



Guide to G6PD deficiency rapid diagnostic testing to support *P. vivax* radical cure



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GLOSSARY

DNA	Deoxyribo-nucleic acid
FST	Fluorescent spot testing
G6PD	Glucose-6-phosphate dehydrogenase
PCR	Polymerase chain reaction
RDT	Rapid diagnostic test
SNP	Single nucleotide polymorphism





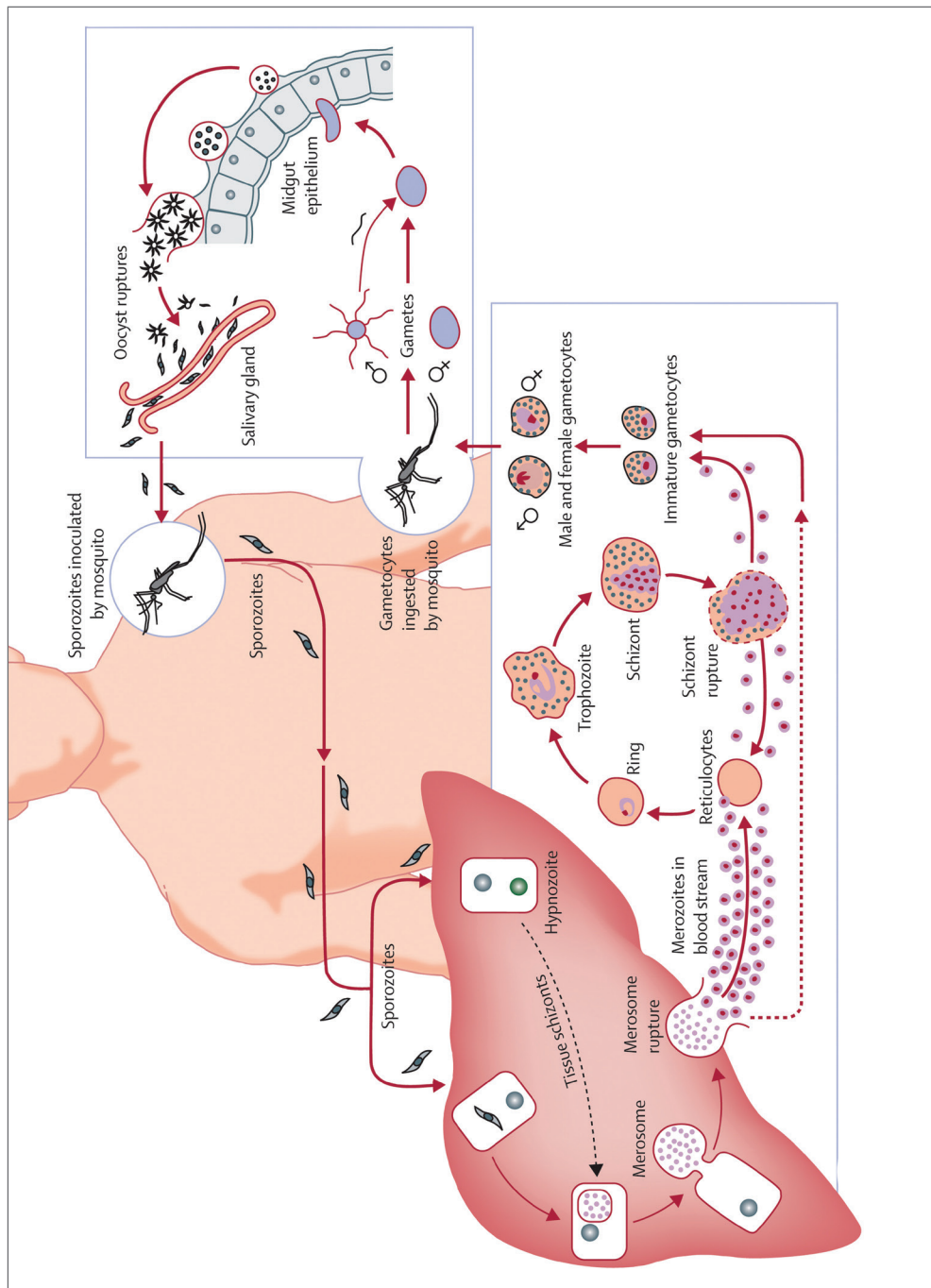
1. Purpose of this document

This user guide is designed to provide national malaria control programmes with general information on glucose-6-phosphate dehydrogenase (G6PD) deficiency. Individuals with this condition may be at risk of adverse effects from medicines commonly used to cure *Plasmodium vivax* malaria, as well as from other medicines and substances [1]. While this document discusses G6PD testing for *P. vivax* case management, this guidance also applies to *P. ovale* malaria as per the WHO guidelines for treatment of malaria. This document includes generic instructions on how to conduct point-of-care testing for G6PD deficiency using currently available rapid diagnostic tests (RDTs). This guide is intended to provide practical information that will support G6PD deficiency testing, principally as part of *P. vivax* malaria control and elimination programmes.

2. Introduction

P. vivax is the most geographically widespread form of malaria and poses unique challenges to elimination. It is estimated that 2.85 billion people are at risk of acquiring *P. vivax* malaria. Although it causes significant morbidity, it rarely results in death; out of 13.8 million estimated cases in 2015, 1400–14 900 deaths globally can be attributed to *P. vivax* (based on analysis of country-level mortality rates) [2]. *P. vivax* is sometimes difficult to detect in patients, as the parasite can remain dormant in the liver in a hypnozoite stage for long periods before re-entering the blood cycle and causing relapse. This hypnozoite stage must be specifically targeted with a medicine to prevent repeated clinical attacks or relapses of illness. Not only do patients become recurrently ill during these relapses, but they are also infective and allow the disease to be transmitted to others through the bite of an *Anopheles* mosquito (Figure 1). Relapse is a major contributor to *P. vivax* in endemic communities, where a significant portion of transmission can be attributed to relapses [3].

