

MALARIA

Signs of Drug Resistance Rattle Experts, Trigger Bold Plan

NEW ORLEANS, LOUISIANA—“A catastrophic scenario,” one researcher calls it. “A global disaster,” predicts another, contemplating what could happen if malaria parasites worldwide developed resistance against the new artemisinin-based combination therapies (ACTs) that have become the gold standard. Large parts of the world would have no drugs to fall back on, and malaria cases and deaths could soar, erasing hope that the world might be on the eve of a huge reduction in the disease. Yet resistance against ACTs is precisely what now seems to be developing in western Cambodia, along the Thai border, according to several studies presented here last week at the annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH).

The data have given new urgency to an audacious proposal hatched last year to eliminate malaria entirely from the areas where resistance seems to arise. Experts are gathering this week in Phnom Penh to discuss the plan’s implementation, which will be coordinated by the World Health Organization (WHO). The Bill and Melinda Gates Foundation plans to bankroll the effort, says WHO malaria expert Pascal Ringwald.

Scientists still don’t fully understand the extent and nature of the problem, stresses Nicholas White of Mahidol University in Bangkok, who has a study about it coming out soon. The main phenomenon researchers have documented so far is a delay in clearing the parasites from the blood of some patients on artemisinin drugs. Most researchers prefer to say that the parasite is now “tolerant” rather than resistant to the drug. Still, says White, the data are worrisome.

Cambodia’s western border has long been the cradle of antimalarial drug resistance: Chloroquine, sulphadoxine-pyrimethamine, and mefloquine all met their match there before becoming useless elsewhere in the world. Scientists believe this may have to do with the misuse of drugs there and the widespread availability of underdose and counterfeit therapies. From Cambodia, gem miners and other migrants have carried resistant parasites to other Southeast Asian countries.

In the case of ACTs, Cambodia has another problem. These combination treatments rely on an artemisinin derivative for their powerful punch and contain a second drug to make it more difficult for the parasite to become resistant. In Cambodia, however, many artemisinin monotherapies are on the market.



On the border. To prevent resistance to ACTs, a massive malaria-elimination campaign is planned along the Thai-Cambodian border (map), where this picture of a malaria patient and his wife was taken.

Nailing down resistance is harder than it might seem. Treatment failures in individual patients—of which there have been several reports in the past 10 years—don’t always signal resistance. Sometimes patients don’t get better because their blood levels of the drug are too low, for instance. Testing parasites’ sensitivity by exposing them to drugs in the test tube is possible, but the results are hard to interpret. Scientists have not yet found unequivocal genetic markers of resistance to artemisinin derivatives, either.

Partly as a result of such problems, malaria scientists have been skeptical of early reports about resistance. When Harald Noedl, then at the U.S. Army Medical Component of the Armed Forces Research Institute of the Medical Sciences in Bangkok, presented resistance

data at an ASTMH meeting in Atlanta 2 years ago, he was “attacked,” says Ringwald, who had trouble publishing data on the topic himself. “People didn’t want to believe it,” he says.

Two years later, new data have accumulated and the skepticism has largely dissipated, says Dyann Wirth of Harvard University. In a paper published in last week’s issue of *The New England Journal of Medicine*, for instance, Noedl—who is now at the Medical University of Vienna—reports that out of 60 patients from western Cambodia treated with artesunate, two had delayed parasite clearance, with times of 133 and 95 hours, compared with the average of 59 hours. Both had adequate drug levels in their blood.

The new containment plan calls for eliminating malaria from the areas where tolerance has been found and greatly reducing transmission in a large surrounding area (see map). The plan, to be carried out by national malaria-control agencies in Cambodia and Thailand with support from various research institutes, includes rapid and widespread treatment with ACTs, improved mosquito control, the distribution of long-lasting insecticide-impregnated bed nets, a ban on monotherapies in Cambodia (they are already rare in Thailand), and an information campaign. Whether the plan can succeed is unclear, but “it’s worth the investment,” says Wirth.

Another type of response is also in the works. At the ASTMH meeting, scientists launched the Worldwide Antimalarial Resistance Network (WWARN), a global database that will collect information on resistance in vivo and in vitro, drug levels in patients’ blood, and molecular markers. Based at Oxford University in the United Kingdom, the network will be led by Philippe Guérin, an epidemiologist currently working for Doctors Without Borders. WWARN is in the late stages of negotiating a Gates Foundation grant.

Resistance data tend to languish on desks and in drawers for years while they await publication, says Guérin. In exchange for rapid reporting, WWARN will offer scientists statistical help in analyzing the numbers and perhaps even tools for producing a standard manuscript. WWARN also hopes to bring harmony to the myriad ways to test for resistance. “We really need data shared in real time,” says Philip Rosenthal of the University of California, San Francisco, who predicts scientists will cooperate. But, he adds, standardizing methods to test for resistance will be a challenge.

—MARTIN ENSERINK

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