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FEVER: IS IT MALARIA?

The first prerequisite for learning anything is thus utterly lacking—I mean, the knowledge that we do not know.

— Gottlob Frege, 1884

The untimely death of Ogonim, the only child of the protagonist in Flora Nwapa's epic novel *Efuru,* illustrates the consequences of failing to intervene quickly and effectively in fevers in malarious areas.[1] Set in an Ibo town close to the Niger River in the early twentieth century, the text depicts the time when Western medicine had arrived in Nigeria but was not yet widely available or trusted by the populace. The characters in Nwapa's tale journey to distant hospitals in the event of major or unusual illnesses, particularly for surgery, but they treat most illnesses in the home or with indigenous medicines. Efuru, the entrepreneurial heroine of the novel whose husband has left her for another woman, devotes all her love and attention to her beloved daughter Ogonim and is very distressed when the girl falls ill. Ogonim's illness begins with loss of appetite, constipation, and a fever. The child's condition deteriorates rapidly, in spite of all the efforts made to care for her, and eventually she goes into convulsions and dies. This fictional account resembles the biographies of many children who died of fever at a time when so-called scientific medicine had not yet become the predominant form of care in Ibo-land. No one can be sure what killed these children. No doubt many died of malaria, but others succumbed to one of the numerous other infectious diseases endemic in this region of Africa.

A visit to Aro-Ndizuogu, a small town located just to the east of Ogonim's fictional home, shows how little has changed in the health situation of people who live in rural Nigeria despite the social changes that have transformed the region over the past century. The Aros, a feisty Ibo clan,[2] migrated directly from their place of origin, Arochukwu, to found this settlement. Prominent Aro-Ndizuogu

families have historically had ample landholdings and great material wealth. As the value of food crops declined and people migrated to the cities, the rural populace became increasingly impoverished and marginalized. In the 1980s, the Nigerian government decided to connect the market town of Onitsha by a new express road to another large city, Okigwe. The road was planned to run right through Obinetiti, a community at the center of Ndi-Aniche village in Aro-Ndizuogu. Villagers whose houses were marked with the fatal letters "ONOK," for Onitsha-to-Okigwe express road, were told that their homes would be demolished to make way for the roadway. Owners whose farmland and homes were eaten up by the road would be eligible for financial compensation. Typically, this sort of task requires wading through bureaucratic mire and expending personal resources to grease the palms of civil servants. Whatever compensation may be obtained is small compared to the value of the property appropriated. Without recompense, even more people would have no choice but to emigrate. The only benefits the road would bring the village were the potential for hawking farm produce and snacks to travelers and a more comfortable ride home for the holidays for the town's sons and daughters in the diaspora.

The graves of Charles Onwenu, an Aro-Ndizuogu politician who contributed to the fight for Nigeria's independence and to the nation's first republican government, and of his brother, a landowner of considerable wealth who bankrolled Onwenu's career, would be desecrated as the road was proposed to run right over them. As the time for construction approached, a popular journalist and Onwenu's daughter narrated a documentary about the unfairness of the road-building projects that was screened on national television.[3] Beyond the loss of village monuments, the road would inflict harm on the living. Not only would there be no sidewalk, but no one had thought to consider a footbridge or tunnel; children on one side of the wide, busy, and dangerous road would be left without a school, and other residents would lose access to the village stream, the principal source of household water at the time. At that time, no Obinetiti resident actually owned a vehicle that could travel on the expressway. In spite of these arguments, the plans could not be halted.

The construction of the road brought unprecedented destruction to Obinetiti. The dichromatic reddish brown and green village was defaced by bright white, crude brushstrokes on mud walls to mark where the road would go. This mark of death was splashed rudely to the left of the front door of an old, blind widow's house. Thankfully, concerns about her losing her bearings were ameliorated by another splash of paint a few weeks later. One morning, the intense orange sunrise over the red clay soil of Aro-Ndizuogu became unusually fiery. Gigantic yellow earthmoving machines tore through the village's narrow and bumpy paths, knocking over cocoa trees and smashing traps children had left to

catch small forest animals that might spruce up dinner. Clouds of red dust rose into the air and coated everything; men in lorries spat out the red grit that collected between their teeth. Children lined the construction sites each day after school and had to be dragged home at dusk by irate mothers.

Young women on their way to the stream were beleaguered by the outsiders employed in road-making. Many local young men had migrated to the city, so village maidens were unaccustomed to male attention. The overworked and poorly paid foremen and laborers evidently regarded consorting with the golden-brown-complexioned Aro-Ndizuogu girls as compensation for their heavy toil in this remote location. Catcalls soon led to lunch-break conversations and then to escorts to the stream and other places. Unfortunately, the bride-price for many an Ibo girl in the 1980s was far in excess of what a laborer could afford, and the protracted negotiations surrounding an Ibo marriage take longer than it takes to build a road. Many young women who strolled too far were left with nothing but a "child of the road."