FIG. 1.
Lifecycle of *P. vivax* parasites



Source: Mueller I, Galinski MR, Carlton JM, Kochar DK, Alonso PL, Portillo HA. Key gaps in the knowledge of *Plasmodium vivax*, a neglected human malaria parasite. *Lancet*. 2009;9(9):555–66 [4].

In addition to treatment of the blood stage infection, the recommended treatment for clearing the liver stage of *P. vivax* infection—known as radical cure—is a 14-day course of treatment with the 8-aminoquinoline-based drug primaquine at a dose of 0.25–0.5 mg/Kg bodyweight daily [5]. However, primaquine can cause potentially life-threatening haemolysis in patients with G6PD deficiency. In patients with G6PD deficiency, an 8-week course of primaquine in weekly doses of 0.75 mg/Kg is recommended, under close medical supervision to manage potential primaquine-induced adverse haematological effects. Restricting access to radical cure due to



unknown G6PD status can lead to increased morbidity and continued transmission of *P. vivax*. Therefore, testing for G6PD deficiency at the point of care can expand access to appropriate treatment of patients with confirmed *P. vivax* infection. Combined G6PD testing and *P. vivax* radical cure will reduce patient morbidity and support overall elimination of the disease.

PLASMODIUM OVALE MALARIA AND G6PD DEFICIENCY

Plasmodium ovale is a form of malaria endemic to sub-Saharan Africa and the western Pacific. Compared to *P. vivax* and *P. falciparum*, *P. ovale* represents a small percentage of the total burden of malaria worldwide. However, like *P. vivax*, *P. ovale* has a hypnozoite stage that requires the administration of radical cure to eradicate. Patients with *P. ovale* and G6PD deficiency are also at risk of primaquine-induced haemolytic anaemia and should be tested for G6PD deficiency prior to administration.

The recommendations in Table 1 have been developed by WHO to guide radical cure in patients with normal and deficient G6PD enzyme activity, as defined by a diagnostic test for G6PD deficiency.

TABLE 1.
Preventing relapse in *P. vivax* or *P. ovale* malaria

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.	Good practice statement
To prevent relapse, treat <i>P. vivax</i> or <i>P. ovale</i> malaria in children and adults (except pregnant women, infants aged <6 months, women breastfeeding infants aged <6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency) with a 14-day course (0.25–0.5 mg/kg bodyweight daily) of primaquine in all transmission settings.	Strong recommendation, high-quality evidence
In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg/kg bodyweight once a week for 8 weeks, with close medical supervision for potential primaquine-induced haemolysis.	Conditional recommendation, very low-quality evidence
When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine.	Good practice statement
In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed; then, on the basis of G6PD status, treat with primaquine to prevent future relapse.	Conditional recommendation, moderate-quality evidence

Source: WHO guidelines for the treatment of malaria, 3rd edition. Geneva: World Health Organization; 2015 [5].

3. What is G6PD deficiency?

G6PD is an enzyme essential to the pentose phosphate pathway—a metabolic pathway that supplies energy to cells. G6PD is particularly important for the survival of red blood cells and their ability to respond to oxidative stress. G6PD deficiency is a hereditary condition resulting from a structural defect in the G6PD enzyme, and affects more than 400 million people worldwide [6]. Over 180 genetic variants of G6PD deficiency have been described, and there is considerable geographical overlap between the prevalence of G6PD deficiency and the prevalence of *P. vivax*. The most severe G6PD variants are found in areas where *P. vivax* is the predominant malaria species [7].

Red blood cells that are deficient in the G6PD enzyme are susceptible to rupture (haemolysis) when subjected to oxidative stress [8]. Oxidative stress and subsequent haemolysis can be triggered by therapy with 8-aminoquinoline-based drugs or certain antibiotics, as well as by foods (e.g. fava beans), substances (e.g. henna) and some infections [1]. G6PD deficiency ranges from mild to severe depending on the level of enzyme activity. Individuals with severe deficiency of G6PD enzyme activity are more at risk for haemolytic anaemia resulting from oxidative stress than those with moderate to mild deficiency.

3.1 Sex differences in G6PD deficiency

The G6PD gene is located on the X chromosome. Males only have one allele copy whereas females have two allele copies. Therefore, males can either be hemizygous G6PD normal or hemizygous G6PD deficient, but females can be homozygous normal (two G6PD normal alleles), homozygous deficient (two G6PD deficient alleles) or heterozygous for G6PD (one normal allele and one deficient allele). During female embryonic development, one or the other X chromosome becomes inactivated, a process known as lyonization. As a result, women who are heterozygous for G6PD have two red blood cell populations: one in which the enzyme with compromised activity is expressed and another in which the enzyme with normal activity is expressed. The relative proportion of deficient to normal cell populations determines the overall G6PD activity in a heterozygous female. As a consequence, heterozygous females can have intermediate G6PD activity levels ranging from 30% to 80% of normal (see Figure 2).

WHAT IS NORMAL G6PD ACTIVITY?

Normal G6PD activity is typically defined as the median G6PD activity value in a target population of males who are not G6PD deficient. Therefore, males and females who do not carry the abnormal G6PD gene will have G6PD activity levels just on either side of this normal/median value (e.g. 110% activity or 90% activity). A value >80% of normal red blood cell G6PD activity is considered G6PD normal.

WHAT IS G6PD DEFICIENCY?

G6PD variants are categorized based on the severity of the G6PD deficiency they cause. The severity of G6PD deficiency is defined as a percentage of the normal value.

In males: Any male who has red cell G6PD activity less than 30% of the normal median must be regarded as G6PD deficient. It is presumed that he is hemizygous for a G6PD deficient allele. Any male who has red cell G6PD activity of 30% or more of the normal median can be regarded as G6PD normal. It is presumed he is hemizygous for a G6PD normal allele.



