MALARIA
AFRICAN RESEARCH

Against All Odds, Victories From the Front Lines

In one of the world's poorest countries, Malian and American researchers attack malaria in the lab and in the clinic

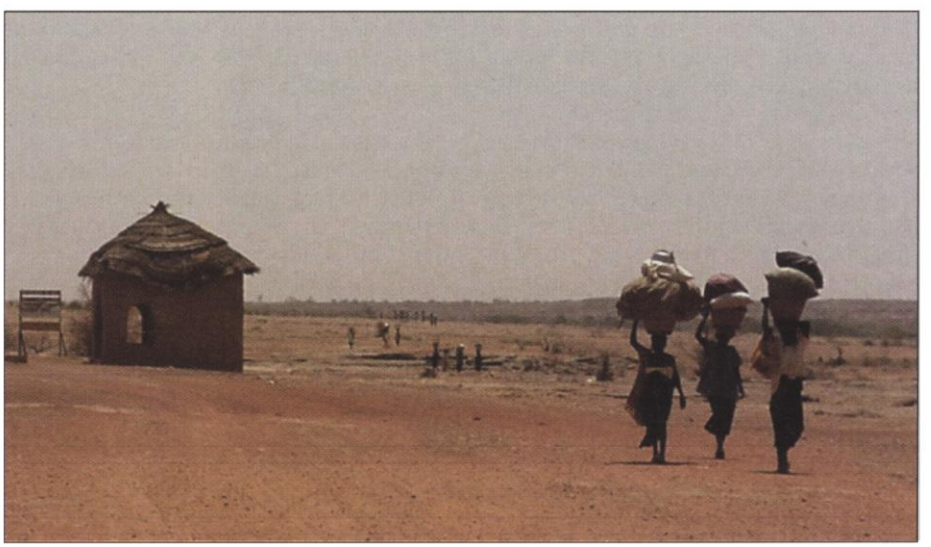
BANDIAGARA, MALI—The rains, when they come, come hard in this remote town a few hundred kilometers south of the Sahara desert. Toward the end of a sweltering afternoon, dark clouds form in the south and east, the glaring sunlight dims, gusts of wind raise choking clouds of dust, and the first large drops smack into the ground. Soon the din of rain on metal roofs drowns out any attempt at conversation. The soil that 6 months of the year receives little or no rain attempts to soak it in, but within minutes dusty streets turn to streams and then to rivers. Gardens and fields turn to swamps and then ponds—even lakes—as the rain pours down in sheets. Then, almost as quickly as it dimmed, the sky brightens, the thunder fades into the distance, and the steady flow of water off the roofs slows to a trickle. The downpour's effects remain, however: Roads become quagmires as heavy trucks churn the mud.

With the rains come the insects. The flies and beetles, which manage to thrive even in the dry season, are suddenly joined by flying ants, damselflies, a profusion of moths, and, of course, mosquitoes. And with mosquitoes comes malaria. The local word for malaria translates literally as "sickness of the green season."

Researchers, too, arrive with the rains. Each year, scientists from Africa and the rich countries of the North come to this community of 12,000, which lies 9 hours from Mali's capital, Bamako, looking for answers to some basic questions about malaria. Bandiagara is best known as a staging point for tourists who visit the villages of the Dogon ethnic group that cling to the famous cliff that shares the town's name—the Bandiagara escarpment. It is a place where research traditions meet ancient cultures.

The researchers who come to study the sickness of the green season are documenting malaria transmission in the community and monitoring the patterns and mechanisms of chloroquine-resistant parasites. They are also probing the complex question of natural immunity—in essence, how people can coexist with the parasite without showing severe symptoms of the disease. And they are looking for clues to one of the most puzzling questions of all: why the parasite kills more than 1 million people each year. Malaria exacts much of its horrific toll on children who develop deadly anemia or a virulent cerebral form of the disease. They come down with a sudden fever, suffer wrenching seizures, and slip into a coma. Without treatmen, half of them die. No one knows why some develop cerebral malaria while their friends and siblings, who also carry the deadly *Plasmodium falciparum* parasite in their blood, do not.

Basic questions about malaria persist in part because the *Plasmodium* parasite is a complex foe. But other, equally complicated diseases such as diabetes are well understood, notes Terrie Taylor of Michigan State University College of Osteopathic Medicine in East Lansing, who studies cerebral malaria in Malawi. Much of the problem, she says, has been a lack of research interest in a disease that affects primarily the developing world. "Malaria remains a scourge because almost no one in an endemic area has looked at it systematically," Taylor says. To make a significant contribution, "you don't have to be brilliant, you just have to be there."