These disturbances were highlights in the lives of the three grandsons of the blind widow who, through last-minute cartographic revisions, lost the wall of her compound but not her home. In many ways, their childhood resembled that of children Nwapa describes in her novel. True, unlike children in the early 1900s, these boys were sent to school, in addition to doing chores, and they were almost always given Western medicines when they were ill. Their grandmother's house bordered the busy road, offering the boys a great vantage point from which to view the progress of construction. The boys' mother, on whose meager income the family was largely dependent, pampered all three of her sons, just as Efuru did Ogonim, but the second son, Emeka, received preferential treatment because, in her view, he earned it by doing well at school. The oldest son cut school altogether to watch the road-building and later descended to petty theft. The youngest boy was having difficulty selecting a role model; the appeal of his delinquent eldest brother's exciting and less demanding life seemed irresistible. But middle son Emeka was special. He was well mannered and polite; above all, he was a good student. When he gained admission and a scholarship to one of the federal government boarding schools, it seemed that it was only a matter of time before his family's poverty would be history. When the road was completed, it carried him away to a new life at a prestigious school and brought him home for the holidays. Villagers debated whether he would become a doctor, a lawyer, or an engineer.

One morning during the summer vacation after his third year at secondary school, Emeka's mother found him shivering on his mat with a raging fever. She thought carefully about where to seek help. The road that had promised to bring modern amenities to Aro-Ndizuogu and facilitate their travel to the city had not

made health care more accessible. It was next to impossible to take him to the clinic in a neighboring town; bus fare for two was too expensive, and hitchhiking with a seriously ill fourteen year old was unlikely to succeed. Besides, primary care clinics were infamous for their long queues and scarce resources. Resorting to a traditional healer who used indigenous medicine was out of the question; one of the boy's distant aunts was a trained nurse, and practitioners of Western medicine frown on indigenous medicine. The mother considered consulting a nearby drug seller, but discounted this option because of the rumor she had heard recently that his tablets were not bitter, and therefore presumably ineffective. She decided to leave the child with his grandmother and visit the more reputable drug dispenser at the other end of the village.

At sunrise, the mother tied her savings in the corner of her wrapper and walked to the dispenser's shack. After describing his condition, she paid for a selection of his best pills containing the usual *iba,* or fever, medicine and memorized the directions by muttering them under her breath as she hurried home. Emeka, now a gangling, slightly underweight fourteen year old, was given more medicine than the last time he had fever. Like all mothers, she worried about her sick son even though, after nursing all three boys through countless bouts of fever, she knew that he would probably be better the next day. She had already lost one child, but her only daughter had died in infancy, as newborns are likely to do. In contrast to her friends, most of the children she had borne had survived that trying period. She knew she was fortunate. After all, one in twenty children in West Africa are estimated to die of malaria before they are five, and another sizable fraction is killed by diarrhea, respiratory infections, and other preventable diseases.[4] The loss of a day's pay here and there to nurse her son was a small price to pay for his survival. In the 1980s, Emeka's mother did not have to worry about compounding or cooking her son's medicine, a task that was incumbent upon mothers who lived in the early 1900s, when Efuru's tale was set, but which they learned to perform with skill and precision. All she had to do was buy standardized tablets and administer them at stated intervals.

It came as a shock that, despite the age-adjusted dose of antimalarials, the boy showed no improvement the next day and suffered a convulsion. Convulsions are not entirely unexpected in malaria but are usually only seen in very young children. The combination of therapeutic failure and convulsions made his mother suspicious. With a child of Emeka's promise, the actions of envious enemies who would work to keep the family down could not be ruled out. Such a stellar character with fine career prospects would be the ideal target for malevolents.[5] After a quick family conference attended predominantly by women with no formal schooling, the boy was carried to a nearby spiritualist church,[6] where he became the center of a night vigil with prayer and fasting.

In the small hours, prostrate on a pew, he had another convulsion and then breathed his last.

Fever Is Malaria, or Is It?

Emeka's illness and death mirrors that of the fictional Ogonim. Over the course of the twentieth century, in Africa as well as in the West, the understanding of fevers due to infectious disease and the repertoire of drugs that can be used to treat them have expanded considerably. Whereas Ogonim's relatives accepted her premature death as a painful fact of life, Emeka's relatives—especially those who were city dwellers—were both saddened and angered by what they saw as inappropriate care for a boy who, in their eyes, obviously had malaria. How could anyone be sure that he had received the correct medicine from an unsanctioned drug dispenser? What if the drugs were fake or the dose insufficient? When the medication did not bring relief, why was he taken to a local church instead of to a medical clinic? Yet, it is not clear that the small health center in the next town could have resolved the unanswered questions that surround his death. How was the mother to have known that she should have taken him to a hospital even further away?

