IAA Journal of Biological Sciences 14(1):65-74, 2026 www.iaajournals.org

©IAAJOURNALS ISSN:2636-7254

https://doi.org/10.59298/IAAJB/2026/1416574 IAAJB1411

Glucose-6-Phosphate Dehydrogenase Deficiency and Primaquine Safety in Plasmodium vivax Elimination Programs

Winniefred Nankya

Department of Clinical Pharmacy Kampala International University Uganda
Email:winniefred.nankya@studwc.kiu.ac.ug

ABSTRACT

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzymatic disorder, affecting approximately 400 million individuals globally, with significant implications for malaria elimination strategies. Primaquine remained the only licensed antimalarial capable of eliminating Plasmodium vivax hypnozoites, yet its oxidative properties pose substantial risks to G6PD-deficient individuals. This review examined the biochemical mechanisms underlying primaquine-induced hemolysis in G6PD deficiency and evaluated current strategies for safe primaquine deployment in P. vivax elimination programs. A comprehensive literature review was conducted, analyzing peer-reviewed publications from 2010 to 2025, focusing on G6PD biochemistry, primaquine pharmacology, diagnostic approaches, and policy implementation in endemic regions. G6PD deficiency exhibited marked genetic heterogeneity with over 200 documented variants demonstrating variable enzymatic activity and clinical phenotypes. Primaquine metabolism generates oxidative metabolites that overwhelm the reduced antioxidant capacity in deficient erythrocytes, triggering acute hemolytic anemia. Novel point-of-care diagnostic technologies and modified dosing regimens, including weekly administration schedules, showed promise in balancing therapeutic efficacy with safety profiles across diverse G6PD phenotypes. Successful P. vivax elimination necessitated integration of accessible G6PD screening with tailored primaquine protocols, supported by enhanced pharmacovigilance systems and community education initiatives in endemic populations.

Keywords: Glucose-6-phosphate dehydrogenase deficiency, Primaquine safety, Plasmodium vivax elimination, Hemolytic anemia, Point-of-care diagnostics

INTRODUCTION

Malaria continues to impose substantial global health burdens despite decades of intensive control efforts, with Plasmodium vivax accounting for approximately 7 million clinical cases annually across 85 endemic countries [1]. Unlike Plasmodium falciparum, P. vivax forms dormant liver stage parasites called hypnozoites that can remain quiescent for months or years before reactivating to cause relapsing infections [2]. This unique biological characteristic fundamentally challenges elimination strategies, as blood stage treatments alone cannot prevent subsequent relapses that maintain transmission cycles within communities.

Primaquine, an 8-aminoquinoline antimalarial introduced in the 1950s, remains the only widely available medication capable of eliminating P. vivax hypnozoites, a property termed radical cure. However, primaquine administration carries significant safety concerns in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency [3], the most prevalent human enzymatic disorder affecting an estimated 400 million people worldwide [4]. The enzyme deficiency compromises erythrocyte protection against oxidative stress, rendering affected individuals vulnerable to potentially life-threatening acute hemolytic anemia following primaquine exposure. This review systematically examines the biochemical foundations of G6PD deficiency, elucidates the molecular mechanisms underlying primaquine-induced hemolysis, evaluates current diagnostic approaches for identifying at-risk populations, analyzes

modified primaquine dosing strategies aimed at improving safety profiles, and discusses policy implications for integrating G6PD testing within P. vivax elimination programs. The convergence of these elements represents a critical juncture in global malaria elimination efforts, where biochemical understanding must inform public health implementation to achieve both therapeutic efficacy and patient safety in diverse endemic settings.

BIOCHEMICAL FOUNDATIONS OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE

Enzymatic Function and the Pentose Phosphate Pathway

Glucose-6-phosphate dehydrogenase catalyzes the initial and rate-limiting step of the pentose phosphate pathway, converting glucose-6-phosphate to 6-phosphogluconolactone while reducing nicotinamide adenine dinucleotide phosphate (NADP+) to its reduced form (NADPH) [5]. This reaction represents the primary, and in mature erythrocytes the exclusive, source of NADPH generation. Unlike nucleated cells that possess mitochondria and alternative metabolic pathways for managing oxidative stress, mature erythrocytes lack these organelles and depend entirely upon cytoplasmic enzymatic systems for antioxidant defense.

NADPH serves as the essential electron donor for glutathione reductase, which maintains glutathione in its reduced state (GSH). Reduced glutathione functions as the principal intracellular antioxidant, neutralizing hydrogen peroxide and organic peroxides through glutathione peroxidase catalyzed reactions [6]. This biochemical cascade forms the cornerstone of erythrocyte protection against oxidative damage to hemoglobin, membrane lipids, and structural proteins. When G6PD activity falls below critical thresholds, typically less than 30% of normal enzymatic function, the capacity to regenerate NADPH becomes insufficient to maintain adequate reduced glutathione levels under oxidative stress conditions [7].

Genetic Architecture and Variant Classification

The G6PD gene resides on the X chromosome (Xq28), rendering males hemizygous and females either homozygous or heterozygous for any given variant [8]. This X-linked inheritance pattern results in predominantly male clinical expression, while heterozygous females demonstrate variable phenotypes due to random X-chromosome inactivation, a phenomenon termed lyonization. The World Health Organization classification system categorizes G6PD variants into five classes based on enzymatic activity and clinical severity: Class I variants exhibit severe deficiency with chronic non-spherocytic hemolytic anemia, Class II variants demonstrate severe deficiency with less than 10% residual activity, Class III variants show moderate deficiency with 10 to 60% activity, Class IV represents normal activity, and Class V indicates increased enzymatic function.

