescription (68% in intervention group, 32% in control group) as well as quinine use (63% reduction in intervention group and 2.49 times increase in control group). This significant reduction is partly because there was excellent
adherence to the test result since only 7% of RDT negative patients received an antimalarial (D’Acremont et al., 2011).

The training helps to explain why this group adhered well- it was presented as a pilot phase of national RDT deployment and health workers did not see it as an isolated research project. The audience additionally appreciated data detailing that malaria actually had a low prevalence in Dar es Salaam, that routine microscopy usually had bad quality, that RDTs performed excellently, and that RDTs help to combat mistrust between laboratory staff and clinicians.

Unfortunately, a side of effect of adherence to RDTs involved antibiotic treatment increasing from 49% to 72%. However, there was no change in those facilities acute diagnosis of respiratory infection, pneumonia, diarrhea, and urinary tract infections (D’Acremont et al., 2011) Therefore, to not simply move the over prescription of antimalarials to the over prescription of antibiotics, more training for the management of other causes of fever should be integrated into RDT learning. It would be a shame if RDT use augmented the problems of antibiotic resistance across the globe. Especially since there was not an increase in diagnosis of other fever causing illnesses that patients may have had instead.

Skarbinski et al. (2009) performed a randomized trial where sixty Kenyan health facilities were either randomized to receive RDTs, training, guidelines, and supervision or randomized to receive just supervision. Of the 1,540 patients used in the analysis (2,004 patients enrolled), only 7% had uncomplicated malaria and AL treatment use only after laboratory confirmation reduced AL consumption by
63% (p = 0.03) since the health workers mostly adhered to RDT results (AL given to 88% of RDT positive results and 9% of RDT negative results). Unfortunately, this also reduced AL prescription to patients that did not have any diagnostic testing done on them, causing some uncomplicated malaria cases to go untreated. In the clinics chosen, about half also had microscopy available (Skarbinski et al., 2009).

Training involved interactive discussion in small groups on RDT use, a presentation of the revised national malaria guidelines for outpatients over 5 years, information on dosing, information on how to administer AL, and information on how to manage severe malaria. Revision of national malaria guidelines was that malaria is defined as fever (temperature over 37.5°C) within the last 48 hours with no apparent alternative cause such as soft tissue infection, urinary tract infection, ear infection, etc. (Skarbinski et al., 2009).

Part of the success in adherence is that each individual health care facility had all of its providers use RDTs or had all of them not use RDTs. Again, this article shows that RDTs should be performed in all patients if possible to determine if they have malaria when presenting with fever, especially since it had the unintended adverse effect of lowering the prescription of AL to patients who did not have a diagnostic tool used on them when some of them did in fact have uncomplicated malaria. However, excessive use of RDT testing would undermine the cost savings that RDT can provide so research needs to be done to better understand why and when health workers order diagnostic tests.
Bisoffi et al. (2009) executed a randomized multi-center trial in 2006 in rural Burkina Faso, involving 852 febrile patients during the dry season and 1,317 febrile patients in the rainy season who were individually randomized (about half and half) to receiving RDT or presumptive treatment. In the dry season RDT, testing was positive in 28.0% of cases and positive 68.2% of the time in the rainy season. However, 80.8% of the RDT negative results in the dry season were still diagnosed as having malaria and treated accordingly as were 85% of RDT negative results in the rainy season being diagnosed as having malaria and treated accordingly. This high percentage of patients being diagnosed with malaria despite the negative RDT result showed almost no difference from the diagnosis of malaria with presumptive treatment. Therefore, there was also no change in the diagnosis of other febrile causing illnesses in the RDT intervention arm (Bisoffi et al., 2009).