Although Emeka's mother's choices were criticized after they proved ineffective, there is nothing to suggest that she did anything wrong during the early stages of her son's illness. In a part of the world where malaria is considered synonymous with fever, she had concluded that the signs and symptoms were consistent with *falciparum* malaria and, consistent with guidelines issued by the World Health Organization (WHO), had sought treatment close to home as quickly as possible.[7] The only relevant diagnostic tool at the nearest primary care center was a thermometer, but it didn't take a thermometer to detect his raging fever. At his initial visit to the clinic, Emeka probably would have been given first-line drugs to treat malaria. If the staff had found his condition particularly alarming, they might have referred him to a hospital. But it is uncertain that his mother, with the limited resources available to her, would have been able to get him there in the short time between his convulsion and his death. She did recognize the severity of his condition and the ineffectiveness of the initial treatment. With hindsight, we might argue that the health-seeking behavior of Emeka's mother was inimical to her child's best interest, but her choices are typical of those made by many Africans.[8] Medical pluralism flourishes on the continent, and the equal or higher weight given to both indigenous medicine and spiritual healing, which are today less patronized but have by no means disappeared in the West, is a function of the failure of the Western medical system to compete effectively with alternative systems of care.

The most important question, which neither the dispenser nor the primary care clinic could have answered, is whether Emeka had malaria at all. That was regarded as a foregone conclusion, which perhaps contributed to suspicions of a noninfectious diagnosis when antimalarials did not work. Other than the possibility that he was felled by a cruel curse cast by enemies, no alternate diagnosis was considered. Although malaria reputedly accounts for 31 percent of childhood deaths in Nigeria, there is a compelling need to consider other possible diagnoses. It is a well-established but little acknowledged fact that, even in areas where malaria is highly endemic, the disease can be diagnosed by clinical signs and symptoms alone in only about 50 percent to 80 percent of cases.[9] Malaria remains a likely cause of Emeka's illness and death, but emerging data from several locations within Africa suggests that there is at least a one-in-four chance that the youth had a bacterial infection that could have been treated successfully with antibacterial medications. Emeka was well above the age at which convulsions are most likely to accompany malaria, and he failed to respond to standard treatments for the disease. So the appropriateness of the treatment that he received remains questionable. Today, as with the deaths of children such as Ogonim so long ago, and in spite of unprecedented advances in health care over the intervening period, we can draw no definitive conclusion about the cause of this teenager's death. Even more seriously, it is not clear that his prognosis would have been any better had his mother taken him to a primary care center.

Standard Western treatment for severe malaria and similarly presenting severe infections is not ideal, but it is certainly better than no treatment at all. More critically, early treatment of malaria and diseases that present with similar symptoms prevents progression to the deadly central nervous system involvement that Emeka may have suffered on his final day. The intervention that would most likely have led to a different outcome for Emeka is consideration of an alternative diagnosis and the prompt administration of appropriate medicines. This course of action might have been undertaken at a hospital, but only if a bacterial infection could be diagnosed, if malaria could be ruled out, or ideally, both. If, on the day that he showed symptoms, Emeka's mother had been told that her child was seriously ill but did not have malaria, she might have got him to a hospital, albeit at great expense.

Fevers are so common in tropical Africa that many children die without precise diagnoses or effective treatments in spite of medical intervention. Emeka's story is representative of millions whose lives end prematurely in a feverish haze. Indeed, he fared better than many other children, who are unable to learn in school because fevers have interrupted or permanently damaged their cognitive development, or whose repeated illnesses so impoverish their families that they cannot then afford to educate them.[10] If Emeka had died of some obscure or

emergent disease, his death might be more understandable, though equally unbearable. What is paradoxical is the claim that the boy died of an age-old disease that is endemic in his hometown and is considered the leading childhood illness in Nigeria, and he died in spite of receiving what is generally accepted as appropriate initial treatment. Malaria has been described as "utterly treatable and highly preventable,"[11] largely because of scientific innovations that occurred a century ago. Dr. Ronald Ross of the University of Liverpool received the Nobel Prize in 1902 for "work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it," a discovery made in 1897.[12] A hundred years later, a young boy treated with antimalarials died without anyone being able to say whether or not this parasite was present in his blood. In cases like Emeka's, why can malaria be neither confirmed nor ruled out?

