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## Old Malaria Drug Blamed for Resistance Gets a New Reputation

An inexpensive drug currently used to treat and prevent malaria in pregnant women—sulfadoxine-pyrimethamine, or “SP” for short—could reduce malaria infection in infants by 30 percent, recent studies have shown. But health officials in the developing world have held off on recommending SP’s widespread use because of concerns that offering it to more people might accelerate the malaria parasite’s resistance to SP and render the drug useless. Two new research articles, drawing on 10 years of field and laboratory studies on SP, suggest the drug may be a safe and effective way to prevent malaria.

Malaria infects hundreds of millions of people worldwide and kills an estimated 900,000 a year, taking an especially high toll on children in sub-Saharan Africa. Despite more than a half century of research, no effective malaria vaccine has been approved, and the resilient parasite that causes the disease has developed resistance to numerous drugs. Although the mechanisms of drug resistance are not completely understood, researchers have shown that it is linked to changes in the malaria parasite’s genes that result in a diminished accumulation of the toxic drug inside the parasite.

Malaria researchers have long assumed that because SP treatment causes a spike in the number of infectious, drug resistant parasites in an individual’s blood, the medication will lead to more malaria transmission and the spread of drug resistance. “Our latest research challenges these assumptions, which were basically not backed by fact,” says Abdoulaye Djimdé, a Howard Hughes Medical Institute international research scholar at the University of Bamako in Mali. Djimdé will present his new data August 18, 2010, at the International Congress of Parasitology meeting in Melbourne, Australia. The studies were published in two articles in the August issue of the *International Journal for Parasitology*.

With a malaria vaccine still years away, health workers throughout the developing world rely on currently approved drugs to treat and prevent malaria. Resistance to these drugs has caused serious problems for health workers in the developing world, who can no longer use several cheap, readily available drugs to treat malaria.

Djimdé and his colleagues in Mali have spent the last decade studying how drug resistance occurs. He began working on SP in 2000— a time when resistance to the widely used antimalarial drug, chloroquine, was on the rise. “We were trying to find drugs we might use should we lose chloroquine,” he says. So Djimdé and his colleagues at the University of Bamako launched a study to compare the effectiveness of SP against chloroquine and another antimalarial medication called amodiaquine. They treated 334 people from two rural villages who had tested positive for *Plasmodium falciparum*, the most common and deadly type of malaria in Africa. For a month, the researchers monitored the participants’ health and collected several blood samples.

In the course of looking at the efficacy of the three drugs, however, they noticed something strange. Typically, malaria parasites float around the human bloodstream in an asexual stage, called a merozoite. Only a small percentage of the asexual parasites become gametocytes, sexual parasites that mosquitoes pick up when they bite a human. Gametocytes are capable of reproducing inside the insect’s gut.

After the researchers administered SP, “very quickly a lot of parasites died and the ones that didn’t die turned into gametocytes,” Djimdé says. The proportion of gametocytes increased dramatically, from roughly 13 percent on the day of treatment to more than 40 percent a week later. This was not surprising—other researchers had reported similar findings—but it was concerning. People with more gametocytes in their blood are more likely to pass them on to a mosquito, where they can reproduce. “We were worried about this leading to increased transmission” of SP-resistant parasites, Djimdé says.

Even more alarming, when the researchers extracted the parasites’ DNA from the blood samples, they found that treatment with SP increased the proportion of parasites carrying the mutations that are known to confer resistance to SP.

For drug resistance to spread, these mutant gametocytes need to travel from the human host back into the gut of a mosquito, where they must breed. Then their offspring have to migrate into the mosquito’s salivary glands and hitchhike into another human host. Djimdé and his colleagues decided to test whether these mutant gametocytes could successfully complete these steps.

In 2002, the researchers took a group of 14 volunteers with malaria who had been treated with SP and let uninfected mosquitoes (*Anopheles gambiae*) bite the legs of the human volunteers. After a week, they dissected those mosquitoes to look for oocysts, malaria spores that turn into new parasites. Only seven of the 928 mosquitoes that fed on the volunteers had oocysts, and each of those contained just a single oocyst. “We realized that although the gametocyte prevalence [in humans] was very high, the infectivity of the gametocytes to the mosquito was very low,” Djimdé says.

These results were met with “strong skepticism,” he says. “One prominent entomologist didn’t believe the data.” So Djimdé and his team double-checked the results in 2003. They got the same results. “The next logical question was to try to understand the basis of this low infectivity,” Djimdé says.

Djimdé and his colleagues collaborated with researchers in Holland on a second study. The researchers dosed immature gametocytes with SP or sulfadoxine and pyrimethamine separately. They found that the drugs didn’t kill these parasites outright, but they did hinder their ability to mature properly. The gametocytes that developed in the presence of drugs were visibly deformed, “odd and sharp-looking,” Djimdé says. These gametocytes could not infect *Anopheles stephensi* mosquitoes, the Dutch group’s research subject of choice.

When mosquitoes fed on a solution containing mature gametocytes and SP or sulfadoxine alone, they ate gametocytes as part of their blood meal, but those parasites weren’t able to reproduce successfully. The researchers noted that a smaller proportion of drug-treated mosquitoes had oocysts when compared against controls. And the mosquitoes that did contain oocysts had fewer of them. Moreover, a surprising number of the mosquitoes that ingested the solution containing gametocytes and SP died, a phenomenon that has never been observed before.

Their findings suggest that SP could be used to treat both infants and children without causing widespread resistance, Djimdé says, at least in places like West Africa where SP is still effective. But he cautions that his results need to be replicated. “If it is confirmed,” he says, “then there’s no reason to think that widespread use of SP is going to have a negative impact.”

Christopher Plowe, an HHMI investigator at the University of Maryland School of Medicine in Baltimore and coauthor on the first paper, points out another implication. With malaria eradication back on the table, researchers are looking for new ways to interrupt malaria transmission.

In order to interrupt transmission, however, they first have to figure out where it’s occurring. “We need more sensitive ways of measuring whether or not a person’s blood really is capable of transmitting malaria than simply seeing gametocytes under the microscope,” he says. “Just because we see them doesn’t mean they’re viable and healthy.”