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Evidence for emerging sulfadoxine-pyrimethamine resistance of *Plasmodium falciparum* isolates in the Northern Province of Sri Lanka

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Sulfadoxine-pyrimethamine (SP) has been used as the treatment of choice for chloroquine resistant uncomplicated *Plasmodium falciparum* infections for many years in Sri Lanka. Resistance to SP results from the progressive accumulation of point mutations in the dihydrofolate reductase (*Pf-dhfr*) and dihydropteroate synthase (*Pf-dhps*) genes of *P. falciparum* following its continuous and extensive use. In this study, we determined the response of *P. falciparum* isolates in the Northern Province of Sri Lanka to pyrimethamine *in vitro* and compared the results with previous data from *in vivo* and molecular assays performed on the same isolates. This was done to determine the response of Sri Lankan *P. falciparum* isolates to SP and to explore the possibility of developing a molecular surveillance method for SP resistance in Sri Lanka. *In vitro* response of 30 field isolates to SP was determined by measuring their IC_{50} values to pyrimethamine through expression of *Pf-dhfr* genes in *Saccharomyces cerevisiae*. Double mutant (S108N + C59R) field isolates comprised 85.1% of the study population with 'pure' alleles. The response curves of these double mutant isolates (mean IC_{50} values ranged from 7.7E-06 – 1.7E-05), closely resembled that of the yeast dependent upon the triple mutant reference strain (1.9E-05) and were about 200-fold more resistant to pyrimethamine than the wild type isolates. However, there were no treatment failures to SP in this study group. As previous evidence shows that the clinical failures become evident when *P. falciparum* isolates become triple mutant in *Pf-dhfr,* even without mutations in *Pf-dhps* gene, our *in vitro* and molecular assay results indicate impending clinical failures to SP in this study area in the near future. Even though we could not perform a risk analysis of allele combinations with regard to S-P treatment failure due to lack of clinical failures, our results indicate that the allele distribution at amino acid residue 51 of *Pf-dhfr* will be a good marker for potential S-P clinical failures in this geographical area.

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