Plasmodium falciparum

Malaria is an ancient disease that probably emerged along with agricultural settlements. Humans who began to congregate in residential communities constituted a pool of hosts, allowing the malaria parasite to propagate. Settlements were often located close to bodies of water and created stagnant pools in which the vector for this disease could breed. By the early nineteenth century, malaria was endemic in most populated places, particularly in tropical and subtropical regions. Early in the twentieth century, the disease was eliminated from the temperate zone as well as from subtropical parts of Western countries such as the United States and Italy. Presently, malaria is endemic only in equatorial Africa and parts of Asia and Latin America.[13] In 2005, 95 percent of recorded malaria cases worldwide occurred in African children, and malaria remains a principal cause of death in this vulnerable population. The most deadly form of the disease, *falciparum* malaria, when promptly diagnosed and appropriately treated, usually has no long-term consequences. When episodes are protracted because of diagnostic failure or improper management, however, many patients—particularly children—can die. Many more children survive multiple and protracted bouts of malaria but suffer from anemia and neurological damage that affects them for the rest of their lives.[14]

Malaria parasites, like frogs and insects, have several stages in their life cycles. Whereas insects metamorphose from egg to larva, larva to pupa, and then pupa to adult in two different habitats, each of the six main stages of the malaria parasite inhabits a different niche. These stages are all one celled and contain the same genetic code, but otherwise they have little or no resemblance to one another.

Malaria parasites, known as *Plasmodia* (sing. *Plasmodium*), enter the human body with saliva from an infected female Anopheline mosquito. As the mosquito finishes her blood meal, the sporozoite stage of the parasite wends its way to the liver of the newly infected host. The sporozoite bores into a liver cell, develops, multiplies, and emerges in about a week (for *Plasmodium falciparum*) or two (for other species) as hundreds of merozoites.[15] The merozoites spill out into the bloodstream, where they infect red blood cells. They grow and divide until the infected cell can no longer hold them and ruptures, spilling out over two dozen merozoites, which in turn infect new blood cells. The blood stage is repeated until the patient is cured or dies. During the cyclic blood stage, particularly when merozoites spew out and attack new targets, the patient becomes feverish and weak. Some merozoites produce sexual forms of the parasite, called gametocytes, which are sucked up with blood by biting mosquitoes. Gametocytes mate in the mosquito and develop into embryonic forms, the last of which burrow through the mosquito intestine and end up in the salivary gland as a sporozoite, completing the cycle. A susceptible host is infected during a future blood meal.

Many people can recognize a fever, and the majority of fevers are initially detected by laypeople, who then seek medical attention. In many parts of Africa, patients do not have access to clinics or hospitals, and even those who do typically commence antimalarial treatment at home before seeking professional care. As a matter of public health policy, home care must be supported because malaria can debilitate and kill very quickly. The WHO recommends immediate antimalarial treatment for feverish patients in endemic areas.[16] At the same time, it has clearly enunciated and recently reiterated that "the signs and symptoms of malaria are nonspecific."[17] For several decades (until 2006), WHO advocated presumptive treatment of febrile patients close to home, not because it is optimal, but because it is the only possible course of action in many places:

> The diagnosis of malaria is based on clinical criteria (clinical diagnosis) supplemented by the detection of parasites in the blood (parasitological or confirmatory diagnosis). Clinical diagnosis alone has very low specificity and in many areas parasitological diagnosis is not currently available. The decision to provide antimalarial treatment in these settings must be based on the prior probability of the illness being malaria. One needs to weigh the risk of withholding antimalarial treatment from a patient with malaria against the risk associated with antimalarial treatment when given to a patient who does not have malaria.[18]

That risk includes the failure to treat the patient's actual infection, which may also be life threatening and could be treatable.

In the vast majority of infectious conditions, even when the patient is acutely ill, his or her appearance and history are not enough for even an experienced clinician to make a definitive diagnosis. Circumstantial evidence, such as the patient's location and contacts, or the diseases endemic in the environment, can only inform an educated guess. Many people claim to "know" when they have malaria, and medical practitioners, who are under greater pressure to make definitive pronouncements, often claim to be able to diagnose the disease using clinical signs alone. In crowded hospitals, a temperature slip from a nurse is enough to prompt a clinician to begin scribbling a prescription for antimalarials for a shivering child before the patient and the mother have had time to take a seat in the consulting room. Contradicting the general confidence that prescribers have in their clinical diagnosis of malaria, scientific studies suggest that fever is little more than a clue that points to malaria as one of several possible diagnoses.[19]

The historical "success" of symptom-based diagnosis of malaria in Africa is linked to the high prevalence of the disease. If 80 percent of fevers in a locality are actually malaria, then anyone diagnosing all fevers as malaria will be right eight out of ten times. This outcome is fine for the lucky majority, but the prognosis for patients with other infections is grim. Using current methods to diagnose bacterial infection in all febrile infections would be expensive and slow. But a negative diagnosis for malaria could serve as a valuable prescreen that could improve these sick patients' survival chances either by short-listing patients for additional tests or by identifying those with a likely bacterial infection for empiric antibiotic treatment. Paul Farmer and others have criticized the developed world for turning its back on the infections that are prevalent among the poor.[20] Failing to diagnose impoverished patients ensures that the costs and benefits associated with their treatment are not even considered. At least 20 percent of febrile patients in areas with a high burden of malaria receive inappropriate treatment because their conditions are regarded as too expensive to diagnose.