Before the rains. Women carry goods to market on the outskirts of Bandiagara, Mali, at the end of the dry season. When the rains arrive, they bring mosquitoes and malaria.

CREDIT: SARA MAY

Being there

That realization has become something of a rallying cry for international organizations funding malaria research. Agencies including the World Health Organization (WHO), the Wellcome Trust, the Bill & Melinda Gates Foundation, and the U.S. National Institutes of Health (NIH) have ramped up funding for malaria research (see p. 428), and all have said that building research capacity in Africa, where 90% of the world's malaria cases occur, is a top priority.

But the logistical hurdles are daunting. Malaria hits hardest in the world's least developed countries, where it kills the poorest of the poor. In places such as Malawi, Kenya, and Thailand, local doctors are stretched to the limit and trained scientists are scarce. Researchers must often build and equip their research space from scratch—providing everything from bedsheets to power generators. And they have to achieve a delicate balance between meeting the ethical standards of U.S. and European research sponsors and respecting the cultural mores of local communities.

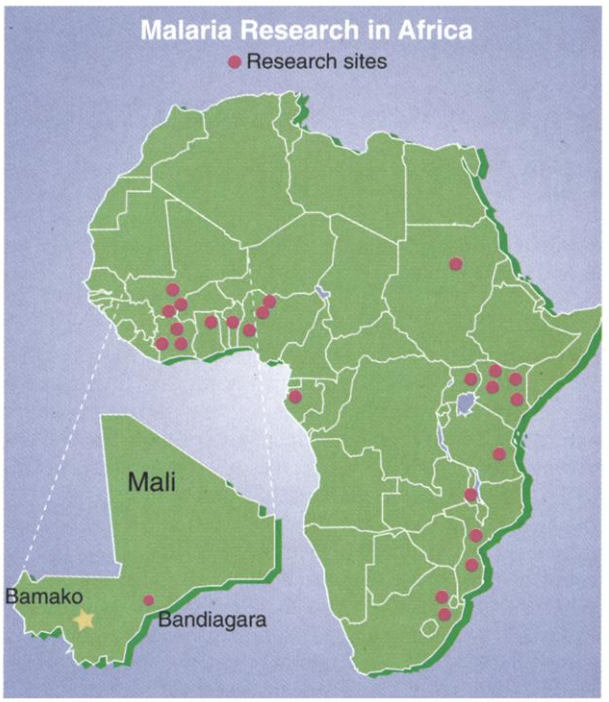
Researchers in this West African nation —one of more than a dozen African countries where malaria research is under way— are proving that these obstacles are surmountable (see map). In Mali, most people live on less than $1 per day, and life expectancy is 47 years. But at the Malaria Research and Training Center (MRTC) in Bamako, "we are showing by example that world-class science can be done in a poor country," says pharmacist and microbiology Ph.D. student Abdoulaye Djimde. The center, funded mainly by NIH, the U.S. Agency for International Development (USAID), WHO, and the European Union, has two goals: researching the multiple facets of malaria and training young scientists. And, despite unreliable Internet connections, crowded labs, and scarce supplies, MRTC is succeeding at both, says Tore Godal, executive secretary of the United Nations Global Alliance for Vaccines and Immunization.

On the edge

Although conditions in Bamako can be trying, the city is strikingly modern compared to much of Mali. Most of the MRTC scientists conduct their main research in remote towns like Bandiagara, where electricity comes only from generators and the food supply is determined by recent harvests. Most buildings in Bandiagara are constructed with wattle and daub, a mixture of straw and mud. Their top edges, carefully sculpted during the dry season, begin to wash away with the first few rains. Pigs roam the streets with goats, sheep, and chickens; donkey carts are far more common than cars. Children and women must draw water from wells scattered throughout town, then carry it home on their heads.

But the remote setting does not hinder the team of Malian and American researchers who have been monitoring malaria here since 1997. Led by epidemiologist and physician Ogobara Doumbo, co-director of MRTC, and Christopher Plowe, an infectious-disease expert at the University of Maryland School of Medicine in Baltimore, the Bandiagara Malaria Project is laying the groundwork for future trials of a hoped-for vaccine. Backed by NIH and the University of Maryland, the team also includes two American physicians, a pharmacist from Niger, and eight Malian doctors and pharmacists.