The people who received training to perform the RDT tests on patients were research assistants who were recently graduated yet still employed junior nurses recruited to the study, and their training involved an intense 3 days where they learned study protocol and how to execute and read an RDT. Dispensary nurses also received training on RDT reading and RDT performance from literature. The main points given to both groups was that RDT negative result virtually excluded clinical malaria while a RDT positive result did not rule out fever being caused by other disease including malaria or in absence of malaria. Health workers were not told to refrain from malaria treatment in case of a
negative result, which the authors admitted was a major flaw in the study design. The nurses felt that the probability of malaria is so high that the disease presence remains likely even after a negative RDT result. Additionally, the authors point out that false positives with RDTs due to being a simple carrier of malaria parasites may make a provider think that the fever is due to malaria when it may be another disease such as pneumonia, this exact case happened to one child in their study (Bisoffi et al., 2009).

The main fault of this training is that the treatment that both people in the control group and in the intervention group received was still to depend on national diagnostic guidelines, which were to treat all febrile cases as malaria until proven otherwise. These health providers did not see the new RDTs as sound evidence to prove otherwise for that old saying (fever equates malaria) and most likely contributed to the incredibly low adherence. Compliance was so low that the investigators could not even determine their goal of evaluating RDT safety. Additionally, use of RDT or presumptive treatment was by each patient and not by the whole health facility as a whole. The same research assistant may utilize presumptive treatment on one patient and RDT on another patient, limiting the importance of the new RDTs. In this study, they essentially ignored the RDT results. In addition, not all people giving the RDT results were trained to use it due to logistical problems.

Kyablayinze et al. (2010) examined how RDTs affected antimalarial prescriptions in Ugandan outpatients at low-level health care facilities with
different malaria epidemiological settings. 21 health facilities had all health workers were trained to use RDTs for all suspected malaria cases despite age. Five low-level health care facilities with clinical diagnosis only were used for comparison. Of the 166,131 people evaluated in the 21 intervention facilities, over 90% of eligible patients received an RDT; that is excellent since the health workers were only encouraged to use RDTs but not restricted to it. Overall, use of antimalarials went down 38%, with the greatest reduction in the hypo-endemic settings (greatest drop was 59% in the Kapchorwa district) but no significant change in the urban settings with hyper-endemic states of malaria. An average of 30% of the RDT negative patients received an antimalarial and of these RDT negative group children less than five years of age were 2.6 times more likely to receive anti-malaria; 49% of children under five and 28% in people over 5 received an antimalarial with an RDT negative result. 99% of the RDT positive group received an antimalarial.

They also partook in in-depth interviews where 92% believed that RDT positive result confirmed malaria while only 49% believed an RDT negative result excluded malaria. After the one day training, 98% said they were committed and willing to perform RDTs on a daily basis to manage febrile outpatients. The health workers admitted during interviews that they sometimes treat RDT negative patients because they are afraid of the challenges of severe malaria because of the long distances to referral hospitals if the need arises. Other health workers stated that negative microscopy results do not exclude malaria due to
the possibility of sequestration of malaria parasites from peripheral blood, even though this does not apply to RDT, it may still attribute to the overall mistrust of negative results. Other thoughts by this group is that health workers found it socially acceptable to offer antimalaria to RDT negative patients and that since some health workers were unable to make a differential diagnosis they were more likely to give antimalaria so patients would appreciate the medical care (Kyabayinze et al., 2010).

Training involved health workers (nursing assistants, nurses, clinical officers, and laboratory technologists) who were trained using the WHO training curriculum to understand parasite-based management of malaria, use of RDTs, record keeping, and waste disposal. In addition, training instructed them to test all presumed malaria cases with RDTs despite age or malaria endemicity setting. However, it also told them to give treatment according to the results and the Ministry of Health treatment guidelines which stated that “any patient with fever or history of fever within the last 24 hours without evidence of other disease should be treated for malarial even with a negative blood smear for malaria parasites” (Kyabayinze et al., 2010). An additional reason for less than ideal adherence is that this group did not have specific guidelines on what to do if it was not malaria.

Msellem et al. (2009) implemented a nonrandomized clinical trial involving four primary health care units in Zanzibar. Febrile patients were allocated to clinical diagnosis alone or clinical diagnosis with RDT diagnosis. 1,887 patients
were enrolled from February to August 2005, 55% of them being children under the age of 5. RDT use was associated with lower antimalarial prescription rates - 36% (361/1,005) versus clinical diagnosis 85% (752/882) prescription rates. Additionally, antibiotic prescription rate was higher in RDT use periods, 37% use versus 27% use in the clinical diagnosis. Only patients diagnosed with malaria in both groups garnered an antimalarial prescription. The majority of antibiotics were prescribed to children below age 5 (65%) in the RDT with clinical diagnosis group versus the clinical diagnosis alone group (Msellem et al., 2009).