One-in-five odds of misdiagnosis and ineffective treatment would be unacceptable to many Western practitioners and their patients, but in parts of Africa where as many as one in ten children die before they are five years old,[21] this level of imprecision continues to be accepted. As children grow older and develop some immunity to malaria, and as antimalarial interventions are implemented, the proportion of misdiagnosed fevers increases. Routine, nonsevere malaria infections typically present with a fever, headache, and weakness—symptoms of generalized malaise. If the infection is caused by certain species of *Plasmodium,* in which the merozoite or blood cycle is synchronized, symptoms appear at precise intervals of three or four days, which is of considerable diagnostic value.

With *Plasmodium falciparum,* the most prevalent species in Africa, there are no such rhythmic clues.

Diagnostic Tests for Malaria

To determine unequivocally whether a patient has malaria, it is necessary to examine stained blood smears for parasite blood stages.[22] A drop of blood collected by pinprick is spread thinly across a glass slide and stained with a dye (Field's or Giemsa stain). Using a microscope, technicians can see blood stages of parasites, if present, as well as the patient's blood cells. Conveniently, *Plasmodium falciparum* is the easiest malaria parasite to identify. The best way to diagnose malaria is to perform a crude count of parasites because most people in malarious areas carry a few parasites even when they are well. The density of parasites in the blood often, though not always, correlates with the severity of the disease. This enumeration is done by counting the parasites in a set volume of blood or comparing the parasite count to the number of white blood cells, which serves as a sample calibrator.[23] The laboratory needs only a microscope, slides and staining reagents, and a trained technician. The entire operation can be performed without electricity if a mirror is used to direct sunlight onto the microscope.[24] Compound light microscopes are expensive but, if well maintained, last for decades. A number of clinics that have offered this service in the past do not do so presently because they lack a properly trained microscopist. However, people with secondary or even elementary schooling can be trained to prepare and view blood smears for malaria parasites.[25] In some African countries, graduate professionals with expertise in microbiology and other biomedical sciences are forced to seek employment in other sectors because there are few biomedical laboratory positions.[26] Many more technicians and aides have experience in parasite microscopy but stopped providing the service because blood smear examination was considered a lower priority than other services, such as dispensing medicines.

Routine diagnosis by reliable blood smear microscopy offers considerable advantages. When adults with fever attending Kenyan health centers were appropriately tested, drug costs were 80 percent lower. Even when the microscopist's skills were not optimal, so that specificity and sensitivity dipped below 90 percent, drug costs still decreased by 50 percent.[27] The long-term savings from avoiding the detrimental overuse of antimalarials in these cases is incalculable. Appropriate diagnosis for malaria, in addition to ensuring that feverish patients who do not have the disease in endemic areas are considered for other diagnoses, can provide sufficient savings to pay for itself.

Blood smear microscopy is a powerful but imperfect tool. If the malaria parasite is present in a non-blood-stage form, for example as the dormant hypnozoites seen in *P. ovale* or *P. vivax,* or in another liver stage, it cannot be detected by microscopy. It takes at least an hour to prepare, stain, and examine slides, although they can be processed in batches. Some technical expertise is necessary. Even in the best situation, Emeka's mother could not have accessed this type of testing locally, but reliable diagnosis needs to be routinely available at every single health post in a malaria-endemic area. To get around the need for skilled parasitologists and microscopists, less technically demanding, less labor-intensive, more sensitive, and more rapid tests have recently been developed.[28] Some take advantage of new biomedical techniques, such as fluorescent microscopy and the polymerase chain reaction, but require additional equipment, special expertise, and expensive consumables, so they cannot readily be introduced when diagnostic infrastructure is poor. Others, however, are potentially well suited to African health centers, particularly the rapid diagnostic tests that are performed without equipment.[29]

Many rapid diagnostic tests for infectious diseases detect the host's response to infection, rather than the pathogen itself. For malaria, however, the host response is of little diagnostic value because of the difficulty in distinguishing between current and previous infection. Malaria rapid diagnostic tests use a parasite protein as the diagnostic target and search for it in much the same way the immune system does. The tests, which are sold in a card, cassette, or dipstick format, detect proteins on the outer surface of the parasite. Two of these, the parasite lactose dehydrogenase and aldolase, are expressed by all *Plasmodia,* and the other, histidine-rich protein-2, is present only in the deadly *P. falciparum* parasites.[30] The advantage of this type of test is that anyone who can draw a pinprick of blood can perform it successfully. No equipment is required, and a positive result is indicated by an easily discerned color mark, typically a line on the test strip. Interest in and use of rapid diagnostic tests for malaria has increased exponentially in the last four years, but their use is still significantly short of need. Far too many health practitioners in Africa have yet to see them, let alone use them to guide patient care. As at 2007, only 20 percent of patients with "malaria" were diagnosed by microscopy or rapid diagnostic test.[31]