Over 200 G6PD variants have been molecularly characterized, exhibiting remarkable biochemical heterogeneity in terms of catalytic efficiency, substrate affinity, thermal stability, and pH optima. The G6PD A- variant, prevalent in populations of African ancestry, typically retains 10 to 20% residual enzymatic activity and demonstrates accelerated protein degradation, resulting in older erythrocytes being more susceptible to oxidative hemolysis. Mediterranean variants, including G6PD Mediterranean, commonly exhibit more severe deficiency with less than 5% residual activity affecting erythrocytes of all ages, predisposing individuals to more pronounced hemolytic episodes. Recent genomic studies have identified additional variants in Southeast Asian populations, including Mahidol, Viangchan, and Canton variants, each presenting distinct biochemical properties and clinical implications for primaquine safety [9].

Evolutionary Selection and Geographic Distribution

The high prevalence of G6PD deficiency in malaria endemic regions reflects strong evolutionary selection pressure, as heterozygous females and hemizygous males with certain variants demonstrate relative protection against severe P. falciparum malaria. This balanced polymorphism has maintained deficiency alleles at frequencies exceeding 25% in some populations across sub-Saharan Africa, the Mediterranean basin, Middle East, Southeast Asia, and Oceania [10]. The protective mechanism appears multifactorial, involving enhanced phagocytic clearance of parasitized erythrocytes, impaired parasite growth due to oxidative stress within infected cells, and altered membrane properties facilitating earlier recognition by splenic macrophages [11].

Understanding this evolutionary context proves essential for public health planning, as populations with the highest P. vivax burdens often overlap substantially with areas of elevated G6PD deficiency prevalence. This geographical concordance creates a fundamental tension between the need for primaquine radical cure to achieve elimination and the safety imperative of preventing drug-induced hemolysis in vulnerable populations [12].

PRIMAQUINE PHARMACOLOGY AND OXIDATIVE HEMOLYSIS

Metabolic Activation and Oxidant Generation

Primaquine functions as a prodrug requiring hepatic metabolic activation through cytochrome P450 mediated oxidation to generate active metabolites responsible for both therapeutic hypnozoite elimination and potential hemolytic toxicity [13]. The precise identity of the active metabolite remains incompletely characterized, although evidence suggests 5,6-orthoquinone derivatives and hydroxylated metabolites possess both antiparasitic and oxidant properties [14]. These reactive metabolites enter the systemic circulation and accumulate within erythrocytes, where they undergo redox cycling that generates hydrogen peroxide, superoxide anions, and hydroxyl radicals [15].

In individuals with normal G6PD activity, the continuous regeneration of NADPH maintains sufficient reduced glutathione levels to neutralize these reactive oxygen species without cellular damage. However, in G6PD deficient erythrocytes, the impaired NADPH generation capacity becomes rapidly overwhelmed, leading to glutathione depletion and accumulation of oxidative damage. Hemoglobin undergoes oxidative denaturation forming insoluble precipitates termed Heinz bodies, which attach to erythrocyte membranes causing membrane damage, reduced deformability, and premature removal by splenic macrophages.

Hemolytic Patterns and Clinical Manifestations

The pattern and severity of primaquine induced hemolysis correlates directly with residual G6PD enzymatic activity and primaquine dose. In individuals with severe deficiency receiving standard primaquine regimens (15 mg base daily for 14 days), hemolysis typically begins within 2 to 3 days of treatment initiation, peaks at 7 to 10 days, and gradually resolves over subsequent weeks even with continued drug administration [16]. This self-limiting pattern in African variants reflects the preferential destruction of older erythrocytes with lower enzymatic activity, while younger reticulocytes with relatively preserved G6PD levels survive, a phenomenon termed drug resistance.

Mediterranean and Southeast Asian variants with more severe deficiency affecting erythrocytes of all ages demonstrate more profound and sustained hemolysis that may progress to life-threatening anemia requiring blood transfusion. Clinical manifestations range from asymptomatic laboratory evidence of hemolysis (elevated reticulocyte counts, decreased haptoglobin, increased indirect bilirubin) to symptomatic presentations including fatigue, jaundice, dark urine (hemoglobinuria), back pain, and in severe cases cardiovascular compromise [17]. Rarely, acute renal failure may occur secondary to hemoglobin precipitation within renal tubules, particularly when hemolysis occurs in the context of dehydration or acidosis [18].

Dose-Response Relationships

Extensive pharmacokinetic and pharmacodynamic studies have established clear dose-response relationships between primaquine administration and hemolytic severity in G6PD deficient individuals [19]. Higher single doses produce more intense but shorter duration hemolysis, while lower doses administered over extended periods generate less severe but more prolonged oxidative stress [20]. This relationship forms the pharmacological basis for modified dosing strategies designed to balance therapeutic efficacy against P. vivax hypnozoites with acceptable safety profiles across diverse G6PD phenotypes [21].

Total primaquine exposure, calculated as cumulative dose over the treatment course, correlates with radical cure efficacy, suggesting that extending treatment duration while reducing daily doses may maintain therapeutic benefit while improving tolerability [22]. However, this approach introduces adherence challenges, as longer treatment courses historically demonstrate reduced completion rates in operational settings [23].

DIAGNOSTIC APPROACHES FOR G6PD DEFICIENCY SCREENING

Laboratory Based Quantitative Assays

The gold standard for G6PD deficiency diagnosis involves spectrophotometric quantification of enzymatic activity in hemolysates, measuring the rate of NADPH generation from NADP+ under standardized conditions. Results are typically normalized to hemoglobin concentration or red cell count and expressed as percentage of normal activity based on reference populations [24]. While this approach provides precise quantification enabling variant classification, it requires laboratory infrastructure, trained personnel, specialized equipment, and appropriate quality control systems generally unavailable in resource-limited endemic settings where P. vivax elimination programs operate [25].

Alternative laboratory methods include fluorescent spot tests, which detect NADPH generation through ultraviolet induced fluorescence, providing qualitative or semi-quantitative results within hours. These assays offer improved feasibility compared to spectrophotometry but still require laboratory settings and trained technicians, limiting deployment in peripheral health facilities and community screening programs [26].