The health care workers were registered nurses with 3 to 4 years of formal training where Malaria Control Programme and District Health management Teams of Ministry of Health trained them in diagnosis and treatment and in the IMCI algorithm. They additionally received one day training on the use of RDTs using the manufacturer’s instructions, encouragement to base antimalarial treatments on RDT results during RDT weeks, and received specific instructions to consider other treatments especially in RDT negative children while encouraging their guardians to return with the child if fever persisted. They also received instruction to prescribe other treatments in accordance with IMCI guidelines and their clinical judgment. Nurses expressed that the main reason to prescribe antimalarial drugs to patients with RDT negative results was fearing a false negative test result and being aware that delays in giving antimalarial treatment can be fatal (Msellem et al., 2009). One of the problems is that this
study did not encourage change to RDTs well since the participants switched between the old and the new methods.

*Prior Training Effect*

Part of the reason that primary health workers do not adhere to the results of RDTs is that throughout their training they learned that fever equates to malaria and they remain attached to that idea despite new trainings. Reasoning for this stems from a multitude of causes such as the health care workers think their knowledge remains smarter than the test and they have a mistrust for the test. This may even lead to higher morbidity and mortality because the true cause of the illness may be left untreated (Masanja et. al, 2010).

Reasons for not following negative RDT results is that health providers feel reluctant to deviate from the sentiment that fever equates to malaria, a perceived lack of alternatives that requires educating health providers on alternatives, and that the drug has a low cost (Masaninga et al., 2012). Additionally, part of the reason for the mistrust regarding what laboratory technicians say when evaluating malaria diagnostic tools from clinicians is that the microscopy used is often poor so they have frequently erred on the side of caution and given antimalarials. Now, the user-friendly RDTs are much less likely to give inaccurate results since they do not require an expert to analyze the results and will potentially boost clinicians’ confidence.
Effect of Ambiguous International, National, and Local Guidelines on Adherence

The WHO and other national guidelines have added to some of the confusion since they have stated in the past that malaria should be considered even if a patient has a negative RDT test result (D’Acremont et al., 2009). In general, CHWs do not know of these national guidelines as much although they may receive such knowledge during their RDT trainings, while hospital workers remain much more aware of them. In Reyburn et. al (2007), perhaps part of the failure is that they were told to re-look at ambiguous Tanzanian national malaria guidelines that said negative test results should simply allow other alternative diagnoses to be considered. Even if the ambiguity was not directly re-stated during the training sessions, it signaled for the providers to do what they had always done prior with the malarial diagnoses.

In Chinkhumba et al. (2010), part of the low adherence to negative RDT test results (54% of patients with RDT negative results received an antimalarial) ensues from the Malawi National Malaria Control Programme which tried to incorporate use of RDT to determine diagnosis and treatment, but only in patients over the age of 5 at centers without microscopy. Although the article did not detail age differences, perhaps many of the participants who received an antimalarial when RDT negative were children less than 5 years. Additionally, many of the health facilities also did have microscopy and it has been shown that frequently hospital workers ignore negative slide results; perhaps they transferred that disregard of negative slide results to negative RDT results.
In Kyabayinze et al. (2010), the massive prescription of antimalarials to children under 5 when RDT was negative most likely stems from the IMCI strategy that Uganda had in 2007 at the time of the study. Additionally, training was under WHO guidelines that stress those febrile cases under 5 should be suspected as having malaria first and treated with antimalarials before other options receive consideration. In addition, the Ugandan guidelines also said that their workers could ignore results and still promoted presumptive treatment.