In females: Any female who has red cell G6PD activity less than 30% of the normal median must be regarded as G6PD deficient. It is presumed that she is either homozygous for G6PD deficient alleles, or heterozygous for a G6PD deficient allele with predominance of a G6PD deficient red blood cell population. Any female who has red cell G6PD activity of 80% or more of the normal median can be regarded as G6PD normal. It is presumed that she is either homozygous for a G6PD normal allele, or heterozygous for a G6PD deficient allele and a G6PD normal allele with predominance of a G6PD normal red blood cell population. Any female who has red cell G6PD activity between 30% and 80% of the normal median must be regarded as intermediate; it is presumed she is heterozygous for a G6PD deficient allele and a G6PD normal allele.

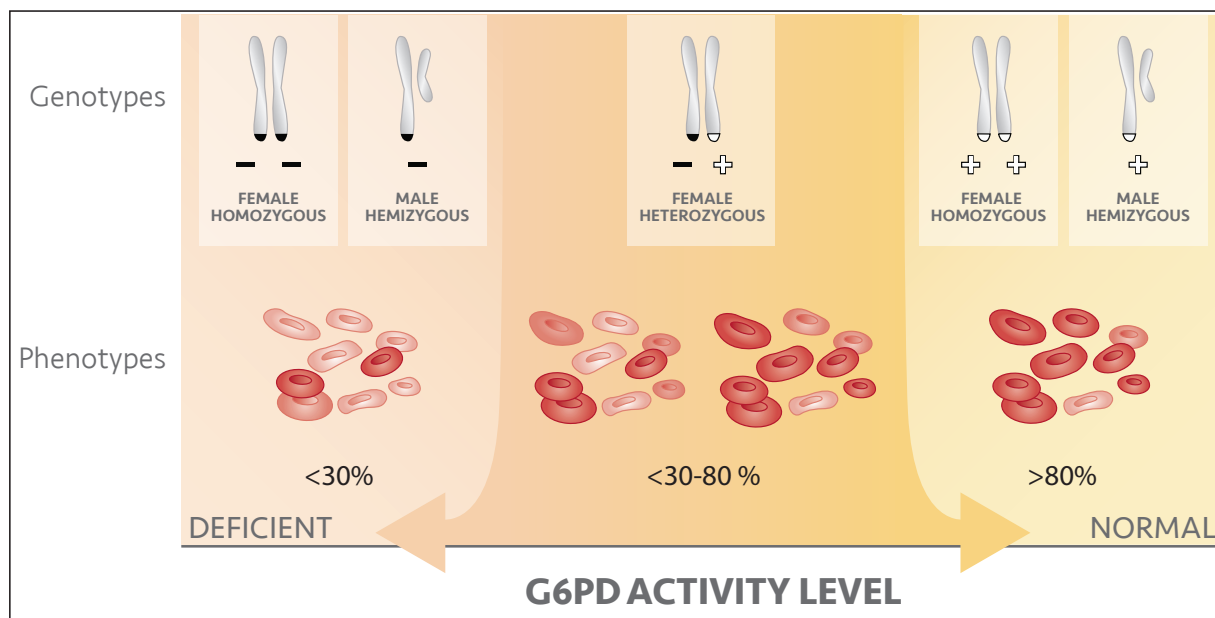
From a diagnostic perspective, qualitative tests tend to diagnose all patients who have G6PD activity less than 30% of normal as G6PD deficient.

HOW DO WE MEASURE G6PD ACTIVITY?

One International Unit (U) is the amount of G6PD activity that will convert one micromole of nicotinamide adenine dinucleotide phosphate (NADP+) per minute under predetermined substrate and reaction conditions. Activity may be expressed in either a standard number of cells (U/10¹² red blood cells) or amount of haemoglobin (U/g Hb). G6PD activity is typically determined by measuring G6PD activity in lysate from a whole blood specimen or a red blood cell preparation from a specimen.

Source: WHO Evidence Review Group (8–9 October 2014). Meeting report: point-of-care G6PD testing to support safe use of primaquine for the treatment of vivax malaria [9].

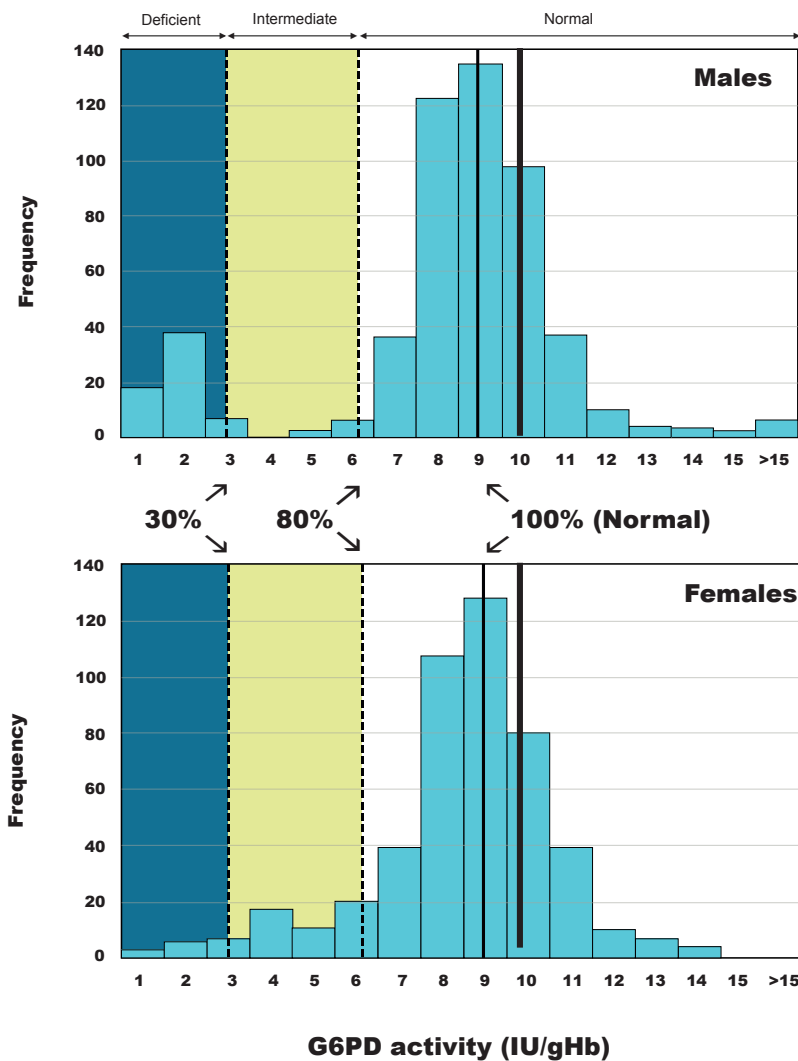
FIG. 2.
Genetics and G6PD deficiency phenotypes



