

Sulfadoxine-pyrimethamine drug resistance markers hint malaria drug policy shift in India

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India is on track of malaria elimination by 2030 but emerging resistance to its first line antimalarials is one of the major roadblocks. Two instances of rapid development, spread & selection of drug resistant mutant parasites have already been evidenced (Chloroquine in whole of India & Artesunate+Sulfadoxine-Pyrimethamine (AS+SP) in India's north-eastern states).

Looking at these rapid changes in SP drug resistance conferring mutation profile of *P. falciparum*, it becomes evident to systematically monitor the validated mutations in *Pfdhfr* & *Pfdhps* genes across India along with the AS+SP therapeutic efficacy studies. However, unfortunately, no systematic & robust countrywide surveillance has been reported for these parameters.

Therefore, we are presenting here the first exhaustive systematic review & data synthesis on the prevalence of WHO-validated SP-resistance markers in *P. falciparum* across India from 2008 to date. This systematic review covers published reports from the major databases including PubMed®, Web of Science™, Scopus®, Embase® & Google Scholar & presents a chronology of reported events of interest across India.

A total of 37 publications that had data collected between 2008 & 2018 were included in the analysis. *Pfdhfr* mutation data were obtained from 3438-3801 samples & that for *Pfdhps* from 2891-3596 samples.

The *PfDHFR* double mutants were the most prevalent (55%) overall. The overall prevalence of triple & quadruple mutations was 7% & 6%, respectively. The most common *PfDHPS* mutation is A437G with rising & near-100% prevalence in some states. For *PfDHFR/PfDHPS* quintuple & sextuple mutations, despite a low overall prevalence, some states had a prevalence of >30%.

This study gains importance in light of the flags raised towards emerging 'artemisinin-resistance' in eastern India & brings forward the SP-resistance hot-spots & emphasizes critical gaps, challenges & suggests malaria genetic surveillance till malaria is successfully eliminated.

The key question is whether the time has come for a change from AS+SP to AL in the rest of India? The evidence for the risks needs to be weighed but taking the risk of continuing AS+SP, particularly in the light of rising flags of artemisinin-resistance might be counterproductive & the decision needs to be made sooner rather than later.