The Bastiaens et al. (2011) trial saw the impact of antimalarial prescription to febrile outpatients under the age of 10 years at three hospitals in different districts (Sumve, Biharamulo, and Rubya) after a Tanzanian governmental policy change stating that antimalarial treatments should strictly be given to RDT positive individuals and RDT negative individuals should have alternative diagnoses looked for them. The study was purely observational and did not attempt to change clinical decisions; training simply explained the new government guidelines to medical officers in charge and the sensitivity of RDTs. Before this policy, there was no association between actual level of transmission intensity and drug-prescribing behavior, after the policy there was a substantial decrease in anti-malaria prescription. This article additionally provides an example that simple provision use of RDT before this Tanzanian policy change is another example of hospital workers not considering diagnostic results when it comes to malaria.
1,608 outpatients under the age of 10 years that presented to the hospitals from September 2009 – February 2010 were included for analysis. Antimalarial prescriptions for RDT parasite-negative individuals after the new policy change decreased from 89.1% (244/274) to 38.7% (46/119) in Biharamulo and from 76.9% (190/247) to 10.0% (48/479) in Rubya; it remained 68.1% in Sumve since it did not receive the training course but used as a comparison group. Parasite prevalence differed greatly among the groups with the lowest in Rubya (1-4%) and the highest in Sumve (42%). Participants prescribed antimalarial drugs to RDT positive patients in all cases. There was also an increase in antibiotic prescriptions: before the policy change in Biharamulo 12.8% of RDT negative patients received an antibiotic and afterwards 59.7%, in Rubya it similarly went up from 70.0% to 94.6%. The authors felt that this increase in antibiotic use meant that the clinicians were finding alternative diagnoses to malaria (Bastiaens et al., 2011).

Although there was no formal training, the authors believe part of the success is having well trained and confident hospital staff, clear guidelines, and having constant availability of the needed resources (RDT, antimalarials, antibiotics); otherwise staff could return to their former diagnostic and prescription habits. The healthcare workers at these hospitals were mainly clinical officers with two to three years of clinical training. Hospital records indicate that common diagnoses for other conditions exist in their outpatients:
pneumonia, HIV, gastrointestinal infections, tuberculosis, malaria, and other parasite infections (Bastiaens et al., 2011).

The governmental change also affected presumptive treatment for patients without an RDT, causing them to abandon it largely. Beforehand, in Biharamulo, 89% of patients without a slide taken were treated with an antimalarial, which went down to 27% after the policy change, this proportion changed from 67.5% to 2.0% in Rubya (Bastiaens et al., 2011). It is interesting that RDT use even affected presumptive treatment in these cases, which could even greater lower the risk of over prescription of antimalarials if people have an RDT stock out for example. However, it is dangerous if people presumptively think febrile cases are not malaria because it may cause missed cases; hospital workers should still definitely use an RDT to verify malaria.

Effect of Children Patients on Adherence

Part of the reason for the hesitance that providers face when withholding antimalarials from young children in both CHWs and hospital workers when they are RDT negative is because there is not much evidence that this approach proves safe (Hamer et al., 2012). On the other hand, other journal articles see that there is a potential that withholding treatment based on negative RDT results can be safe (Masaninga et al., 2012).

D’Acremont et. al wrote a response to Reyburn et. al (2007) and note that part of the reason for lack of adherence was that guidelines from Tanzania state
that if results are negative and no signs of severe disease exist then children under age 5 should be treated as having uncomplicated malaria and to look for another condition, similar guidelines exist in Uganda (D’Acremont et. al, 2007). Overall, the idea that children under 5 years should receive malaria treatment irrespective of test results because the disease has a more rapid course in them is inadequate (D’Acremont et al., 2007).

In Mtove et al. (2011), 965 children aged 3-59 months were enrolled over a one-year testing period of RDTs in a hospital that serves a rural population in Tanzania. 16.4% had an RDT positive result and all were treated with AL. 83.4% were RDT negative and were treated with non-anti-malarial medicines as per the study protocol. 47.5% of the RDT negative cases and 18.4% of the RDT positive children met WHO criteria for non-severe pneumonia and received amoxicillin treatment, additionally 4.2% of RDT negative, and 12% of RDT positive children met WHO criteria for non-severe pneumonia but did not receive amoxicillin. There was no evidence in terms of respiratory rate values to predict why there was prescriber confidence in withholding antibiotic treatment in the latter cases (Mtove et al., 2011). These health care providers already knew of pneumonia as an alternative reason for illness in febrile patients.