At the genetic level, females have two alleles of the G6PD gene, and therefore three genotypes are possible: 1. homozygous deficient, with two G6PD deficient alleles (--); 2. heterozygous normal, with one G6PD deficient and one normal allele (-+); or 3. homozygous normal, with two G6PD normal alleles (++). Males only have one allele and so can only be hemizygous deficient (-) or hemizygous normal (+). Deficient

homozygous females and hemizygous males will have very low G6PD activity levels in their red blood cells and therefore will exhibit the deficiency phenotype in G6PD diagnostic tests. Normal homozygous females or hemizygous males will exhibit a high or normal phenotype in G6PD diagnostic tests. Heterozygous females will exhibit intermediate enzyme activity in G6PD diagnostic tests (Figure 3).

FIGURE 3.
G6PD activity distribution in 1000 healthy adult volunteers attending the outpatient department of Township Medical Centers of Ahlone and Insein Townships in Yangon region, Myanmar



Source: Oo NN et al. Validation of G6PD point-of-care tests among healthy volunteers in Yangon, Myanmar. PLoS One. 016;11(4):e0152304 [10].

Males and females are shown in two separate histograms. 100% normal activity (indicated by solid lines on both histograms) is defined as the median G6PD activity for males with greater than 10% activity. The numbers of males and females with G6PD deficiency less than 30% (which can be detected by qualitative screening tests) are indicated in the blue boxes; those with intermediate activity (between 30% and 80% of normal) that require a quantitative test to be identified are indicated in the green boxes.



4. Where does G6PD deficiency occur?

G6PD deficiency is most common in sub-Saharan Africa and the Arabian peninsula, with the highest allele prevalence reaching 32.5% in males in some countries [11]. The majority of G6PD-deficient individuals live in central Asia or South-East Asia due to the large population sizes in these countries (Table 2). However, allele frequencies are generally lower in most areas of Asia, rarely exceeding 20% in males. G6PD deficiency is least common in the Americas, occurring in $\leq 1\%$ of the population in some populations. It is important to note that, even within a region or country, the prevalence of G6PD deficiency is highly heterogeneous and often varies between ethnic populations. As such, when assessing the risk of adverse reactions to radical treatment in a community, national prevalence rates of G6PD deficiency are less informative than the prevalence rates within the specific populations and communities at risk of malaria infection.

TABLE 2.
Estimated G6PD-deficient population by WHO region

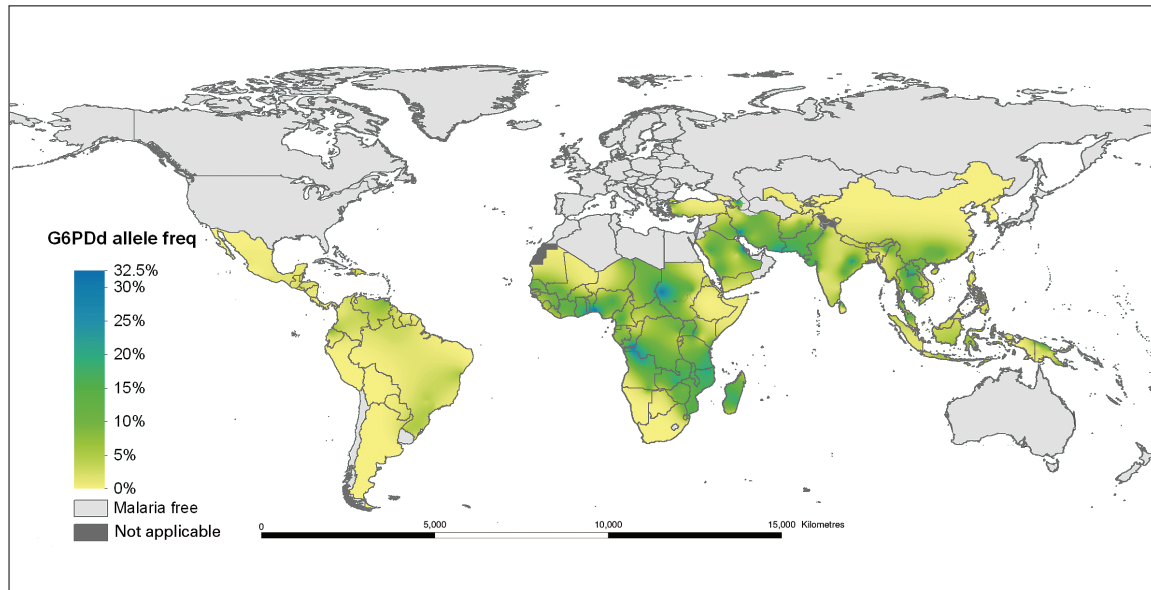
WHO REGION	G6PD ALLELE FREQUENCY (%) ¹	G6PD MALES (000'S) ²	G6PD FEMALES (000'S) ³	HOMOZYGOUS FEMALES (000'S) ⁴
Africa	12.1	53 267	33 792	8.7
America	2.6	9 081	5 225	0.4
Eastern Mediterranean	9.0	27 620	16 536	3.6
Europe	2.9	2 080	1 149	0.1
South-East Asia	5.8	68 588	38 525	5.2
Western Pacific	9.2	41 793	23 250	2.2
World	8.0	202 428	118 476	20.3

1. Average of median estimate of G6PD deficiency allele frequency in countries within region
2. Sum of median estimated number of males with G6PD deficiency in malaria-endemic countries
3. Sum of median estimated number of females with G6PD deficiency in malaria-endemic countries
4. Sum of median estimated number of females homozygous for G6PD deficiency in malaria-endemic countries

Source: Control and elimination of *Plasmodium falciparum* malaria: a technical brief. Geneva: World Health Organization; 2015 [12].