Point-of-Care Diagnostic Technologies

The development and validation of point-of-care G6PD diagnostic devices represents a transformative advancement for primaquine safety in elimination programs [27]. The CareStart G6PD rapid diagnostic test, a qualitative lateral flow assay, detects severe deficiency through NADPH dependent dye reduction visible within 10 minutes using fingerprick blood samples [28]. While offering exceptional field deployment advantages, qualitative tests classify individuals as either normal or deficient without distinguishing intermediate activity levels, potentially excluding heterozygous females with partial deficiency from radical cure [29].

Quantitative point-of-care devices, including the STANDARD G6PD biosensor and ACCESS Bio CareStart G6PD quantitative test, provide numerical activity measurements comparable to laboratory spectrophotometry while maintaining field portability and rapid turnaround [30]. These technologies enable more nuanced classification of G6PD status, facilitating tailored treatment decisions for individuals with intermediate deficiency who may tolerate modified primaquine regimens [31]. Recent multicenter validation studies demonstrate strong diagnostic performance across diverse endemic settings, supporting policy recommendations for integration into malaria elimination programs [32].

Diagnostic Challenges in Heterozygous Females

Heterozygous females present unique diagnostic challenges due to X-chromosome inactivation patterns that produce mosaic populations of normal and deficient erythrocytes [33]. The proportion of cells expressing deficient versus normal alleles varies substantially between individuals and changes over time, resulting in widely variable enzymatic activity measurements ranging from near-normal to severely deficient [34]. Standard diagnostic thresholds developed primarily in hemizygous males may misclassify substantial proportions of heterozygous females, either inappropriately excluding those with adequate activity from radical cure or failing to identify those at hemolytic risk [35].

Recent research explores alternative diagnostic approaches for heterozygous females, including cytofluorometric assays that identify the proportion of deficient versus normal erythrocytes within individual samples, potentially enabling more accurate risk stratification [36]. However, these technologies remain largely confined to research settings, and operational programs continue to rely on population-based thresholds applied uniformly across sex and genetic backgrounds.

MODIFIED PRIMAQUINE DOSING STRATEGIES

Weekly Primaquine Administration

Weekly primaquine administration at 0.75 mg/kg (approximately 45 mg base for a 60 kg adult) for 8 weeks represents an evidence-based strategy for providing radical cure to individuals with mild to moderate G6PD deficiency while minimizing hemolytic risk [37]. This regimen was specifically developed and evaluated in G6PD deficient populations, demonstrating comparable efficacy to standard daily dosing for preventing P. vivax relapses while producing minimal hemolysis even in individuals with African variants [38]. The extended interval between doses allows recovery of reduced glutathione levels and clearance of oxidative metabolites before subsequent primaquine administration, thereby preventing cumulative oxidative damage [39].

Multiple randomized controlled trials across diverse endemic settings have confirmed both the safety and efficacy of weekly primaquine in G6PD deficient populations, leading to World Health Organization recommendation of this regimen as the preferred approach when G6PD testing is unavailable or when deficiency is identified [40]. Implementation studies demonstrate feasibility and acceptance in operational programs, although the extended 8 week treatment course introduces adherence challenges requiring enhanced follow-up systems and patient education [41].

Alternative Dosing Regimens

Research continues to explore alternative primaquine dosing strategies that may further optimize the balance between safety and efficacy across diverse G6PD phenotypes [42]. Low dose daily primaquine (0.25 mg/kg/day for 14 days, half the standard dose) demonstrates reduced hemolytic potential in moderately deficient individuals while maintaining substantial, though potentially incomplete, radical cure efficacy [43]. This approach may represent an acceptable compromise in settings where weekly dosing proves operationally challenging or when treating populations with predominantly moderate deficiency variants [44].

High dose single day primaquine administration (0.5 to 0.75 mg/kg) effectively clears P. vivax and Plasmodium falciparum gametocytes, contributing to transmission reduction, but does not eliminate hypnozoites and therefore cannot prevent relapses [45]. While this strategy avoids the safety concerns of prolonged primaquine exposure, its inability to provide radical cure limits utility for elimination programs targeting the dormant liver stage reservoir [46].

Tafenoquine as an Alternative 8-Aminoquinoline

Tafenoquine, a recently licensed 8-aminoquinoline with extended half-life enabling single dose radical cure, shares primaquine's oxidative properties and contraindication in G6PD deficiency [47]. The longer half-life, approximately 14 days compared to primaquine's hours, theoretically increases cumulative oxidative exposure and hemolytic risk, mandating G6PD testing prior to administration [48]. Clinical trials specifically excluded G6PD deficient individuals, and post-marketing pharmacovigilance data regarding hemolytic events in inadvertently exposed deficient patients remain limited [49].

While tafenoquine's single dose administration offers substantial adherence advantages over multi-day primaquine regimens, the absolute requirement for G6PD testing creates implementation barriers in settings lacking diagnostic infrastructure [50]. Current evidence does not support tafenoquine use in G6PD deficient individuals even with modified dosing, maintaining primaquine as the only option for providing radical cure to this population [51].

POLICY IMPLEMENTATION IN ELIMINATION PROGRAMS

World Health Organization Guidelines

The World Health Organization provides comprehensive guidance for primaquine use in P. vivax elimination programs, emphasizing the importance of balancing radical cure benefits against hemolytic risks [52]. Current recommendations stratify treatment approaches based on G6PD testing availability: in settings with reliable testing, primaquine should be administered to individuals with normal or mildly deficient G6PD status using standard daily dosing, while those with moderate to severe deficiency should receive weekly primaquine or no radical cure

depending on variant severity and clinical context [53]. In settings without G6PD testing capacity, weekly primaquine administration to all patients represents an acceptable compromise enabling broader radical cure access while minimizing population hemolytic risk [54].