Malaria rapid diagnostic tests are easy to perform, and results are ready in less than twenty minutes but three important challenges have been associated with their use. The first is cost: as each quality controlled, disposable stick or strip must be impregnated with test proteins and detection reagents, and can only be used once, rapid diagnostic testing is not cheap. OptiMAL, a dipstick-type test that detects *falciparum* and *vivax* malarias within fifteen minutes, cost over U.S. $3.00 per test in 2003, more than the cost of a course of most antimalarials

in Africa at the time. By 2008, the cost of rapid diagnostic tests had fallen to $0.67 to $1.00 per test, below the $1.00–2.40 cost of recommended combination therapies for malaria, excluding subsidies.[32] Ideally, a malarial diagnostic should cost less than 40 cents per test, and similar subsidies would be applied to tests as to drugs. Although rapid diagnostic tests remain beyond the reach of many patients in most malaria-endemic countries, their price continues to fall as the market expands due to more widespread use. Thus, if proper diagnosis were integral to malarial care, testing would be much more affordable. Furthermore, savings from inappropriate antimalarial use could be funneled into the cost of diagnostics.

The second challenge associated with rapid diagnostic tests for malaria is test quality, which determines reliability. Following donor interest in diagnostics for malaria, the number of commercially available rapid diagnostic tests increased from zero in 1993 to over a hundred different brands fifteen years later. In addition to the general requirements for test production, manufacturers need to produce tests that work reproducibly under real conditions. Real patients might be infected with multiple pathogens, and storage and use temperatures are high in tropical Africa. Not all tests that were initially marketed were sufficiently robust to compel health policymakers to incorporate them into their malaria treatment programs. In 2009, WHO published its quality assessment of 120 brands, for the first time providing health systems with data that allows them to select brands that are cost effective and perform well.[33] In a sense, the technical resolution of a century-long malaria diagnostics problem—from test development to quality assurance—in as little as a decade illustrates how concerted interest in a disease, rigorous assessment of treatment protocols, and global leadership can lead to rapid and effective diagnostic development.

The final challenge associated with rapid diagnostic tests is getting clinicians in endemic Africa, who have for decades been educated to believe that "fever is malaria," to use the tests and pay heed to the results. Yoel Lubell and his colleagues recently investigated diagnostic testing in fifteen year olds—children who, had they lived in eastern Nigeria, might have been Emeka's classmates. They found that 60 percent of fevers were actually malaria but the tests were not cost effective because antimalarials were still prescribed for patients who tested negative.[34] It is probable that the clinicians trusted their judgment better than the tests, and the absence of tests to diagnose confounding infections may also have prompted the prescribers to offer antimalarials. Rapid diagnostic tests for malaria are an important first step, but they cannot be used in a vacuum. Health providers need support in making the transition and will be more likely to do so as the quality and reliability of diagnostic tests improves and the diagnostic and treatment protocols for other febrile diseases catch up with the recent progress for malaria.

On May 13, 1998, Gro Harlem Brundtland, the then WHO director general, initiated a new goal-oriented and sustained effort to "Roll Back Malaria." By 2010, this global effort was implemented by a consortium of over five hundred government, humanitarian, and scientific organizations with the intermediate goal of reversing the incidence of malaria by 2015 and a long term objective of eradication.[35] Zambia, a pioneer country in the effort to Roll Back Malaria, issued new treatment protocols in 2003. A strategy to use rigorous diagnostics to delineate patients who needed the new effective antimalarials was not issued until 2006, with a target date of 2008 for 80 percent implementation. The 2003 guidelines, which as of 2009 operated in many of the country's health institutions, advocate laboratory diagnosis through blood smears "if possible" at health centers and hospitals. These criteria are realistic, but the position illustrates long-standing official acceptance of extremely weak diagnostic criteria for a major killer, even when there is global interest in combating malaria. The pattern of policy adjustment is reflective of a general willingness to increase spending on drugs that typically does not extend to the diagnostics required to use them optimally.[36] These problems are not limited to Zambia. In Kenya, where malaria policy is just a step behind Zambia, treatment protocols were adjusted in 2004 but policy recommending diagnostic testing took two more years to emerge. It took three years to implement the 2004 drug changes at the grassroots and the shift required considerable health personnel training. By 2008, most patients were receiving the recommended new therapy, artemether-lumefantrine. However, by that time only 36 percent of the 193 health centers evaluated in one survey had any kind of testing available.[37]

