Cause of malaria drug resistance in SE Asia identified

December 11 2014

Ground zero: A child walks along the forest fringe in western Cambodia, where drug resistance in Plasmodium falciparum often emerges. New studies confirm the role of K13 mutations in causing artemisinin-resistant malaria and reveal the molecular mechanism of this problem in Southeast Asia. Credit: Rick Fairhurst

Growing resistance to malaria drugs in Southeast Asia is caused by a single mutated gene inside the disease-causing Plasmodium falciparum

parasite, according to a study led by David Fidock, PhD, professor of microbiology & immunology and of medical sciences (in medicine) at Columbia University Medical Center.

This finding provides public health officials around the world with a way to look for pockets of emerging resistance and potentially eliminate them before they spread.

Though malaria deaths have dropped by 30 percent worldwide since the introduction of artemisinin-based combination therapies (ACTs) in the late 1990s, these gains are now threatened by the emergence of resistance to the core artemisinin component of ACTs in Southeast Asia. No alternative therapy is currently available to replace ACTs should resistance spread to other parts of the world.

The study, published in *Science*, builds on a recent report that mutations in the gene—K13—are frequently found in drug-resistant parasites in Southeast Asia.

Dr. Fidock, working with scientists at the Pasteur Institutes in Paris and Cambodia, the University of Toulouse III, Sangamo Biosciences Inc., and the National Institutes of Health (NIH), showed definitively that K13 mutations directly cause drug resistance.

"The bad news about our finding is that it shows that resistance can arise through single mutations in one gene and pop up anywhere, at any time," Dr. Fidock says. "That's quite different from past instances with former first-line drugs, when complex sets of multiple mutations were required and resistance spread only as the mutated parasites spread."

The good news is that K13 mutations produce a relatively weak resistance. A related study published in the same issue of *Science* found that K13 mutations enable the parasite to hide in red blood cells in a

developmental state that is naturally less vulnerable to artemisinin.

"This allows them to temporarily survive treatment, but it will not be enough for ACTs to fail across Africa, particularly as the partner drugs continue to be highly effective," Dr. Fidock says. "But it may be a foundation for parasites to evolve stronger degrees of resistance to these therapies, so we have to watch for increasing resistance very carefully."

Field reports suggest that not all K13 mutations are capable of causing resistance, and the genetic system developed by Dr. Fidock to study K13, based on DNA repair approaches that are being used in human gene therapy studies, will be critical in identifying real hot spots of resistance.

"There's been confusion in the field because multiple novel K13 mutations have been identified in Africa, but clinically we see no signs of resistance," he says. "Our system can now determine which of those pose the greatest threat."

More information: "K13-Propeller Mutations Confer Artemisinin Resistance in Plasmodium falciparum Clinical Isolates," by J. Straimer et al. *Science*, www.sciencemag.org/lookup/doi/ … 1126/science.1260867

Provided by Columbia University Medical Center