The researchers' presence has already had a measurable effect. Before they arrived, malaria killed scores of children every year. But in the past few years, malaria deaths have been rare; indeed, last year only one child from an outlying village succumbed. When a child develops a high fever or slips into a coma, parents now know to bring the child to the research team's clinic, which provides treatment without charge. "When we first met the team [members] ... I thought they were [with] another of the many programs that do nothing," says a community elder through an interpreter. "But 3 years later I know that's not true. There are more small children alive today thanks to their presence here."

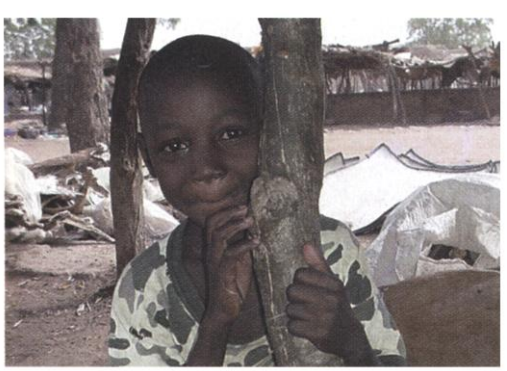


Expanding network. International collaborations sponsor more than 23 projects in 14 countries, including the Bandiagara Malaria Project in Mali.

Building that kind of trust is essential. Before the researchers can begin their work each rainy season, they must pay their respects to Bandiagara's leaders. Team representatives present the local leaders with traditional gifts of kola nuts (bitter, caffeine-containing nuts that are a traditional sign of respect) wrapped in banana leaves and request their permission to begin research. In rural Mali, as in much of West Africa, decisions are made by a council of elders on behalf of the whole community. "You can't do anything if you don't have consent from the community leaders," says Djimde, who grew up in a small village not far from Bandiagara. "They want to know who you are, whether your words are trustworthy." The leaders, in turn, explain the projects to the rest of the community. "To win their trust is the most difficult part. And once you win their trust, you have to keep it. Every year, you have to go through the whole process again," says Djimde. At first, the leaders were suspicious. Many were disturbed that, by collecting so much blood, the researchers might harm the children. And some of the local doctors and traditional healers were afraid the researchers might undermine their business. But Doumbo, who also grew up nearby, was able to allay their fears (see sidebar).

Traditional and Modern Medicine Merge to Save Lives

BANDIAGARA, MALI—Before the Bandiagara Research Project began, cerebral malaria was not associated with the "the disease of the green season," the local term for malaria. Seizures and coma were considered symptoms of *wabu*, caused by a bird that cries out at the same time a child cries and steals a child's spirit. Parents did not consult the local doctor but rather the traditional healers.



Happy ending. Researchers revived this son of a local leather craftsman from a malarial coma—known as *wabu* in the local language.

The traditional treatment for *wabu* is to expose the child to the fumes of a particular herbal brew and then bathe the child in the infusion. This may lower the malarial fever somewhat, says malaria expert Ogobara Doumbo, co-director of the Malaria Research and Training Center in Bamako. But when he and his colleagues persuaded some of the traditional healers to tally their records for *wabu* cases, the traditional healers had a 50% mortality rate—the same rate as untreated cerebral malaria. Doumbo and the other researchers proposed a plan: When parents brought their *wabu*-afflicted children to the traditional healers, the healers would refer the children to the researchers for treatment with intravenous quinine and sulfadoxine-pyrimethamine (better known as Fansidar)—successful in more than 90% of cases here even when administered in a former storage room equipped with floor mats, a rigged IV apparatus, and flashlights. Initially some of the healers feared that the researchers would compete with them for patients, but the team was careful to give public credit to the healers, saying they had correctly identified the disease and had taken the right steps—referring the child to the research team. Today, the researchers enjoy high enough esteem that many parents bring their *wabu*-afflicted children directly to them. But "without the traditional healers, we could never have done what we have," says Doumbo.

The respect seems to flow both ways. At a meeting to discuss the current research project at the beginning of the rainy season, one healer told the team, "Before the study started, many children suffered, and we lost many 2- and 3-year-olds. But two hands can wash each other. I hope the collaboration will continue forever."

–G.V.

CREDITS: (TOP TO BOTTOM) MODIFIED FROM MIM/TDR; SARA MAY

After securing the leaders' blessings, the team recruits families to participate based on a random geographic distribution. By now, says Boureïma Ouologuem, one of the team's two local translators and "guides," most parents jump at the chance. For the trouble of bringing their children into the medical center once a week, which often interrupts field work, the families are compensated with a sack of millet or rice at the end of the study season. The children also receive regular checkups and free medication for common ailments such as intestinal parasites, persistent coughs, and of course malaria. One of the team doctors, Ando Guindo, claims he can tell a distinct difference between the children in the study and those who aren't enrolled: The study children are, in general, both bigger and healthier.