Patients, health systems, and donors have traditionally been unwilling to foot the bill for diagnostic tests that cost more than available drugs.[38] The cost of the test in fact may be justifiable, but because many of the benefits accrue to the health care system rather than to the patient, the advantages are often not recognized. The new impetus to use diagnostic tests has been prompted by the emergence of resistance to affordable antimalarials, which have recently been replaced by artemisinin-based combination therapies (ACTs), such as artemether-lumefantrine used in Kenya. Since the cost of ACTs is high (up to U.S. $3.00 per course in 2004) rapid diagnostic tests (some costing about $0.60 in 2004) became easier to justify.[39]

The almost prohibitive cost of ACTs creates access problems and makes these life-saving medicines attractive to counterfeiters; a recent global effort has proposed that these drugs should be heavily subsidized through an Affordable Medicines Facility for Malaria.[40] An important omission from this program, however, is the partnering of drugs with diagnostics that are essential to assure appropriate use. Just before the inception of that program, about five billion antimalarial

regimens were handed out each year, and at least a fifth of these may have been unnecessary in high-burden areas, that is African countries with endemic, stable transmission. The 2000 annual estimate was between 122 and 303 million malaria attacks in areas of high burden. Therefore, at least 25 million antimalarial regimens are consumed needlessly each year in these countries. In areas with lower endemicity or seasonal variation in malaria infection rates, more people without malaria may be being treated with precious antimalarials than individuals who actually have the disease. Based on data collated by Julie Thwing and her coworkers in Angola, this translates to between $500 million and $960 million per billion U.S. dollars in wasted funds donated for antimalarial treatment.[41]

When absolute and immediate cost-effectiveness is computed in settings where expensive ACTs are employed, malaria microscopy and rapid diagnostic tests are cost effective.[42] Analysis that takes accuracy into account greatly increases the cost-effectiveness of rapid diagnostic tests in areas where quality assurance for microscopy is weak. Factoring in indirect and long-term costs from avoidance of antimicrobial resistance, adverse effects from unnecessary medication, and diagnostic delay for other infections, the cost-effectiveness of malaria diagnostics at the population level is indisputable.

By comparison, policies of clinical diagnosis are uniformly unsuccessful and the WHO's recently altered malaria diagnostic recommendations insist on parasite, rather than clinically based, diagnosis.[43] Improving access to, and the sensitivity and specificity of, testing can best be achieved with rapid diagnostic tests, even though a few technical challenges associated with their use remain. Currently, rapid diagnostic tests work well when performed by laboratory technicians or health workers.[44] The yet-to-be-developed but ideal home-based or village health worker rapid diagnostic test would require urine or saliva instead of blood, and would detect only high levels parasitemia that are associated with malaria. Village health workers could instruct patients who test negative to go to a health center for alternate diagnosis. In health centers, tests need to be specific enough to detect low-level parasitemia and at least a few of the other causes of fever. Testing rubrics should be enhanced, and the variety of tests available for the etiologic agents of febrile disease should be increased, to provide prescribers with clear directions for treating malaria test-negative patients.

"The billion-dollar malaria effort is flying blind"

Malaria researchers are aware that development and deployment of diagnostics is a priority, and health policymakers acknowledge that the current state of

diagnostic testing for malaria is below par.[45] However, diagnostic development and deployment is frequently low on the list of priorities for malaria control. The current scarcity of functioning diagnostic laboratories continues to cow decision makers into accepting that laboratory diagnostics are beyond the means of African health systems. A report on the 2005 Multilateral Initiative on Malaria conference held in Yaoundé, Cameroon, entitled "What Are the Priorities in Malaria Research?" and published in January 2006, summarized ten "crucial issues," including new directions in drug and vaccine development as well as improving the delivery of interventions. More recent expert discourse has emphasized diagnostics, but the list emanating from that pivotal meeting lacked any reference to diagnostic development, either in terms of new technologies or promoting the more effective use and simple availability of existing ones.[46] The consequences of underprioritizing diagnostics are visible. Zambia, a front-runner in the effort to Roll Back Malaria across Africa, has shown phenomenal progress in halting transmission due to successful use of insecticide-treated bed nets and indoor residual insecticide spraying and treatment programs, but parasite-based diagnosis has lagged. The 2008 World Malaria Report noted similar progress, and the same diagnostic slowdown, in other African countries and inadequate uptake or scale up of interventions in some countries because of the difficulty in measuring the impact of different interventions due to underuse of diagnostics.[47]

In 2006, the newly appointed director of WHO's malaria program, Arata Kochi, declared that until science addresses the problem of malaria diagnosis, malaria control strategies will be "like religion, based on faith."[48] Modern malaria control interventions, such as insecticide-impregnated bed nets, targeted insecticide use, and new antimalarial drugs, are largely chemical interventions. When used without epidemiological monitoring, chemical strategies for disease control have always been rendered ineffective by drug or insecticide resistance—this is why an earlier attempt to eradicate malaria failed.[49] The effective use of both existing and new therapies depends on the routine deployment of diagnostic tests for malaria.

