A race against RESISTANCE

Several African nations could strike a major blow against malaria by sacrificing the efficacy of some older drugs. Can they make it work?

BY AMY MAXMEN

It is September in southeastern Mali, and Louka Coulibaly is standing in the shade of a squat, concrete building, giving instructions to a dozen men and women perched on a wobbly wooden bench. Coulibaly, a local medical supervisor, hands out nylon backpacks, each filled with bags of pills, plastic cups and a porcelain mortar and pestle that the women pause to admire. By noon, the men and women are packing up and heading back to their respective villages on foot, bicycle and motorcycle.

The following day, they and about 1,400 other health workers throughout the region will set up shop in public spaces: under the shade of mango trees, in one-room schools, at market stands and in district health centres. They will mix and mash the pills with the mortar and pestle, dissolve them in water in a cup, and hand the bitter dandelion-coloured liquid to about 164,000 children.

The effort is part of a broad campaign to prevent malaria by providing African children with drugs usually used to treat the disease. Nearly 1.2 million healthy children from parts of Mali, Togo, Chad, Niger, Nigeria and Senegal received these drugs during the rainy season — from around July to November — when malaria usually ravages the population.

The countries' governments are deploying this intervention — known as seasonal malaria chemoprevention, or SMC — with financial support from the United States, the United Nations and the medical aid organization Médecins sans Frontières (MSF), also called Doctors Without Borders. Next year, many plan to expand the campaigns, and other countries hope to launch their own, encouraged by

recommendations from the World Health Organization (WHO).

Preventive use of anti-malarial drugs is not new: tourists routinely swallow them when travelling. But public-health officials have long instructed people living in regions where the disease is endemic to refrain from taking drugs prophylactically, in part because of concerns that the parasite that causes malaria will develop resistance when many people take the medicine on a long-term basis.

That risk has not disappeared. In fact, scientists fully expect SMC to encourage widespread drug resistance. No one knows when, exactly, but it could happen within as few as five years. Until then, SMC has the power to prevent 8.8 million cases and 80,000 deaths each year if implemented in regions with high rates of seasonal malaria. That is considered a powerful enough benefit to justify losing the drugs.

"Life is a risk," says Coulibaly, a Malian hired by MSF to train local health workers. "And if you don't take risks, you don't win."

The project is designed to forestall drug resistance as long as possible, and to work in concert with mosquito nets and other preventive methods. Supporters hope that the combination will significantly suppress malaria, so that even if resistance eventually spreads, the caseload should be smaller and manageable with other treatments. But SMC will not be as successful if funding and infrastructure falter — and so far, programmes have had a shaky start. Still, advocates say that the challenges can be overcome.

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"SMC is feasible," says Estrella Lasry, technical adviser for malaria chemoprevention at MSF. "But it requires organization, a series of steps and money to back it."

AMY MAXMEN

WHEN INTENTIONS BACKFIRE

Previous attempts at large-scale malaria chemoprevention offer lessons on what not to do. In the 1950s, David Clyde, a malaria researcher with the British Colonial Medical Service, administered the drug pyrimethamine to villagers in Tanzania. At the time, pyrimethamine had a strong track record of clearing the parasite. But with any drug, there is a slim chance that some strains of parasite will be resistant and will survive to infect others — a chance that increases when many people take the medicine in an area where the parasites are abundant and circulate year-round.

Clyde's experiment drove this concept home: malaria rates dropped at first, but after five months, 37% of infections in the village no longer responded to the drug¹. Eight years later, pyrimethamine resistance had spread: up to 40% of infections within 25 kilometres of the original intervention site were unresponsive.

In the Debela village in southeastern Mali, a mother gives her baby drugs meant to stave off malaria.

The 1960s brought more lessons — this time, when scientists tried adding the drug chloroquine to table salt. Clinical trials had shown² that the salt drastically lowered malaria rates. But when the tactic was scaled up and the salt was distributed to markets in Guyana and Brazil, people consumed only what met their tastes. Others opted for untreated salt when they could, because the chloroquine made their skin itch. As a result, many people carried sub-therapeutic levels of the drug — not enough to reduce the malaria burden, but enough to promote resistance. “The salt campaigns were a disaster,” says Christopher Plowe, a malariologist at the University of Maryland School of Medicine in Baltimore.