In Malian society the consent of the elders implies consent from the whole community. The written consent documents required by ethics boards and funding agencies in the United States mean little in this setting, where two-thirds of the population is illiterate. But the research team, working in two cultures, takes both types of consent seriously. Ouologuem and Akouni Dougnon carefully explain to parents the aims of the study, the requirements for participants, and the possible risks—in French at first, but often switching to a local language: Peuhl, Bambara, or one of the dozens of Dogon dialects. Those languages have no words for foreign concepts like "research," much less "case-control study," but the Malian members of the team have devised ways to explain the work. Most parents apply a thumbprint to the signature line of the several-page consent document, written in English and French.

Notable successes

At the health center, the children line up to register for this season's study. In a cinderblock building with simple ceiling fans, no running water, and screenless windows, two team members record each child's family, location of home, and birth date—often noted simply as 15 June of a given year, as many birthdays go unrecorded. Four team doctors chart the children's weight, height, and temperature, then check for any signs of anemia or other illness. Other team members draw blood. Several drops go onto a glass slide to be checked for malaria parasites; some blood is checked for iron and hemoglobin levels; and some is analyzed for immune system cells, antibodies, and other proteins. By comparing samples from children who develop cerebral malaria or severe anemia with controls who are infected but show no symptoms, the team hopes to discover more about what triggers the deadly symptoms. A drop of blood from each participant also goes on a slip of filter paper for later DNA analysis to check the genetic traits of both parasite and host.

Front line. Members of the Bandiagara Malaria Project include (left to right) pharmacist and lab supervisor Mahamadou Diakité, pediatrician and severe malaria specialist Abdoulaye Koné, physician Ando Guindo, technician Dramane Coulibaly, and physician Karim Traoré.

The team has already produced notable results. This month in *Blood*, NIH parasitologist Tom Wellems, Doumbo, Plowe, and colleagues report that a genetic trait common in the Dogon ethnic group—two-thirds of the population in Bandiagara—seems to protect children against severe malaria. The trait, a mutation in one of the genes that codes for the hemoglobin protein, seems to be as effective in protecting carriers as the sickle cell trait is in other populations. The team has also been able to document the presence of a newly identified chloroquine-resistance gene in the local population, lending strong support to the lab-based results Wellems's team reported in the 18 October issue of *Molecular Cell*.

At the clinic. Women line up to enroll their children in this season's study. Participation provides access to medical treatment.

CREDITS: (LEFT TO RIGHT) G. VOGEL; SARA MAY

Growing connections

Until now, the project's main link to the outside world has been a satellite phone. When its batteries are correctly charged, the connection isn't bad, although the $3 per minute fees add up quickly. Now NIH is installing equipment in Bamako and the MRTC's field sites that will bring high-quality Internet and phone connections to researchers in their villages. It may also provide MRTC with a U.S. phone number—so that a call to or from NIH in Bethesda, Maryland, will be local.

The MRTC laboratories in Bamako were already an oasis of technology compared to the field sites. And over the past year, lab space at the facility has doubled, thanks to funds from NIH and USAID. The new labs are equipped with state-of-the-art freezers, fume hoods, polymerase chain reaction (PCR) machines, and computers, as well as a section that complies with U.S. Food and Drug Administration clinical laboratory standards, says entomologist Robert Gwadz of NIH, who has been instrumental in developing the facility.

Access to such technology will be vital to the careers of the younger scientists at MRTC, such as Djimde, who earned his pharmacy degree in Bamako and expects to receive his Ph.D. in microbiology from the University of Maryland School of Medicine in early 2001. Djimde will return to Mali full time next summer to set up his lab in the new addition. He will join two other recent Ph.D.s as a full-time faculty member at the medical school in Bamako. Both have won prestigious reentry grants from WHO that support their research for 2 years, and Djimde hopes to win one as well. Still, "they need to come to a place where they don't have to worry that purchasing a PCR machine would be their entire budget for a year," says Richard Sakai, an entomologist who has been the U.S. National Institute of Allergy and Infectious Diseases' scientist-in-residence in Bamako for nearly 10 years. The returning researchers are first-rate, he says. "We need to give them sufficient funds and sufficient challenges to keep them interested. The challenge for us is to make those conditions available to them."

—GRETCHEN VOGEL