In malaria-endemic areas, the prevalence of G6PD deficiency is higher than in non-endemic countries (Figure 4); this overlap is hypothesized to be due to the selective advantage of protection against severe *P. falciparum* malaria in G6PD-deficient individuals.

FIGURE 4.
Estimated G6PD deficiency allele frequencies in malaria-endemic countries



Source: Howes RE et al. Spatial distribution of G6PD deficiency variants across malaria-endemic regions. *Malaria J.* 2013;12:418 [13].

5. Why test for G6PD deficiency?

5.1 Radical cure for *P. vivax* malaria

Due to the risk of haemolytic anaemia associated with primaquine treatment, G6PD deficiency poses a challenge to treating the liver stage of *P. vivax* malaria so as to prevent relapse. Therefore, the aim of G6PD testing is to determine whether a patient can be safely treated with primaquine. Risk of haemolysis is dependent on the dose of primaquine, as well as on the degree of G6PD deficiency. Patients with G6PD levels <30% of normal will have most red blood cells with low or compromised G6PD activity levels; such individuals are considered to be at high risk of primaquine-induced haemolysis with a 14-day course (0.25–0.5 mg/kg bodyweight daily) of primaquine. These patients should only receive the weekly regimen of 0.75 mg/kg bodyweight per week over 8 weeks, if this can be done under close medical supervision. Patients with 30–80% of normal G6PD activity—mostly females heterozygous for G6PD activity—may also be at risk of haemolysis. Patients with G6PD levels at 80% of normal and above are not at risk of primaquine-induced haemolysis. However, current qualitative screening tests cannot distinguish between females with 30–80% activity and other females with G6PD activity >80%. Therefore, in all cases before starting a 14-day or weekly regimen of primaquine, patients should be counselled on how to recognize symptoms and signs of haemolytic anaemia and instructed to stop the drug if they experience symptoms.

If G6PD testing is not available, a decision to prescribe or withhold primaquine should take into account the potential for haemolysis (G6PD prevalence and variants) and the capacity of health services to identify and manage haemolytic reactions. These risks must be weighed against the benefits of preventing relapses and interrupting *P. vivax* transmission in the community.

5.2 Neonatal screening

Neonatal jaundice is the earliest indication of G6PD deficiency. Newborn infants with G6PD deficiency are at risk of hyperbilirubinaemia, which can progress to kernicterus

(brain damage resulting from severe jaundice), often a fatal condition. Therefore, WHO recommends that neonatal screening be performed where G6PD deficiency is common (i.e. where it affects more than 3–5% of males) [14].

5.3 Prevention of adverse drug reactions

In patients with G6PD deficiency, haemolytic anaemia may be triggered by specific antibiotics and anti-inflammatory drugs. Inherited differences in drug metabolism and genetic variations in G6PD deficiency can result in varied reactions to drugs among individuals. The risks and severity of haemolysis is almost always dose related. Although manufacturers do not routinely test drugs for their effects in G6PD deficient individuals, the best available evidence identifies a number of drugs as likely to cause clinically significant haemolytic anaemia in patients with G6PD deficiency (see Appendix 1). G6PD deficiency testing should be performed before these drugs are administered.

6. What kinds of tests are available to diagnose G6PD deficiency?

There are multiple ways to determine individuals' G6PD status. Some methods are more suited for population studies (e.g. genetic tests) and others are more suited for case management decision-making (e.g. tests that measure enzyme activity). Tests for G6PD deficiency can be categorized as either genotyping assays, which determine at the DNA level whether someone is G6PD deficient, or phenotyping assays, which measure the G6PD activity in the individual's blood. Phenotypic assays can be quantitative (providing a precise measure of G6PD activity) or qualitative (indicating normal or abnormal activity).

6.1 Genetic assays

G6PD deficiency is usually caused by mutations in the G6PD gene that result in below-normal G6PD activity, a condition that particularly affects red blood cells. DNA sequencing can determine if any mutation is present in the G6PD gene; in the case of females, sequencing can determine if one or both genes are affected in order to determine if the female is heterozygous or homozygous for G6PD deficiency.

Genotypic assays are both expensive and technically complex. For the reasons outlined below, they cannot be used to provide accurate risk estimates of G6PD deficiency in individuals. Most genotyping studies perform polymerase chain reaction (PCR)-based single nucleotide polymorphism (SNP) analysis. PCR-SNP analysis is limited to identifying the presence or absence of known genotypes; therefore, it may not correctly identify G6PD deficiency in patients with mutations not included in the reference panel. On the other hand, DNA sequencing methods can identify all mutations in an individual's G6PD gene, but any new mutations detected need to be characterized through phenotypic assays in order to determine whether the mutation has resulted in G6PD deficiency. Neither DNA sequencing nor PCR-SNP analysis measures the relative proportion of G6PD deficient to G6PD normal red blood cell populations in heterozygous females. Consequently, neither method can determine whether a female is at high or low risk for G6PD deficiency.

Genotypic assays are best suited for population studies because this method is not dependent on intact enzymatic activity, which would require samples to be processed quickly after collection; instead, samples can be collected for later analysis using preservation methods such as dried blood spots. Genotyping can also provide fairly robust estimates of the prevalence of G6PD deficiency in a population. These tests are



more cost-effective if performed using large sample sizes. However, because there can be a great deal of variance in the prevalence of G6PD deficiency within a country, extreme care must be taken in study design, sampling approach, and interpretation of results.

6.2 Phenotypic assays

Phenotyping can be used in case management, as it can determine the overall G6PD activity in red blood cells. Until recently, phenotypic testing for G6PD deficiency was only available in newborn screening facilities and clinical laboratory facilities with the infrastructure and capacity required to perform complicated assays. There has been a lack of tools suitable for use at the point of care, but recently, new RDTs have been developed that can be used where patients typically access care (i.e. rural, low-infrastructure settings such as health posts).