Toward the end of the twentieth century, as other infectious diseases were brought under control, the unruliness of malaria became more evident, more intolerable, and more embarrassing. *Plasmodium falciparum* is responsible for many of Africa's ills and erroneously blamed for many others, forcing individuals, organizations, and countries that only a few decades ago were barely aware of the devastation from malaria to support a global effort to tackle the disease head-on. WHO's Roll Back Malaria program's target was to halve malaria deaths by 2010, and halting the upward trend in the number of malaria infections is a 2015 Millennium Development Goal.[50] Plans and budgets for reaching these targets have been drawn up, donors have been wooed, and the hopes of affected

people in Africa and other malaria-endemic areas have been raised. Funding support for malaria reportedly increased tenfold between 1998 and 2006, and African governments have announced "rolling back malaria" as national and regional priorities.[51]

In 2005, when the global effort to roll back malaria was under way, although behind schedule, Oxford malariologist Bob Snow and his co-workers suggested that previous World Health Organization estimates of how many people actually had malaria each year were all wrong. From South America and Asia, the disease is underreported, and in Africa, where 79 percent of malaria infections occur, researchers handicapped by "a notoriously weak system of reporting infectious diseases"[52] derive uncertain estimates by extrapolating from sometimes biased research data. The Snow group suggested a 2002 estimate of 515 million (range 300–600 million), which is much greater than the WHO's figures of 213 and 273 million in 1990 and 1998. Malaria epidemiologists and policy makers have debated the accuracy of various estimates; they agree only that "it is preferable to present any malaria incidence estimate as a range."[53] The differences between the upper and lower limits of this range typically approach two hundred million people.

Inaccurate estimates of the true prevalence of malaria in Africa means that those who are sickened and impoverished by the disease do not have an effective voice. But knowledge of the true burden of malaria is of more than humanitarian and academic value: it would help public health planners to define at-risk populations, to distribute resources rationally, and to evaluate and refine intervention programs. Only reliable methods of estimating malaria cases will give the world the capacity to detect any gains that may result from current initiatives. A case in point is Mto wa Mbu or the "River of Mosquitoes" area in Tanzania, historically rampant with malaria. In 2009, the entomological infection rate, or chance of being bitten by a malaria-infected mosquito, was less than one: malaria had gone from being very common to rare. However, based on data from 1981, 40 percent of outpatients in 2006–2007 were still receiving expensive antimalarials.[54] On a global scale, any intervention that leads to a decline of fifty million cases per year or less would have a valuable but potentially undetectable effect on malaria worldwide simply because such effects can only be measured if diagnosis is parasite-based. Snow, who is working continuously to improve malaria estimates, correctly concludes: "Inadequate descriptions of the global distribution of disease risk make it impossible to determine priorities and advise funding agencies appropriately. Redressing these deficiencies with robust data must be a priority if international agencies are to understand the size of the challenge set by their targets over the next ten years."[55] Progress has been made: some countries, such as Zambia and Tanzania, are noticing declines in the incidence of all fevers,

and declines in pediatric admissions due to malaria ranging between 28 percent and 63 percent were recently reported from three coastal hospitals in Kenya.[56] Given the questionable quality of available reliable data that is dependent on routine testing, progress will be difficult to quantify.[57]

Disease control programs typically find it easiest to recruit support at the beginning of a campaign, when millions are sickened or killed. But it is the endgame that is most crucial and ensures that the health and economic gains of a successful program are not lost. The endgame can be compromised by "donor fatigue." In the upcoming decade, as malaria control improves, better data that makes it easier to showcase progress could convince results-oriented donors to stay on board.

As more malaria cases are prevented, the proportion of febrile illnesses caused by other pathogens will rise. The possible range of confounders is tremendous. In addition to bacteria and hemorrhagic viruses, there are hundreds of well-known possible causes of fever in malaria-endemic areas. Some causes are underrecognized; for example, a serological screen of Gabonese schoolchildren recently pointed to influenza as one of them. In the absence of diagnostic tests for the major confounders, alternate causes of fever are essentially invisible.[58] If today's interventions against malaria are effective, clinical diagnosis of fevers will become even more imprecise because only a minority of febrile illnesses will actually be malaria. In order to increase, or even maintain the effectiveness of care, laboratory diagnostics will have to be employed more intensively.

Between 15 percent and 83 percent of parents of ill children in different parts of Africa procure medicine for their sick children from a local dispensing point or shop, typically staffed by a semitrained village health worker or an untrained dispenser.[59] Therefore, malaria diagnosis needs to be possible at or close to the home-based level. Only then might a child like Emeka, with a sudden high temperature and chills, receive appropriate therapy in time to save his life.