Changes in the frequencies of *Plasmodium falciparum dhps* and *dhfr* drug-resistant mutations in children from Western Kenya from 2005 to 2018: the rise of *Pfdhps* S436H

Abstract

Background

Sulfadoxine-pyrimethamine (SP) is the only anti-malarial drug formulation approved for intermittent preventive treatment in pregnancy (IPTp). However, mutations in the *Plasmodium falciparum dhfr* (*Pfdhfr*) and *dhps* (*Pfdhps*) genes confer resistance to pyrimethamine and sulfadoxine, respectively. Here, the frequencies of SP resistance-associated mutations from 2005 to 2018 were compared in samples from Kenyan children with malaria residing in a holoendemic transmission region.

Methods

Partial sequences of the *Pfdhfr* and *Pfdhps* genes were amplified and sequenced from samples collected in 2005 (n = 81), 2010 (n = 95), 2017 (n = 43), and 2018 (n = 55). The frequency of known mutations conferring resistance to pyrimethamine and sulfadoxine were estimated and compared. Since artemisinin-based combination therapy (ACT) is the current first-line treatment for malaria, the presence of mutations in the propeller domain of *P. falciparum kelch13* gene (*Pfk13*) linked to ACT-delayed parasite clearance was studied in the 2017/18 samples.

Results

Among other changes, the point mutation of *Pfdhps* S436**H** increased in frequency from undetectable in 2005 to 28% in 2017/18. Triple *Pfdhfr* mutant allele (C**IRN**I) increased in frequency from 84% in 2005 to 95% in 2017/18, while the frequency of *Pfdhfr* double mutant alleles declined (allele C**I**C**N**I from 29% in 2005 to 6% in 2017/18, and CN**RN**I from 9% in 2005 to undetectable in 2010 and 2017/18). Thus, a multilocus *Pfdhfr*/*Pfdhps* genotype with six mutations (**HGE**AA/C**IRN**I), including *Pfdhps* S436**H**, increased in frequency from 2010 to 2017/18. Although none of the mutations associated with ACT-delayed parasite clearance was observed, the *Pfk13* mutation A578S, the most widespread *Pfk13* SNP found in Africa, was detected in low frequency (2.04%).

Conclusions

There were changes in SP resistance mutant allele frequencies, including an increase in the *Pfdhps* S436**H**. Although these patterns seem consistent with directional selection due to drug pressure, there is a lack of information to determine the actual cause of such changes. These results suggest incorporating molecular surveillance of *Pfdhfr*/*Pfdhps* mutations in the context of SP efficacy studies for intermittent preventive treatment in pregnancy (IPTp).

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