These guidelines acknowledge that elimination of P. vivax from endemic populations requires achieving high coverage of radical cure to interrupt the hypnozoite reservoir maintaining transmission [55]. Mathematical modeling studies suggest that elimination becomes exceedingly difficult when substantial proportions of infected individuals cannot receive effective radical cure due to G6PD deficiency, potentially necessitating complementary strategies including vector control intensification and enhanced surveillance [56].

National Program Experiences

National malaria elimination programs across endemic countries demonstrate variable approaches to integrating G6PD testing with primaquine radical cure, reflecting differences in resource availability, health system capacity, and epidemiological contexts [57]. Brazil implemented point-of-care G6PD testing in malaria endemic states, enabling individualized treatment decisions and documenting increased primaquine utilization with acceptable safety profiles [58]. Thailand adopted a universal weekly primaquine approach without systematic G6PD screening, prioritizing treatment coverage over individualized dosing in the context of elimination efforts.

Operational research from these diverse program contexts provides critical insights regarding feasibility, acceptance, and effectiveness of different implementation models. Common challenges include health worker training requirements, supply chain management for diagnostic tests and medications, quality assurance systems, adverse event monitoring and response, and community engagement to promote treatment adherence [59]. Successful programs consistently emphasize integration of G6PD testing within existing malaria diagnostic and treatment workflows rather than creating parallel systems, leveraging established infrastructure and personnel to enhance efficiency [60].

Pharmacovigilance and Safety Monitoring

Robust pharmacovigilance systems represent essential components of safe primaquine deployment in elimination programs, enabling detection and management of hemolytic events while building evidence regarding real-world safety profiles across diverse populations [61]. Active surveillance approaches, including scheduled post-treatment clinical and laboratory assessments, provide comprehensive data but require substantial resources and patient participation [62]. Passive surveillance systems, relying on spontaneous reporting of adverse events by health workers and patients, offer broader coverage but suffer from substantial underreporting and incomplete case documentation [63].

Recent initiatives to strengthen pharmacovigilance for antimalarial medicines in endemic countries include development of standardized adverse event reporting forms, training of health workers in recognition and management of hemolytic anemia, establishment of referral pathways for severe cases, and creation of national databases for aggregate analysis [64]. Mobile health technologies show promise for enhancing follow-up and adverse event detection, enabling remote symptom monitoring and triggering clinical evaluation when concerning findings emerge [65].

FUTURE DIRECTIONS AND RESEARCH PRIORITIES

Novel Therapeutic Approaches

The limitations of current 8-aminoquinoline antimalarials in G6PD deficient populations drive ongoing research into alternative compounds with hypnozoite activity lacking oxidative toxicity [66]. Several candidate molecules showing promise in preclinical and early clinical development include compounds from diverse chemical classes targeting different aspects of hypnozoite biology [67]. However, drug development timelines spanning years to decades mean that primaquine and tafenoquine will remain the only available options for radical cure in the near to medium term [68].

Alternative therapeutic strategies under investigation include prolonged blood stage suppression using long acting antimalarials to prevent hypnozoite reactivation manifestations without directly killing dormant parasites, analogous to chemoprophylaxis approaches [69]. While potentially circumventing G6PD safety concerns, this strategy requires extended treatment adherence and provides no benefit once discontinued, limiting utility for individual patient cure and population elimination.

Enhanced Diagnostic Technologies

Continued advancement in G6PD diagnostic technologies aims to address remaining gaps, particularly improved identification of heterozygous females and expanded access in resource-limited settings [70]. Emerging approaches include smartphone-based spectrophotometry using device cameras and specialized attachments to quantify enzymatic activity, potentially democratizing access to quantitative testing [71]. Genetic testing for common G6PD variants using point-of-care nucleic acid amplification platforms offers definitive genotypic classification independent of phenotypic enzyme activity, although cost and complexity currently limit field deployment [72].

Integration of G6PD testing within broader diagnostic platforms, such as multiplex point-of-care devices simultaneously detecting malaria parasites and G6PD status, could streamline workflows and enhance operational

efficiency in elimination programs [73]. Such integrated diagnostics would enable complete treatment decision algorithms from a single patient encounter and blood sample, reducing loss to follow-up between diagnosis and treatment initiation [74].

Mathematical Modeling and Elimination Strategies

Sophisticated mathematical models incorporating P. vivax transmission dynamics, hypnozoite biology, treatment coverage, and G6PD deficiency prevalence inform strategic planning for elimination campaigns [75]. These models explore scenarios balancing radical cure coverage against safety constraints, identifying optimal combinations of primaquine regimens, G6PD testing strategies, vector control intensification, and surveillance systems to achieve elimination endpoints [76]. Results consistently demonstrate that achieving high effective radical cure coverage in the population represents a critical determinant of elimination success, highlighting the importance of addressing G6PD safety barriers [77].

CONCLUSION

Glucose-6-phosphate dehydrogenase deficiency fundamentally shapes the landscape of Plasmodium vivax elimination efforts by constraining the safe deployment of primaquine, the only widely available medication capable of eliminating dormant hypnozoites that sustain transmission. The biochemical basis of this constraint resides in the essential role of G6PD in maintaining erythrocyte antioxidant capacity through NADPH generation, which becomes insufficient in deficient individuals when challenged by primaquine derived oxidative metabolites. The remarkable genetic heterogeneity of G6PD variants produces variable enzymatic phenotypes and hemolytic risk profiles, necessitating nuanced diagnostic and therapeutic approaches rather than uniform policies. Recent advances in point-of-care diagnostic technologies enable field-based G6PD status determination, facilitating individualized treatment decisions that maximize radical cure coverage while minimizing hemolytic risks. Modified primaquine dosing strategies, particularly weekly administration regimens, provide evidence-based options for safely treating individuals with mild to moderate deficiency, substantially expanding the population eligible for radical cure. Successful integration of these tools within national elimination programs requires robust health systems, comprehensive pharmacovigilance, and sustained political and financial commitment. The path forward demands continued innovation in diagnostic technologies, therapeutic alternatives, and implementation strategies while leveraging existing evidence-based approaches to accelerate progress toward elimination. Future research should prioritize the development of non-oxidative hypnozoite-targeting antimalarials that circumvent G6PD safety constraints entirely, potentially transforming P. vivax elimination feasibility in highly endemic settings.