Six (0.6%) of children became RDT positive after enrollment which diminished health care workers attitude that RDT worked well; it is not impossible to distinguish between new and missed diagnosis of malaria with routine follow-up of RDT but in this case the investigators felt those 6 children were new cases.
To guard against the strong preference diagnosis of malaria among parents and clinicians, and the perception from those groups that due to application of new guidelines of RDTs that a child was denied treatment, researchers should remind clinicians and parents that no test is perfect and to bring children back to the health center if they remain ill. This could lead to over diagnosis of non-severe pneumonia as per use of the IMCI guidelines especially since there is no gold standard for pneumonia diagnosis (Mtove et al., 2011). Overall, this study helps to prove the case that it is all right not to treat children with antimalarials when they are RDT negative because this study did not result in missed diagnoses of malaria.

Effect of Microscopy Presence on Adherence

The hospital workers in Hamer et. al (2012) trusted the new RDTs more than microscopy since those clinicians were twice as likely not to prescribe antimalarials when having a negative RDT result as opposed to a negative blood smear with microscopy. Part of the reason for mistrusting or ignoring the results is that parasite detection usually gets performed by someone other than the prescriber (Hamer et al., 2012).

In Masanja et al. (2010), part of the reason for the high adherence to not prescribe antimalarials after receiving an RDT negative result (only 4% received an antimalarial when RDT negative) may be because there was no other
microscopy or diagnostic tool to use. Therefore, they more heavily relied on the RDT.
DISCUSSION OF HOW TO IMPROVE ADHERENCE

Many studies have examined the ability of CHWs and hospital workers to interpret the rapid diagnostic testing results with options on how to treat, which remains imperative. However, if a patient presents with fever and does not fit into the category of the few potential fever-causing illnesses that they received training about, both groups of workers may feel at a loss and prescribe malarial treatment. A methodology to combat this mistrust of negative results and assuage feelings of helplessness is to teach hospital workers and CHWs about other causes of fever besides malaria such as respiratory illnesses. Therefore, if they receive a negative result they do not have to feel guilty about not giving an antimalarial treatment if/when they find another disease to treat. An example of a good algorithm flow chart for them to follow (see Figure 7) is from Thiam et al. 2012, which had excellent adherence. Hamer et. al (2012) is also an effective example of how training with alternate diagnoses algorithm flow charts helps to heighten adherence (see Figure 8).

A proposed method is to make RDTs more widely available and to enhance quality control measures to raise confidence in the tests by health care providers. To increase use of CHWs in rural areas since they already adhere well and to increase their potential by designating health facilities in the area where CHWs can refer RDT negative patients. CHWs should be picked by people in their villages to ensure that they are of high quality.
Thiam et. al (2012) also suspects that maintenance of high adherence by Home Care Providers to RDTs stems from the gradual scale-up of RDT use in the region; this group also plans to train Home Care Providers to manage other fever producing illnesses such as pneumonia and diarrhea. One method is to make sure that in scale-up operations and clinical trials that everyone in a health facility should use RDT and not have, for example, the same physician use RDT on one patient but microscopy on another (D’Acremont et al., 2011).

**Figure 7: Algorithm Flow Chart for Fever Management by Home Care Providers.** Taken from Thiam et al. 2012.
Malaria guidelines in the national and international scale need to become unambiguous and the new guidelines should be dispersed among the
community. A component of the new guidelines should include allowing denial of antimalarials to children when RDT negative. In regions where previous guidelines have been ambiguous, there should be advertising campaigns arranged to show the new changes. The new changes include the fact that malaria is declining in many areas and that fever does not equate to malaria as it did in the past due to many efforts to reduce malaria such as insecticides, larval control, insecticide-treated nets, etc. This will be beneficial when seen by hospital workers and CHWs, but also when seen by laypersons since it will make them less likely to request antimalarial treatments and to request antimalarial tests as frequently as they do now.

