

Potential use of allele distribution at codon 51 of *Plasmodium falciparum* dihydrofolate reductase (pfDhfr) gene as evidence for early clinical failures to sulfadoxine-pyrimethamine in an operational area in the Northern Province of Sri Lanka

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ABSTRACT

Sulfadoxine-pyrimethamine (S-P) is currently used as the first line treatment for chloroquine resistant, uncomplicated *Plasmodium falciparum* infections in Sri Lanka. The use of S-P has increased in the country' because of increasing chloroquine resistance. The point mutations *QiP.falciparum* dihydrofolate reductase (pfDhfr) and dihydropteroate synthase (pfDhps) genes that confer resistance to S-P occurs in a step wise pattern, commencing from mutation at codon 108 of Dhfr. Mutations tend to accumulate more rapidly with increasing drug pressure. This study was designed to determine the frequency of mutations at codons 108, 5 U 59 and 164 of Dhfr and 436,437 and 540 of Dhps of *P.falciparum* using a PCR-RFLP method and to utilize the data to develop a surveillance method for S-P resistance. Samples were collected in an operational area of the Northern Province where more than 50% of *Rfalciparum* infections were found to be chloroquine resistant during a previous study. Those who received S-P were followed up for 42 days to determine its *in vivo* efficacy. Laboratory results showed that 86.7% of the 30 isolates studied (all chloroquine-resistant infections) were double mutants at codons 108 (Ser to Asn) and 59 (Cys to Arg) of the Dhfr gene. None had mutant alleles at either 51 or 164 codon positions. With regard to the Dhps gene, 73.3% and 83.8% of isolates showed wild type alleles at codons 436 and 437; all had wild type allele at codon 540. However, none of the patients showed clinical evidence of resistance to S-P. Our results showed that the majority of *P.falciparum* isolates in this sample were double mutants at codons 108 and 59 of Dhfr. Based on previous evidence, these double mutants should next develop a mutant allele at codon 51, to become triple mutants, at which stage the clinical failures will begin to appear. Thus, screening for alleles at codon 51 of pfDhfr alone in future surveillance activities should provide a strong indicator for impending clinical failures with S-P in this area.

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