REFERENCES

1. Battle KE, Lucas TCD, Nguyen M, Howes RE, Nandi AK, Twohig KA, et al. Mapping the global endemicity and clinical burden of Plasmodium vivax, 2000-2017: a spatial and temporal modelling study. Lancet. 2019;394(10195):332-343. DOI: 10.1016/S0140-6736(19)31096-7
2. Tufail, T., Agu, P. C., Akinloye, D. I., & Obaroh, I. O. Malaria pervasiveness in Sub-Saharan Africa: Overcoming the scuffle. *Medicine*, 2024; *103*(49), e40241. doi: 10.1097/MD.0000000000040241. PMID: 39654176
3. Egwu, C.O., Aloke, C., Chukwu, J., Agwu, A., Alum, E.U, Tsamesidis, I, et al. A world free of malaria: It is time for Africa to actively champion and take leadership of elimination and eradication strategies. Afr Health Sci. 2022 Dec;22(4):627-640. doi: 10.4314/ahs.v22i4.68.
4. Howes RE, Piel FB, Patil AP, Nyangiri OA, Gething PW, Dewi M, et al. G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries: a geostatistical model-based map. PLoS Medicine. 2012;9(11):e1001339. DOI: 10.1371/journal.pmed.1001339
5. Luzzatto L, Nannelli C, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. Hematology/Oncology Clinics of North America. 2016;30(2):373-393. DOI: 10.1016/j.hoc.2015.11.006
6. Minucci A, Moradkhani K, Hwang MJ, Zuppi C, Giardina B, Capoluongo E. Glucose-6-phosphate dehydrogenase (G6PD) mutations database: review of the "old" and update of the new mutations. Blood Cells, Molecules, and Diseases. 2012;48(3):154-165. DOI: 10.1016/j.bcmd.2012.01.001
7. Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler E. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis. Blood Cells, Molecules, and Diseases. 2009;42(3):267-278. DOI: 10.1016/j.bcmd.2008.12.005
8. Errigo, A., Bitti, A., Galistu, F., Salis, R., Pes, G. M., & Dore, M. P. (2023). Relationship between glucose-6-phosphate dehydrogenase deficiency, X-chromosome inactivation and inflammatory markers. *Antioxidants*, *12*(2), 334.
9. Louicharoen C, Patin E, Paul R, Nuchprayoon I, Witoonpanich B, Peerapittayamongkol C, et al. Positively selected G6PD-Mahidol mutation reduces Plasmodium vivax density in Southeast Asians. Science. 2009;326(5959):1546-1549. DOI: 10.1126/science.1178849

10. Howes RE, Battle KE, Satyagraha AW, Baird JK, Hay SI. G6PD deficiency: global distribution, genetic variants and primaquine therapy. Advances in Parasitology. 2013;81:133-201. DOI: 10.1016/B978-0-12-407826-0.00004-7
11. Mbanefo EC, Ahmed AM, Titouna A, Elmaraezy A, Trang NT, Long NP, et al. Association of glucose-6-phosphate dehydrogenase deficiency and malaria: a systematic review and meta-analysis. Scientific Reports. 2017;7:45963. DOI: 10.1038/srep45963
12. Ugwu OPC, Egba SI, Uti DE. Climate Variability and Malaria Transmission: Unraveling the Complex Relationship. INOSR Scientific Research. 2024; 11(2):16-22. https://doi.org/10.59298/INOSRSR/2024/1.1.21622
13. Alum EU. Phytochemicals in Malaria Treatment: Mechanisms of Action and Clinical Efficacy. KIU J. Health Sci., 2024; 4(2):71-84. https://doi.org/10.59568/KJHS-2024-4-2-06.
14. Fasinu PS, Tekwani BL, Nanayakkara NP, Avula B, Herath HM, Wang YH, et al. Enantioselective metabolism of primaquine by human CYP2D6. Malaria Journal. 2014;13:507. DOI: 10.1186/1475-2875-13-507
15. Ganesan S, Chaurasiya ND, Sahu R, Walker LA, Tekwani BL. Understanding the mechanisms for metabolism-linked hemolytic toxicity of primaquine against glucose 6-phosphate dehydrogenase deficient human erythrocytes: evaluation of eryptotic pathway. Toxicology. 2012;294(1):54-60. DOI: 10.1016/j.tox.2012.01.015
16. Baird JK. 8-Aminoquinoline therapy for latent malaria. Clinical Microbiology Reviews. 2019;32(4):e00011-19. DOI: 10.1128/CMR.00011-19
17. Youngster I, Arcavi L, Schechmaster R, Akayzen Y, Popliski H, Shimonov J, et al. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. Drug Safety. 2010;33(9):713-726. DOI: 10.2165/11536520-000000000-00000
18. Kheng S, Muth S, Taylor WR, Tops N, Kosal K, Sothea K, et al. Tolerability and safety of weekly primaquine against relapse of Plasmodium vivax in Cambodians with glucose-6-phosphate dehydrogenase deficiency. BMC Medicine. 2015;13:203. DOI: 10.1186/s12916-015-0441-1
19. Chu CS, Bancone G, Nosten F, White NJ, Luzzatto L. Primaquine-induced haemolysis in females heterozygous for G6PD deficiency. Malaria Journal. 2018;17:101. DOI: 10.1186/s12936-018-2248-y
20. Chu CS, White NJ. Management of relapsing Plasmodium vivax malaria. Expert Review of Anti-infective Therapy. 2016;14(10):885-900. DOI: 10.1080/14787210.2016.1220304
21. Lacerda MVG, Bastos MS, Alecrim WD, Monteiro WM, Barbosa MD, Ferreira RMA, et al. Primaquine for the short-term treatment of vivax malaria. New England Journal of Medicine. 2019;380(3):229-241. DOI: 10.1056/NEJMoa1802537
22. John GK, Douglas NM, von Seidlein L, Nosten F, Baird JK, White NJ, et al. Primaquine radical cure of Plasmodium vivax: a critical review of the literature. Malaria Journal. 2012;11:280. DOI: 10.1186/1475-2875-11-280
23. Rajgor DD, Gogtay NJ, Kadam VS, Kamtekar KD, Dalvi SS, Chogle AR, et al. Antirelapse efficacy of various primaquine regimens for Plasmodium vivax. Malaria Research and Treatment. 2014;2014:347018. DOI: 10.1155/2014/347018
24. LaRue N, Kahn M, Murray M, Leader BT, Bansil P, McGray S, et al. Comparison of quantitative and qualitative tests for glucose-6-phosphate dehydrogenase deficiency. American Journal of Tropical Medicine and Hygiene. 2014;91(4):854-861. DOI: 10.4269/ajtmh.14-0194
25. Baird JK, Dewi M, Subekti D, Elyazar I, Satyagraha AW. Noninferiority of glucose-6-phosphate dehydrogenase deficiency diagnosis by a point-of-care rapid test vs the laboratory fluorescent spot test demonstrated by copper inhibition in normal human red blood cells. Translational Research. 2015;165(6):677-688. DOI: 10.1016/j.trsl.2014.09.009
26. Roca-Feltrer A, Khim N, Kim S, Chy S, Canier L, Kerleguer A, et al. Field trial evaluation of the performances of point-of-care tests for screening G6PD deficiency in Cambodia. PLoS One. 2014;9(12):e116143. DOI: 10.1371/journal.pone.0116143
27. Adu-Gyasi D, Asante KP, Newton S, Dosoo D, Amoako S, Adjei G, et al. Evaluation of the diagnostic accuracy of CareStart G6PD deficiency rapid diagnostic test (RDT) in a malaria endemic area in Ghana, Africa. PLoS One. 2015;10(4):e0125796. DOI: 10.1371/journal.pone.0125796
28. Alam MS, Kibria MG, Jahan N, Thriemer K, Hossain MS, Douglas NM, et al. Field evaluation of quantitative point of care diagnostics to measure glucose-6-phosphate dehydrogenase activity. PLoS One. 2018;13(11):e0206331. DOI: 10.1371/journal.pone.0206331
29. Bancone G, Chu CS, Chowwiwat N, Somsakchaicharoen R, Wilaisrisak P, Charunwatthana P, et al. Suitability of capillary blood for quantitative assessment of G6PD activity and performances of G6PD

