

Perspective

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Advancing *Plasmodium vivax* malaria treatment in India: The vital role of glucose 6−phosphate dehydrogenase point−of−care tests

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For India to achieve elimination by 2030, the challenges posed by *Plasmodium (P.) vivax* cannot be overlooked owing to its burden and unique biology. In 2023, in India, about 224 000 malaria cases were reported, and a significant proportion (40%) were *P. vivax* cases. In *P. vivax* infection, the persistence of dormant liver stage of parasite, *i.e*., hypnozoites, leading to relapses weeks or months later poses challenge in its elimination. For obviating further transmission chain and achieve elimination, it is imperative to get rid of the hypnozoites. The mainstay of treatment for eliminating hypnozoites is currently primaquine in India, and is given as 0.5 mg/kg/day for 14 days. Recently, tafenoquine, another 8-aminoquinoline, has been approved by FDA[1]. Compared to primaquine, it has a long half-life of 16 days, and thus it is suitable for single dose administration for radical cure of *P. vivax*. Both primaquine and tafenoquine acts as a hypnozoitocidal (targets hypnozoites in the liver). Importantly, if recommended doses of primaquine are not consumed and metabolized by the patients, it can lead to relapse months/years following the initial infection. Evidence suggests that the relapse rate of *P. vivax* in India varies from 8.1% to 38% following unsupervised radical cure[2]. Also, the recommended lower dose (0.25 mg/kg/day) of primaquine for 14 days is challenged with low compliance among the patients, and higher daily dose of primaquine (0.5 mg/kg/day) requires mandatory ruling out glucose 6-phosphate dehydrogenase (G6PD) deficiency owing to increased risk of hemolysis[3]. G6PD deficiency is among the most common X-linked enzymopathies globally, with prevalence in the Indian subcontinent ranging from 2.3% to 27%[4]. Deficient red blood cells are highly susceptible to oxidative stress, leading to potentially life-threatening hemolysis upon exposure to 8-aminoquinolines. Thus to prevent hemolysis in patients during anti-malarial treatment for *P. vivax* (both high-dose primaquine or tafenoquine), it is important to test for G6PD enzyme activity before initiating treatment. Further, if G6PD status is known, higher daily doses of primaquine, for example, 0.5-1 mg/kg can be safely dispensed[5]. Higher dose has been tested in various studies for efficacy, and recent systematic review and meta-analysis points towards the limited evidence from India on the topic[3]. Studies have reported drop in hemoglobin and hemolytic episodes among G6PD deficient patients during treatment with primaquine. Brita-Sousa *et al*. have reported primaquine induced hemolytic anemia in G6PD deficient patients[6]. Majority of patients developed signs of hemolysis after their 3rd dose of primaquine, and required 6 days of in-hospital management with the requirement of blood transfusion in half (48.9%) of the patients. Moreover, one-fourth of the patients also developed acute kidney injury resulting from hemolysis.

Since it is X-linked recessive disorder, in a population, males could be either deficient or normal, and females could have a spectrum of G6PD enzyme activity: >70% - normal activity (homozygous for normal allele), <30% - deficient (homozygous for deficient allele), or 30%-70% - intermediate activity (heterozygous).

Thus, to avoid life-threatening hemolytic episodes, it is crucial to rule-out G6PD deficiency in remote clinical settings. The gold standard test for assessing G6PD enzyme activity is spectrophotometric assay. However, this is resource intensive and it requires laboratory support, a UV light source, and a trained personnel. This method quantifies G6PD enzyme activity based on NADPH formation and the absorbance of UV light at 340 nm over time.

Another commonly used method is fluorescent spot test (FST), a semi-quantitative method. This requires mixing blood with G6PD and nicotinamide adenine dinucleotide. The reaction generates a fluorescent product, its quantity varies depending upon G6PD levels, which is then checked under UV light by dropping a small amount of blood on filter paper.

Realizing the need of economical point-of-care tests (POCTs) for

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minimizing the untoward side effect of hemolysis in G6PD deficient, several point of care tests which can be used at the level of primary care have been developed and are in various stages of testing.

The World Health Organization prequalified point of care device, SD Biosensor includes a SD Biosensor equipment and test strip, and works on the principle of colorimetric reaction similar to spectrophotometry. The method involves adding 10 μL blood to the buffer solution, followed by adding 10 μL blood buffer solution to the single use test device inserted into the Biosensor device. G6PD enzyme converts 5-bromo-4-chloro-3-indolyl-phosphate (BCIP) present in the test strip to violet nitro blue tetrazolium (NBT), colour intensity varying in accordance to G6PD activity. This device also estimates hemoglobin in the blood. It provides estimate of G6PD activity normalized according to hemoglobin within two minutes. The studies have shown around 90% accuracy in identifying individuals with intermediate and deficient G6PD levels in comparison to spectrophotometry. SD Biosensor seems to perform fairly well in terms of sensitivity, and specificity as reported by a recent individual level meta-analysis. The pooled sensitivities for assessing G6PD activity <30% of normal were 0.82 (0.72-0.89) for capillary and 0.93 (0.75-0.99) for venous blood samples. The corresponding values for measuring <70% G6PD activity were 0.93 (0.67-0.99) and 0.89 (0.73-0.96), respectively[7].

Most malaria patients in India are diagnosed and treated at the primary healthcare level by Accredited Social Health Activists (ASHAs) and Auxiliary Nurse Midwives (ANMs). For radical cure to be safely and effectively scaled-up, front line workers must have access to robust, easy-to-use G6PD POCTs. To ensure rural and tribal populations (where both malaria G6PD deficiency is high) must receive the access to diagnostics and safe radical cure, following updation may be required: (1) Embedding G6PD POCTs within the National Centre for Vector Borne Disease Control (NCVBDC) guidelines to ensure uniform adoption; (2) Training ASHAs/ANMs in device use, interpretation, and counseling for treatment adherence; (3) Establishing procurement systems to ensure consistent availability of POCT kits alongside antimalarials.

Safe and effective radical cure of *P. vivax* malaria in India is contingent on reliable G6PD testing. POCTs for G6PD deficiency offer a promising solution to bridge scientific advances with public health delivery. Adoption of G6PD POCTs will not only mitigate risks of hemolysis but also enable higher-dose primaquine or tafenoquine administration, improving compliance, reducing relapses, and moving India closer to achieving malaria elimination by 2030.

Conflict of interest statement

The authors declare that there is no conflict of interests.

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Authors' contributions

NN and PKB did the literature search and drafted the manuscript; NN, and PKB gave intellectual comments, and reviewed the final version.

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