Additionally, a push to move from microscopy confirmed diagnostics to rapid diagnostic testing in all facilities, not just facilities that do not have adequate microscopy techniques, needs to happen in order to diagnose malaria succinctly. RDTs have a high sensitivity and high positive predictive value and prove useful.
CONCLUSION

There is a discrepancy, especially in low endemicity settings, of perceived and actual malaria cases. The use of RDTs is especially important in areas of Africa that have declining malaria prevalence so that the prescription of antimalarials also declines with its reducing existence. The use of RDTs also seems like it could be most favorable in areas that have low endemicity ratings because the reduction in antimalarial prescriptions that they will have if they comply with RDTs will be massive. On the other hand, places that have a high malaria endemic rate will not see as much of a decline in malaria cases diagnosed and therefore may not see RDTs as useful since they will be confirming what they already thought.

When different agencies first implemented the use of RDTs for malaria management, many assumed that providers would exactly follow the RDT result and treat patients accordingly but that simply was not the case. The groups must first deal with steadfast attitudes among many communities where fever equates to malaria even when presented with evidence to the contrary. Overall, effective implementation of RDTs requires an attitude change in health care providers on both the community and hospital level.

In general, health care providers give antimalarial with positive RDT results in essentially a 1:1 ratio, it is only when faced with a negative RDT result that adherence begins to falter. In order to improve this, cascade models seem to
be effective as well as gradually introducing RDTs into practice so as to maintain efficient use of RDTs. Good training helped to decrease antimalarial prescribing to negative result patients but never as much in hospital workers as CHWs prescribe.

Trained clinicians and health care workers are more reluctant to adopt the changed protocols that RDT brings because they feel that they already know a lot about the malaria subject. Part of the reason for high adherence in CHWs is that in their training they were more likely to be offered options to take if the RDT result was negative. Additionally, they adhere better than hospital workers do because hospital workers do not have anyone to refer the patients to, they are the referral, and that poses a lot of pressure to try to prove the symptoms of the patient. Overall, training was not that different between CHWs and hospital workers but with the hospital workers, a lot more prior knowledge needs overcoming before they adhere to RDT results. It is not so much that CHWs adhere to RDT results in spite of their lack of overall medical training but that they adhere to RDT results precisely because of this lack of overall medical training.

Perhaps the presence of multiple diagnostic tools at hand makes it more difficult to adhere to the RDT result. Of course, a solution to this would not be to limit the use of microscopy in order to boost RDT adherence, especially when it should be used in combination to confirm one another. It might be beneficial to give extra training to health care facilities that are fortunate to have both
diagnostic tools on the benefit of adhering to RDTs. This discrepancy could be because microscopy is expensive and health care facilities that have both options have more highly paid and well-trained physicians who have more medical training and may feel more reluctant to change their methodologies.

The future direction of malaria management needs to improve malaria treatment in Africa by limiting patients’ exposure to antimalarial side effects unnecessarily, reduce resistance to antimalarial drugs, find alternative febrile causing diseases to treat them, and to improve cost. The use of rapid diagnostic testing is an excellent way to accomplish that.
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EDUCATION

Boston, MA
Sep. 2011 – May 2013
Boston University School of Medicine: Masters of Arts in Medical Sciences.
Coursework: Physiology, Pathology, Biochemistry, Pharmacology, Statistics.

Hanover, NH
Sep. 2007 – June 2011
Dartmouth College: Bachelor of Arts with majors Psychology, Spanish (fluent), Pre-Medicine.
Transfer Term: Harvard University (Cambridge, MA) for Organic Chemistry, Summer 2010.
Foreign Study: Universidad de Complutense (Madrid, Spain) for Spanish immersion, Fall 2009.