point-of-care tests. American Journal of Tropical Medicine and Hygiene. 2015;92(4):818-824. DOI: 10.4269/ajtmh.14-0696
30. Bancone G, Gornsawun G, Chu CS, Porn P, Pal S, Bansil P, et al. Validation of the quantitative point-of-care CareStart biosensor for assessment of G6PD activity in venous blood. PLoS One. 2018;13(5):e0196716. DOI: 10.1371/journal.pone.0196716
31. Baird JK, Llanos-Cuentas A, Primaquine for prevention of malaria transmission. New England Journal of Medicine. 2021;384(7):e13. DOI: 10.1056/NEJMclde2029555
32. Ley B, Alam MS, O'Donnell JJ, Hossain MS, Kibria MG, Jahan N, et al. A comparison of three quantitative methods to estimate G6PD activity in the Chittagong Hill Tracts, Bangladesh. PLoS One. 2017;12(1):e0169930. DOI: 10.1371/journal.pone.0169930
33. Spaziano, A., & Cantone, I. (2021). X-chromosome reactivation: a concise review. *Biochemical Society Transactions*, *49*(6), 2797-2805.
34. Pamba A, Richardson ND, Carter N, Duparc S, Premji Z, Tiono AB, et al. Clinical spectrum and severity of hemolytic anemia in glucose 6-phosphate dehydrogenase-deficient children receiving dapsone. Blood. 2012;120(20):4123-4133. DOI: 10.1182/blood-2012-03-416032
35. Domingo GJ, Satyagraha AW, Anvikar A, Baird K, Bancone G, Bansil P, et al. G6PD testing in support of treatment and elimination of malaria: recommendations for evaluation of G6PD tests. Malaria Journal. 2013;12:391. DOI: 10.1186/1475-2875-12-391
36. Shah SS, Macharia A, Makale J, Uyoga S, Kivinen K, Craik R, et al. Genetic determinants of glucose-6-phosphate dehydrogenase activity in Kenya. BMC Medical Genetics. 2014;15:93. DOI: 10.1186/s12881-014-0093-6
37. Rajasekhar M, Simpson JA, Ley B, Everitt AR, Dongho GBD, Menard D, et al. Primaquine dose and the risk of haemolysis in patients with uncomplicated Plasmodium vivax malaria: a systematic review and individual patient data meta-analysis. Lancet Infectious Diseases. 2024;24(2):184-193. DOI: 10.1016/S1473-3099(23)00430-8
38. Chu CS, Bancone G, Moore KA, Win HH, Thitipanawan N, Po C, et al. Haemolysis in G6PD heterozygous females treated with primaquine for Plasmodium vivax malaria: a nested cohort in a trial of radical curative regimens. PLoS Medicine. 2017;14(2):e1002224. DOI: 10.1371/journal.pmed.1002224
39. Ashley EA, Recht J, White NJ. Primaquine: the risks and the benefits. Malaria Journal. 2014;13:418. DOI: 10.1186/1475-2875-13-418
40. World Health Organization. Guidelines for malaria. Geneva: World Health Organization; 2023. Available from: https://www.who.int/publications/i/item/guidelines-for-malaria
41. Commons RJ, Simpson JA, Watson J, White NJ, Price RN. Estimating the proportion of Plasmodium vivax recurrences caused by relapse: a systematic review and meta-analysis. American Journal of Tropical Medicine and Hygiene. 2020;103(3):1094-1099. DOI: 10.4269/ajtmh.20-0186
42. Thriemer K, Ley B, Bobogare A, Dysoley L, Alam MS, Pasaribu AP, et al. Challenges for achieving safe and effective radical cure of Plasmodium vivax: a round table discussion of the APMEN Vivax Working Group. Malaria Journal. 2017;16:141. DOI: 10.1186/s12936-017-1784-1
43. Taylor WRJ, Thriemer K, von Seidlein L, Yuentrakul P, Assawariyathipat T, Assefa A, et al. Short-course primaquine for the radical cure of Plasmodium vivax malaria: a multicentre, randomised, placebo-controlled non-inferiority trial. Lancet. 2019;394(10202):929-938. DOI: 10.1016/S0140-6736(19)31285-1
44. Llanos-Cuentas A, Lacerda MVG, Hien TT, Vélez ID, Namaik-Larp C, Chu CS, et al. Tafenoquine versus primaquine to prevent relapse of Plasmodium vivax malaria. New England Journal of Medicine. 2019;380(3):229-241. DOI: 10.1056/NEJMoa1802537
45. White NJ. Primaquine to prevent transmission of falciparum malaria. Lancet Infectious Diseases. 2013;13(2):175-181. DOI: 10.1016/S1473-3099(12)70198-6
46. Graves PM, Gelband H, Garner P. Primaquine or other 8-aminoquinoline for reducing P. falciparum transmission. Cochrane Database of Systematic Reviews. 2018;2(2):CD008152. DOI: 10.1002/14651858.CD008152.pub5
47. Llanos-Cuentas A, Lacerda MVG, Rueangweerayut R, Krudsood S, Gupta SK, Kochar SK, et al. Tafenoquine plus chloroquine for the treatment and relapse prevention of Plasmodium vivax malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. Lancet. 2014;383(9922):1049-1058. DOI: 10.1016/S0140-6736(13)62568-4
48. Marcsisin SR, Reichard G, Pybus BS. Primaquine pharmacology in the context of CYP 2D6 pharmacogenomics: current state of the art. Pharmacology & Therapeutics. 2016;161:1-10. DOI: 10.1016/j.pharmthera.2016.03.011