Governments and aid organizations mostly shelved chemoprevention programmes after that, but resistance continued to grow — albeit slowly — as people used drugs to treat malaria infections. Between 1960 and 2000, chloroquine resistance crept around the globe and the malaria death toll steadily rose. That trend started to reverse around 2005, after the widespread adoption of the drug artemisinin,

derived from Chinese sweet wormwood (*Artemisia annua*). Today, artemisinin-based drugs are the gold standard for treating malaria.

SECOND CHANCE

Alassane Dicko, a malariologist at the University of Bamako in Mali, was a graduate student in Plowe’s laboratory in 2001, when he started to think seriously about reviving chemoprevention. As a child, Dicko had lost his older brother and his best friend to malaria. Later, as a medical student working in hospitals, he was distraught at the number of children he saw dying. “You really feel it,” he says. “If we want to do anything for this country in terms of health, we need to stop malaria first.”

Dicko suggested that older antimalarials might be repurposed for prevention in places where resistance to them is not yet widespread. By using drugs seasonally, only in uninfected children and in combination rather than alone, he hoped to avoid some of the mistakes of the past. With drug combinations, parasites need to acquire several mutations to survive. These mutations usually come at a cost to the parasite, so removing the selective pressure of the

drugs during the dry season would give parasites still sensitive to the treatment a chance to outcompete resistant ones.

Dicko proposed using a mixture of sulphadoxine and pyrimethamine called SP, which was known to be relatively safe over the long term. In 2002, his team treated 130 children with SP for two months in a placebo-controlled trial in Mali³. The treatment reduced malaria by 68%.

Other West African scientists followed the study. Among them was Badara Cissé, a Senegalese researcher then pursuing his doctorate with malariologist Brian Greenwood at the London School of Hygiene and Tropical Medicine. Greenwood had been considering chemoprevention since the 1980s, and he and Cissé immediately grasped the potential in Dicko’s approach. In 2004, they began a trial in Senegal to test three monthly doses of SP plus artesunate, an artemisinin derivative. Compared with the placebo group, nearly nine out of ten malaria cases were averted⁴.

With a US\$4.5-million grant from the Bill & Melinda Gates Foundation in 2008, Cissé and his colleagues launched an as-yet-unpublished, 3-year clinical trial to study SP with another drug, amodiaquine (to preserve the efficacy of artemisinin). They treated nearly 200,000 children under 10 years old and found that they had 83% fewer cases of malaria than controls, says Cissé. Smaller trials in other African nations reported similar findings.

These are impressive numbers, especially given how recalcitrant malaria has been to preventive measures. No vaccine has ever proved fully effective against the disease, for example. And the one that is closest to approval — RTS,S — has shown disappointing results in ongoing clinical trials, with less than a 50% reduction in cases (see *Nature* 502, 271–272; 2013).

RESISTING THE CRITICS

SMC raised some concerns that slowed its adoption. Some health officials suggested that natural, partial immunity to the parasite — built up as a child survives multiple bouts of malaria — would be compromised. Others fretted about the potential side effects of taking the drugs regularly. But the loudest complaints were about losing the drugs to resistance.

In a cramped office in a makeshift building at the University of Dakar, Cissé explains how he was frustrated by the deliberations among public-health officials as malaria waged war on Senegal’s children. He slumps in a chair that seems much too small for him and asks, “Isn’t it selfish to sit in our offices with air conditioning, saying that we should save these drugs?” He recalls a single night, 20 years ago, when he watched five children die of malaria. There was nothing he could do to save them. “If this happened to you, you would not be debating about the fear of losing a drug,” he says.