Tampa, FL
HB Plant High School
Awards: National Merit Semi-Finalist, graduated honors in top 7% of class, AP Scholar, National Honor Society, scores of Excellent in Orchestral Solo and Ensemble Festivals

RESEARCH/WORK EXPERIENCE

VA NY Harbor Healthcare System
New York, NY
Oct. 2012 – Present
The Respiratory Protection Effectiveness Clinical Trial (ResPECT)
Health Science Specialist
• Determine if medical masks or N95 respirators protect health personnel more from respiratory illness with Dr. Michael Simberkoff (Executive Chief of Staff), sponsored by Johns Hopkins and the CDC.
• Enrolled 160 people (Manhattan, Queens, Brooklyn), monitor subjects’ health, collect bodily fluids (blood, mucus) and test them, monitor hand washing/mask wearing, and collaborate with six other sites.

Dartmouth College
April – June
Neurosurgery Research
• Investigated memory consolidation by lesioning retrosplenial and postrhinal cortices in rats.
2011 • Operated on 12 rats, executed fear conditioning tasks, evaluated results, for 10hrs/wk.

**Dartmouth College**

**April–June 2010**

**Independent Study in Psychology**
• Studied effects of exercise and mood on cognition. Advertised, pre-screened students, and enrolled 25. • Scheduled appointments, delegated computer tasks, sent daily surveys for 28 days, compiled database.

**Dartmouth College**

**April–Aug. 2009**

**Howard Hughes Medical Institute Life Science Internship**
• Investigated effects of Kynurenic acid and nicotine on learning/memory in 48 rats, for 10hrs/wk.

**Women’s Daytime Drop-In Center**

**Berkeley, CA**

**Jan.–Mar. 2009**

**Tucker Foundation: Dartmouth Partners in Community Service**
*Full-Time Intern at an Advocacy Center for Homeless Women and Children*
• Assisted clients’ attainment of independence through resources (healthcare, education, housing, etc.).
• Supported staff by overseeing office facilities, fundraising, facilitating group therapy, cooking.

**Dartmouth College**

**Sep. 2008–June 2011**

**Office of Residential Life**
*Undergraduate Advisor*
• Promoted health/safety of 20 freshmen via counseling, crises resolution, weekly meetings, and bulletins until fall 2010. Then guided 60 upper class students, 1/3 in Arabic and Russian programs, for 15hrs/wk.
• Fostered community in up to 650 residents alongside a community director and other advisors.
• Inducted into National Residence Hall Honorary that recognizes top 1% of residence hall leaders.

**Dartmouth College**

**Sep. 2007–June 2011**

**Hopkins Center for the Arts**
• Played violin in Dartmouth Chamber Orchestra and chaired as strings manager (9/2007–12/2008).
• Inspected pianos and conditions of music rooms daily, for 7hrs/wk (2/2008–6/2011).
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<td>Eko Hospital</td>
<td><strong>Full-Time Shadowing Intern</strong></td>
<td>• Similarly to a medical student, observed doctors practicing surgery, pediatrics, neurophysiology, cardiology, pathology, gynecology, IVF, radiotherapy.</td>
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<td>Lagos, Nigeria</td>
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<td>Aug. 2011</td>
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<tr>
<td>Phoenix, AZ</td>
<td><strong>Alternative Spring Break Trip for the Homeless (Maggie’s Place and André House)</strong></td>
<td>• Served guests by organizing donations, meals, laundry service, and showers.</td>
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<td>March 2011</td>
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<tr>
<td>Hanover, NH</td>
<td><strong>Nathan Smith Society Shadowing Program at Dartmouth Hitchcock Medical Center</strong></td>
<td>• Observed Anesthesiologist C. Dodge MD (2010) and Psychiatrist D. West MD (2011) for 20 hrs. total.</td>
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<td>April–Jun 2010/2011</td>
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<tr>
<td>Dartmouth College</td>
<td><strong>Alpha Phi Sorority</strong></td>
<td>• Assisted in fundraising projects for medical research and cooked for low-income persons monthly.</td>
</tr>
<tr>
<td>Dartmouth College</td>
<td><strong>Eating Disorders Peer Advisor</strong></td>
<td>• After an 8-week class, supported individuals and organized termly campus awareness events.</td>
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<td>July 2008–June 2011</td>
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