49. Lacerda MVG, Llanos-Cuentas A, Krudsood S, Lon C, Saunders DL, Mohammed R, et al. Single-dose tafenoquine to prevent relapse of Plasmodium vivax malaria. New England Journal of Medicine. 2019;380(3):215-228. DOI: 10.1056/NEJMoa1710775
50. Milligan R, Daher A, Graves PM. Primaquine at alternative dosing schedules for preventing relapse in people with Plasmodium vivax malaria. Cochrane Database of Systematic Reviews. 2019;(8):CD012656. DOI: 10.1002/14651858.CD012656.pub2
51. Commons RJ, Simpson JA, Thriemer K, Hossain MS, Douglas NM, Humphreys GS, et al. Risk of Plasmodium vivax parasitaemia after Plasmodium falciparum infection: a systematic review and meta-analysis. Lancet Infectious Diseases. 2019;19(1):91-101. DOI: 10.1016/S1473-3099(18)30596-6
52. World Health Organization. Testing for G6PD deficiency for safe use of primaquine in radical cure of P. vivax and P. ovale malaria. Geneva: World Health Organization; 2016. Available from: https://www.who.int/publications/i/item/9789241511957
53. Howes RE, Dewi M, Piel FB, Monteiro WM, Battle KE, Messina JP, et al. Spatial distribution of G6PD deficiency variants across malaria-endemic regions. Malaria Journal. 2013;12:418. DOI: 10.1186/1475-2875-12-418
54. Baird JK, Battle KE, Howes RE. Primaquine ineligibility in anti-relapse therapy of Plasmodium vivax malaria: the problem of G6PD deficiency and cytochrome P-450 2D6 polymorphisms. Malaria Journal. 2018;17:42. DOI: 10.1186/s12936-018-2190-z
55. White NJ, Qiao LG, Qi G, Luzzatto L. Rationale for recommending a lower dose of primaquine as a Plasmodium falciparum gametocytocide in populations where G6PD deficiency is common. Malaria Journal. 2012;11:418. DOI: 10.1186/1475-2875-11-418
56. White MT, Karl S, Battle KE, Hay SI, Mueller I, Ghani AC. Modelling the contribution of the hypnozoite reservoir to Plasmodium vivax transmission. eLife. 2014;3:e04692. DOI: 10.7554/eLife.04692
57. Mwesigwa J, Achan J, Di Tanna GL, Affara M, Jawara M, Worwui A, et al. Residual malaria transmission dynamics varies across The Gambia despite high coverage of control interventions. PLoS One. 2017;12(11):e0187059. DOI: 10.1371/journal.pone.0187059
58. Monteiro WM, Val FF, Siqueira AM, Franca GP, Sampaio VS, Melo GC, et al. G6PD deficiency in Latin America: systematic review on prevalence and variants. Memorias do Instituto Oswaldo Cruz. 2014;109(5):553-568. DOI: 10.1590/0074-0276140123
59. Mezieobi KC, Ugwu OP, Uti DE, Egba SI, Ewah CM. Economic burden of malaria on developing countries: A mini review. Parasite Epidemiol Control. 2025 May 29;30:e00435. doi: 10.1016/j.parepi.2025.e00435. PMID: 40519859; PMCID: PMC12163157.
60. Douglas NM, Lampah DA, Kenangalem E, Simpson JA, Poespoprodjo JR, Sugiarto P, et al. Major burden of severe anemia from non-falciparum malaria species in Southern Papua: a hospital-based surveillance study. PLoS Medicine. 2013;10(12):e1001575. DOI: 10.1371/journal.pmed.1001575
61. Newby G, Bennett A, Larson E, Cotter C, Shretta R, Phillips AA, et al. The path to eradication: a progress report on the malaria-eliminating countries. Lancet. 2016;387(10029):1775-1784. DOI: 10.1016/S0140-6736(16)00230-0
62. malERA Refresh Consultative Panel on Characterising the Reservoir and Measuring Transmission. malERA: an updated research agenda for characterising the reservoir and measuring transmission in malaria elimination and eradication. PLoS Medicine. 2017;14(11):e1002452. DOI: 10.1371/journal.pmed.1002452
63. Hsiang MS, Hwang J, Tao AR, Liu Y, Bennett A, Shanks GD, et al. Mass drug administration for the control and elimination of Plasmodium vivax malaria: an ecological study from Jiangsu province, China. Malaria Journal. 2013;12:383. DOI: 10.1186/1475-2875-12-383
64. von Seidlein L, Auburn S, Espino F, Shanks D, Cheng Q, McCarthy J, et al. Review of key knowledge gaps in glucose-6-phosphate dehydrogenase deficiency detection with regard to the safe clinical deployment of 8-aminoquinoline treatment regimens: a workshop report. Malaria Journal. 2013;12:112. DOI: 10.1186/1475-2875-12-112
65. Thriemer K, Bobogare A, Ley B, Gudo CS, Alam MS, Anstey NM, et al. Quantifying primaquine effectiveness and improving adherence: a round table discussion of the APMEN Vivax Working Group. Malaria Journal. 2018;17:241. DOI: 10.1186/s12936-018-2380-8
66. Wells TNC, Burrows JN, Baird JK. Targeting the hypnozoite reservoir of Plasmodium vivax: the hidden obstacle to malaria elimination. Trends in Parasitology. 2010;26(3):145-151. DOI: 10.1016/j.pt.2009.12.005
67. Mikolajczak SA, Vaughan AM, Kangwanrangsan N, Roobsoong W, Fishbaugher M, Yimamnuaychok N, et al. Plasmodium vivax liver stage development and hypnozoite persistence in human liver-chimeric mice. Cell Host & Microbe. 2015;17(4):526-535. DOI: 10.1016/j.chom.2015.02.011