In 2012, SMC finally won over most officials. The Cochrane Collaboration — an international group based in Melbourne,

Australia, that specializes in evidence assessment — analysed results from trials in Senegal, Mali, Burkina Faso, Ghana and Gambia, and concluded⁵ that SMC could prevent more than three-quarters of malaria cases in places where the disease struck seasonally. In the trials, the signs of side effects, resistance and reduced immunity were all minimal. According to another report⁶, nearly 21 million children in these regions stood to gain from SMC each year. And prevention is cheaper than treatment. Each month, chemoprevention costs \$1.50 per child, which pales in comparison to the costs of travel and medical care for a child who falls ill. In November 2012, the WHO published SMC-implementation guidelines that enabled countries to apply for funds from international organizations⁷.

SLOW START

Implementation has been a challenge, however. Mamadou Lamine Diouf, the drug-procurement manager for Senegal's National Malaria Control Program, says that the rollout there was supposed to reach nearly 600,000 children each month, starting in July and August. But he and the US agency footing the bill for the medicine had underestimated how much time it would take to get these older drugs manufactured anew and assessed by various organizations. By early November, health workers had managed to reach only 53,000 children. "We are learning by doing," says Diouf. "Now we know that if we don't master this long supply chain, nothing will be possible."

Drug delays set back chemoprevention pilots in northern Nigeria by a month. Togo's campaign did not start until September. Burkina Faso's project failed to launch when funds came up short. And the size of Mali's intended intervention dropped after a *coup d'état* and an invasion by al-Qaeda affiliates last year sent the nation into disarray.

"IF WE JUST ROLL THIS OUT WITHOUT SURVEILLANCE, WE RISK REPEATING ALL OF THE MISTAKES MADE IN THE PAST."

Still, with the lessons learned, supporters say that they will be better prepared next year (see 'A million ounces of prevention'). In March, some countries plan to apply for funding from the Global Fund to Fight AIDS, Tuberculosis and Malaria. Scott Filler, a disease coordinator at the Global Fund, which is based in Geneva, Switzerland, says, "There are not many things that can prevent malaria in 75% of children, so we will fully support it when countries come to us."

As the programmes continue, researchers will keep watch to see if resistance to the drugs mounts. Randomly selected people who come to hospitals to be treated for malaria in Mali, Chad and Niger will have a spot of their blood

A MILLION OUNCES OF PREVENTION

By November 2013, seasonal malaria chemoprevention (SMC) reached almost 1.2 million children in areas that receive at least 60% of their annual rainfall in the rainy season. If SMC were scaled up to cover all areas where it might be effective, it could reach 25 million children and prevent an estimated 80,000 deaths each year.

smear on filter paper, placed in a ziplock bag and shipped to a laboratory in Bamako, where Dicko and his colleagues will look for mutations associated with resistance to SP and amodiaquine. The University of Dakar will conduct similar tests.

For the campaigns to have a long-lasting effect, chemoprevention must work faster than the parasites acquire resistance. Supporters hope that the treatments will destroy most malaria parasites over the next several years, driving down infection rates and keeping them down even when resistance begins to spread.

Ramanan Laxminarayan, director of the Center for Disease Dynamics, Economics and Policy, a health-policy think tank in Washing-

village in the Koutiala region of Mali just after sunrise in September. Awa Damale, 25 years old and clad in an embroidered aqua dress and matching headscarf, arrives by donkey cart with her four children and two from another family. Five of the children swallow their medicine, but one of Damale's sons has felt ill this week. He tests positive for malaria and gets a referral to the nearest clinic. SMC is for prevention only.

The boy's illness may be a sign that the drugs he took last month are not 100% effective — or that he did not swallow all of the medicine — but his condition does not dampen Damale's enthusiasm. It is the first time this year that one of her children has had malaria. Before the intervention, she constantly juggled working on the farm with caring for sick children. She does not want to hear about the possibility of the programme drying up or the drugs losing potency years down the road. Most of her children are healthy now, and that is what matters most. ■

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Amy Maxmen is a freelance science journalist in New York City. Travel for this story was paid for by a grant from the Pulitzer Center on Crisis Reporting in Washington DC.

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