PHENOTYPIC ASSAY TYPES

Phenotypic assays can be categorized into three types.

Qualitative assays distinguish whether an individual has G6PD activity above or below a given threshold (typically 30–40% of normal activity). Qualitative test results indicate if the individual has normal or abnormal G6PD activity. These tests tend to diagnose all patients with G6PD activity less than 30% of normal as G6PD deficient.

Quantitative assays provide a precise measure of an individual's G6PD activity in terms of units of enzyme activity normalized either for red blood cell count or haemoglobin concentration.

Cytochemical assays observe G6PD activity at the individual red blood cell level either through microscopy or flow cytometry (an electronic detection technique for quantifying and analysing cells suspended in fluid).

In order to understand the implications of different types of phenotypic assays for informing case management, it is important to consider typical G6PD activity ranges for the different G6PD genotypes in a population. In Figure 3, a significant number of heterozygous females have intermediate G6PD activity within the 30–80% range, but this was not detected using a qualitative test. Ideally, a quantitative test that can identify heterozygous females with intermediate (<80%) G6PD activity is needed to guide treatment decision-making for these females.

6.3 Quantitative tests for G6PD activity

Quantitative tests measure G6PD activity in a whole blood sample and provide a quantitative result for G6PD activity. Quantitative tests are able to accurately measure G6PD activity for all individuals, from those with severe G6PD deficiency (<10% normal) to those with high G6PD activity (>100% normal). Typically quantitative tests normalize the G6PD activity per red blood cell count or haemoglobin concentration in order to account for varying individual haematocrit ranges at the time of sampling. Most importantly, quantitative tests can detect individuals with intermediate G6PD activity, such as females who are heterozygous for G6PD deficiency. Quantitative tests can be used to independently determine the threshold at which to exclude patients from the standard daily dose of primaquine, based on an assessment of risks and benefits.

Such tests are most suitable for making treatment decisions for heterozygous females with intermediate G6PD activity (see next section for WHO-recommended guidelines for high-dose primaquine treatment).

However, most currently available quantitative tests for G6PD activity require highly complex laboratory equipment and facilities, and therefore are only performed in newborn screening facilities or reference laboratories. New quantitative tests for use at the point of care are under development, but no published performance data on these are commercially available yet.

6.4 Qualitative tests for G6PD activity

Qualitative tests can be used to determine whether an individual is above or below a threshold predetermined by the diagnostic test for G6PD activity (30–40% of normal activity). Deficient results (sometimes referred to as positive results) indicate that the individual has G6PD activity below this threshold and should be considered G6PD deficient. Normal results (sometimes referred to as negative results) mean that the individual has G6PD activity above the threshold for G6PD normal activity, but this is a wide range. Qualitative tests are able to provide good performance characteristics (sensitivity and specificity) at a 30–40% G6PD activity threshold.

As males have either normal or deficient activity, qualitative tests have very good performance in males; however, qualitative tests have lower sensitivity and specificity in heterozygous females with variable activity (between 30–80%), which may result in “intermediate” classification by some qualitative tests.

For several decades, fluorescent spot testing (FST) has been recommended as a qualitative test for G6PD deficiency screening. This test has been used extensively in operational settings to guide treatment of patients and to determine which patients should be included in clinical trials. However, FST requires basic laboratory infrastructure and user training, which makes it unsuitable for routine use in field settings. (For more information on the use of FST for G6PD deficiency, see *A guide to fluorescent spot testing for G6PD deficiency*.) [15].

More recently, new and affordable lateral flow tests that can be used at the point of care have become available for the diagnosis of G6PD deficiency. Lateral flow tests for G6PD consist of a plastic or paper cartridge containing a pad that holds reagents. These reagents react to G6PD enzyme activity and change colour based on the activity level in the sample. Samples of either capillary or venous whole blood can be used with this type of test. Some G6PD lateral flow tests are suitable for use in malaria-endemic areas, as they are stable at high temperatures and do not require sophisticated laboratory infrastructure or user training.

Lateral flow RDTs for G6PD deficiency have some limitations. First, these tests are qualitative and cannot be used to quantify the exact level of G6PD deficiency in a patient. The RDTs that are currently available can only distinguish between patients above or below 30–40% normal G6PD activity, and therefore cannot distinguish heterozygous females with normal activity from those with intermediate activity. In addition, abnormally low or high haematocrit levels can affect the results of a lateral flow RDT, resulting in false-deficient samples (in the case of low haematocrit levels) or false-normal samples (in the case of high haematocrit levels). Lastly, the lateral flow tests for G6PD deficiency that are currently available do not have a control line to indicate that samples are migrating properly within the test cartridge.



INTERPRETATION OF QUALITATIVE TEST RESULTS IN FEMALES

Heterozygous females with intermediate G6PD activity (30–80% of normal) may yield results that are difficult to classify on qualitative tests because they are not obviously normal or deficient. Due to the subjectivity of the test interpretation these females may be classified as G6PD normal or G6PD deficient. In tropical settings, when temperatures exceed 35 °C, it may be more likely that these women will be classified as G6PD normal due to accelerated enzyme activity. This is why all females should receive counselling on signs and symptoms of haemolysis prior to primaquine (see Figure 5) and why manufacturers' recommended instructions for operating temperature and storage should be followed strictly.

6.5 Cytochemical assays for measurement of intracellular G6PD activity

Several assays have been developed to observe G6PD activity in red blood cells (Table 3). Cytochemical assays are currently the only method for determining the relative proportions of allele representation in the red blood cell populations of heterozygous females. However, these assays are currently only available as research tools; while the information they provide is useful in understanding the physiology of G6PD activity in heterozygous females, they cannot be used to inform case management.

