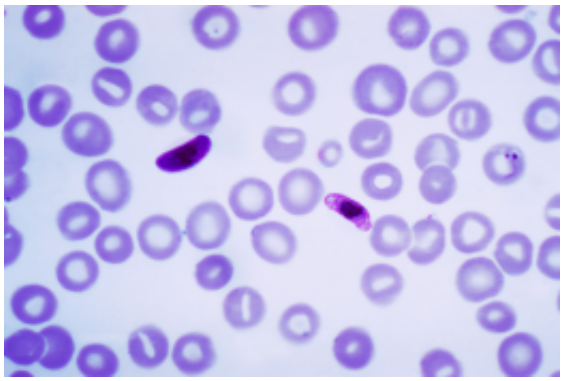
Biologists find malaria parasites lost drug resistance after health policy changes

13 August 2015, by Christopher Packham



This photomicrograph of a blood smear contains a macro- and microgametocyte of the Plasmodium falciparum parasite. Credit: Wikipedia.

(Medical Xpress)—Chloroquine (CQ) is a first-line treatment for Plasmodium falciparum infections, which like many other malaria treatments, eventually resulted in the selection of parasites with resistance to the drug. The evolutionary dynamics of antimalarial drug resistance are driven by many factors, including differing transmission contexts and new drug pressures on parasites. Recently, a group of researchers published a study in the *Proceedings of the National Academy of Sciences* that examined the loss of CQ resistance (CQR) in French Guiana following a health policy change.

To conduct their study, the researchers studied P. falciparum isolates collected between 1994 and 2013 from symptomatic patients in French Guiana. They conducted DNA extraction and phenotyping from samples to compile a database of genetic information about the various strains. Their analysis revealed the presence of a single mutation in the *pfcrt* allele encoding a substitution associated with a return of parasite susceptibility to CQ.

In 1995, CQ had become ineffective against the prevalent CQR parasite strains in much of French Guiana and surrounding countries, and was officially abandoned as a course of treatment because of poor clinical efficacy. Quinine plus doxycycline became the subsequent treatment through 2007. Researchers used a gene marker, K76T, as a marker for CQ resistance.

After a sustained period during which CQ pressure was removed in the country, parasites lost their resistance to CQ, even though the resistance marker K76T remained fixed in the parasite population—this was caused by the acquisition of an additional C350R substitution in the gene that expresses the K76T mutation scientists used to spot drug resistance. This substitution also resulted in new resistance to piperaquine, another drug used to treat malaria.

The authors write, "The successive implementation over time of various first-line drugs after the official cessation of CQ use has created a complex selection landscape operating on the *pfcrt* gene, which is known to impact the efficacy of multiple antimalarials." The drug profiling data from which they drew their conclusions also demonstrated the increased susceptibility of parasites to a number of other antimalarials. "This result reveals a pleiotropic role for this recently emerged *pfcrt* allele in modulating parasite susceptibility to clinically important antimalarials," the researchers write.

This phenotypic reversion was caused by the acquisition of a single mutation that abolished resistance, as opposed to the alternative scenario in which the original wild type gene reemerged in the parasite population. In fact, the research revealed that the wild type *pfcrt* gene had been completely purged from the population, and that the small percentage of parasites with the original haplotype imported from other regions was insufficient to gain a foothold in French Guiana during the period in which CQ treatment was abandoned.

The authors write, "In conclusion, this work illustrates a unique evolutionary path taken by the *pfcrt* gene as a consequence of an altered drug policy," and that "the usefulness of standard molecular markers for drug resistance will require periodic phenotypic validation to contend with ongoing parasite evolution."

More information: "Adaptive evolution of malaria parasites in French Guiana: Reversal of chloroquine resistance by acquisition of a mutation in pfcrt." *PNAS* 2015 ; published ahead of print August 10, 2015, DOI: 10.1073/pnas.1507142112

Abstract
In regions with high malaria endemicity, the withdrawal of chloroquine (CQ) as first-line treatment of Plasmodium falciparum infections has typically led to the restoration of CQ susceptibility through the reexpansion of the wild-type (WT) allele K76 of the chloroquine resistance transporter gene (pfcrt) at the expense of less fit mutant alleles carrying the CQ resistance (CQR) marker K76T. In low-transmission settings, such as South America, drug resistance mutations can attain 100% prevalence, thereby precluding the return of WT parasites after the complete removal of drug pressure. In French Guiana, despite the fixation of the K76T allele, the prevalence of CQR isolates progressively dropped from >90% to