68. Ng CL, Siciliano G, Lee MC, de Almeida MJ, Corey VC, Bopp SE, et al. CRISPR-Cas9-modified pfmdr1 protects Plasmodium falciparum asexual blood stages and gametocytes against a class of piperazine-containing compounds but potentiates artemisinin-based combination therapy partner drugs. Molecular Microbiology. 2016;101(3):381-393. DOI: 10.1111/mmi.13397
69. McCarthy JS, Sekuloski S, Griffin PM, Elliott S, Douglas N, Peatey C, et al. A pilot randomised trial of induced blood-stage Plasmodium falciparum infections in healthy volunteers for testing efficacy of new antimalarial drugs. PLoS One. 2011;6(8):e21914. DOI: 10.1371/journal.pone.0021914
70. Kim S, Nguon C, Guillard B, Duong S, Chy S, Sum S, et al. Performance of the CareStart G6PD deficiency screening test, a point-of-care diagnostic for primaquine therapy screening. PLoS One. 2011;6(12):e28357. DOI: 10.1371/journal.pone.0028357
71. Pal S, Myburgh J, Bansil P, Hann A, Robertson L, Gerth-Guyette E, et al. Reference and point-of-care testing for G6PD deficiency: blood disorder interference, contrived specimens, and fingerstick equivalence. PLoS One. 2019;14(9):e0217443. DOI: 10.1371/journal.pone.0217443
72. Cunnington AJ, Njie M, Correa S, Takem EN, Riley EM, Walther M. Prolonged neutrophil dysfunction after Plasmodium falciparum malaria is related to hemolysis and heme oxygenase-1 induction. Journal of Immunology. 2012;189(11):5336-5346. DOI: 10.4049/jimmunol.1201028
73. Espino FE, Bibit JA, Sornillo JB, Tan A, von Seidlein L, Ley B. Comparison of three screening test kits for G6PD enzyme deficiency: implications for its use in the radical cure of vivax malaria in remote and resource-poor areas in the Philippines. PLoS One. 2016;11(2):e0148172. DOI: 10.1371/journal.pone.0148172
74. Tinley KE, Loughlin AM, Jepson A, Barnett ED. Evaluation of a rapid qualitative enzyme chromatographic test for glucose-6-phosphate dehydrogenase deficiency. American Journal of Tropical Medicine and Hygiene. 2010;82(2):210-214. DOI: 10.4269/ajtmh.2010.09-0416
75. Robinson LJ, Wampfler R, Betuela I, Karl S, White MT, Li Wai Suen CS, et al. Strategies for understanding and reducing the Plasmodium vivax and Plasmodium ovale hypnozoite reservoir in Papua New Guinean children: a randomised placebo-controlled trial and mathematical model. PLoS Medicine. 2015;12(10):e1001891. DOI: 10.1371/journal.pmed.1001891
76. Battle KE, Karhunen MS, Bhatt S, Gething PW, Howes RE, Golding N, et al. Geographical variation in Plasmodium vivax relapse. Malaria Journal. 2014;13:144. DOI: 10.1186/1475-2875-13-144
77. White MT, Shirreff G, Karl S, Ghani AC, Mueller I. Variation in relapse frequency and the transmission potential of Plasmodium vivax malaria. Proceedings of the Royal Society B: Biological Sciences. 2016;283(1827):20160048. DOI: 10.1098/rspb.2016.0048

CITE AS: Winniefred Nankya (2026). Glucose-6-Phosphate Dehydrogenase Deficiency and Primaquine Safety in Plasmodium vivax Elimination Programs. IAA Journal of Biological Sciences 14(1):65-74. https://doi.org/10.59298/IAAJB/2026/1416574