TABLE 3.
Summary of test types for G6PD deficiency

CLASS OF TEST	UTILITY	BENEFITS	LIMITATIONS
Genotypic assays			
PCR-SNP analysis	Population studies	More affordable and accessible than DNA sequencing	<ul style="list-style-type: none"> No measurement of activity Cannot predict individual risk for heterozygous females Only identifies the subset of known SNPs included in the tests Expensive and sophisticated equipment required
DNA sequencing	Population studies	Categorically identifies heterozygous females	<ul style="list-style-type: none"> No measurement of activity Cannot predict individual risk for heterozygous females Expensive and requires sophisticated equipment
Phenotypic assays			
Quantitative tests	Screening, population studies and case management	Performs well for: Hemizygous males; Homozygous females; Heterozygous females	<ul style="list-style-type: none"> Expensive and requires sophisticated equipment
Qualitative tests	Screening, population studies and case management	Performs well for: Hemizygous males; Homozygous females	<ul style="list-style-type: none"> Cannot distinguish normal from intermediate activity in heterozygous females
Cytochemical assays	Research	<ul style="list-style-type: none"> Provides information on intracellular G6PD level; Valuable for observation of relative deficient to normal cells in heterozygous females 	<ul style="list-style-type: none"> Complex Biohazardous Expensive The output is not easily aligned with the current clinical standards for case management



7. G6PD deficiency and guidelines for primaquine treatment

The objective of treating *P. vivax* (and *P. ovale*) malaria is to provide radical cure in order to prevent relapse of illness and recrudescence of infectivity. Any person (male or female) with G6PD activity <30% of normal is at high risk of experiencing clinically severe haemolysis following the administration of high-dose primaquine. The severity of haemolytic anaemia depends on the dose of primaquine and the variant of the G6PD enzyme. As a result, heterozygous females with relatively low G6PD activity may still suffer haemolysis following primaquine treatment. Fortunately, in these patients, primaquine-induced haemolytic anaemia is less severe than in deficient patients; furthermore, since this medicine is eliminated rapidly, stopping the treatment can halt further haemolysis. (See Table 1 for WHO guidelines on administering primaquine treatment.)

7.1 Patient counselling

Patients should receive counselling from their health care provider on both the rationale for G6PD testing and the treatment options for *P. vivax* malaria. Health care providers should have materials about G6PD deficiency and primaquine side effects that can be provided to patients in the local language and for non-literates. More specifically, these materials should include information on G6PD deficiency (i.e. what it is, methods of testing, risks associated with certain drugs and foods) and the link between G6PD deficiency and the signs and symptoms of haemolysis resulting from high-dose primaquine and other agents. (See Appendix 2 for outlines of materials that can be used to provide patient counselling on G6PD deficiency.)

8. Current WHO recommendations on G6PD testing in support of primaquine

Where feasible, all patients should be tested for G6PD deficiency before administering primaquine. Testing for G6PD deficiency in *P. vivax* malaria cases should be considered an integral part of ensuring universal access to diagnosis and treatment.

G6PD testing should be incorporated into treatment guidelines and diagnostic services made available, possibly with referral of patients from lower to higher level health facilities to receive both G6PD testing and primaquine radical cure.

8.1 What to do if G6PD testing is unavailable

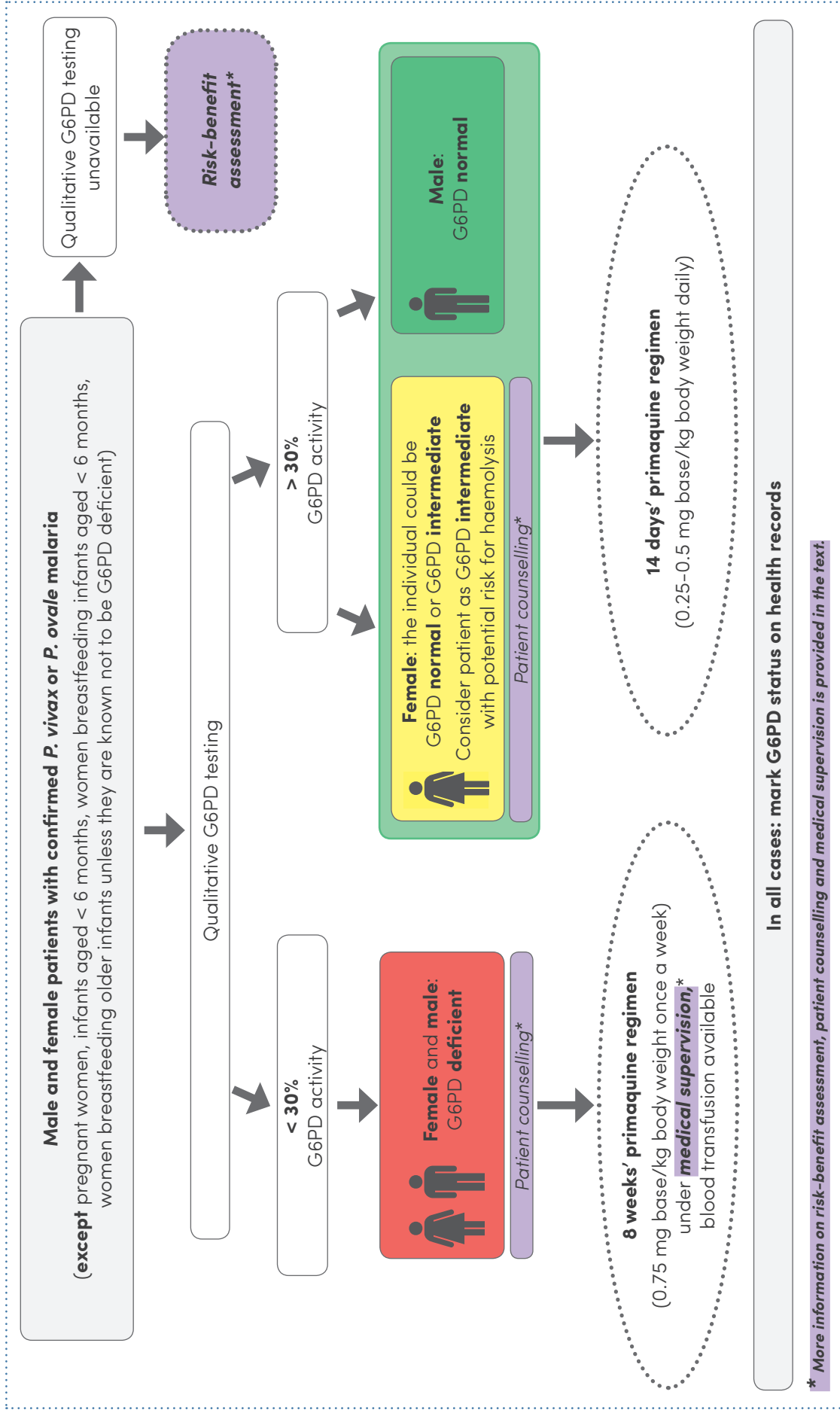
Where no G6PD test is available, the decision to prescribe primaquine should be based on individual assessment of the risks and benefits. The risk of adverse reactions is dependent upon the dose of primaquine required, the prevalence and severity of G6PD deficiency in the local population, and the capacity of local health systems to recognize and treat primaquine-induced haemolysis, including the availability of blood transfusion. The primary benefit of primaquine treatment is to lower the probability of relapses, and thus to prevent morbidity as well as the transmission of *P. vivax* malaria.

If no primaquine is administered, patients should be advised on when to return to seek treatment for suspected malaria relapses.

Patients who are prescribed primaquine should receive close medical supervision and patient counselling. Patients should be instructed to stop taking primaquine if signs or symptoms of haemolytic anaemia appear (e.g. weakness, pallor, or if their urine becomes red or black).

FIGURE 5.

Clinical algorithm for G6PD testing at point of care and interpretation of results by sex to administer primaquine radical cure



9. Programme guidance for G6PD deficiency testing



9.1 Selecting an RDT

The RDTs for detecting G6PD deficiency that are currently on the market are limited, but additional options are expected to become available in the coming years.

The following product characteristics are considered ideal:

1. >95% sensitivity (compared to spectrophotometry or equivalent quantitative tests) in detecting G6PD enzyme activity levels <30% of normal
2. Negative predictive value of >95% (95% probability that the patient has >30% normal G6PD activity when the diagnostic test yields a non-deficient result)
3. Stable at temperatures expected in tropical settings (30–40°C)
4. Visual readout that clearly distinguishes between “deficient” and “normal” patients.

Other considerations should be the price of the product, which will differ by brand, and the ease of use of the RDT, which will vary depending on the format of the test, number of steps, time for processing, ease of interpreting results, and time to results. Among the G6PD tests currently available on the market, the CareStart™ G6PD RDT is the only point-of-care qualitative G6PD test that, in independent studies, meets characteristics 1 and 2. However, the upper limit of storage temperature is 32°C, and therefore, a cool chain will be required in some tropical settings [17].

ADDITIONAL INFORMATION TO AID IN RDT SELECTION

The following is a list of additional information that can be requested from RDT manufacturers during the tendering process in order to inform decision-making when selecting an RDT:

1. Real-time temperature stability data on the product and accelerated data on the purchased lot;
2. Evidence of good manufacturing practice (e.g. GMP or ISO certification; ISO13485:2003 is a standard specific to medical devices);
3. Evidence of successful operational use or good quality field data on the product;
4. Long-term viability of manufacturer (to ensure continuity of supply);
5. Availability of product support;
6. Provision of sample products for assessing ease of use;
7. Agreement for replacement of products that fail agreed-upon quality control procedures; and
8. Box sizes appropriate to the tests’ rate of use in the intended area (to minimize storage time in poor conditions and limit the need to split boxes).

9.2 Budgeting and costing

When considering whether to implement a G6PD testing programme as part of routine *P. vivax* care, it is important to budget for direct costs and consider indirect costs that may result from not implementing such a programme.

Direct costs will depend on the type and quantity of RDT used, shipping costs and tariffs, transport and storage requirements, training and supervisory activities, and quality control.

Indirect costs include lost productivity due to disease, transport to health care facilities for patients experiencing relapse or haemolytic events due to primaquine administration, and increased vulnerability to other illnesses as a result of *P. vivax* infection and relapse. Furthermore, consideration should be given to the direct and indirect costs of ongoing *P. vivax* transmission in the community if radical cure is not administered due to lack of awareness of patients' G6PD status.

9.3 Training

Health managers at the national and subnational level, health workers, clinicians, supervisors, and others involved in *P. vivax* control programmes should be sensitized to the need for G6PD deficiency testing in the context of the clinical management of *P. vivax*. This user guide can be employed for providing introductory training on how to perform an RDT for G6PD deficiency. Product-specific job aids need to be developed by programmes and/or the manufacturer, clearly showing all of the steps required to perform the test correctly (see Section 10 below).

9.4 Transport and storage

RDTs should not be exposed to high temperatures or humidity for extended periods of time, as these conditions can compromise the reliability of tests and reduce their shelf life. Precautions should be taken throughout the transport chain and during short- and long-term storage to ensure that test kits are maintained at the appropriate temperature and humidity levels. Where possible, RDTs should be stored in temperature- and moisture-stable environments within manufacturer specifications.

Exposure to temperatures exceeding manufacturer recommendations should be avoided. It is often difficult to avoid exposure to high temperatures during transport, but precautions should be taken to minimize this occurrence. Communicating regularly with the shipper, paying attention to shipping logistics, and notifying the shipper and port authority regarding temperature requirements can all reduce the likelihood that test kits will be compromised. Ground transport should be undertaken promptly with attention to ambient temperature and conditions. Test kits should not be left in vehicles or containers in the sun for extended periods of time.

Storage in controlled, centralized conditions (such as at a central storage facility) should be maximized in order to reduce the amount of time that tests spend in uncontrolled field storage environments. In rural and remote locations where tests are likely to be used, test kits should be kept in cool areas, such as thatched-roof structures. Daily monitoring and recording of temperature conditions should be conducted, and conditions improved if temperatures exceed manufacturer specifications. Careful attention should be paid to stock levels and usage in order to prevent stockouts and reduce wastage.



For general guidance on transporting and storing RDTs, see *Transporting, storing, and handling malaria rapid diagnostic tests at central and peripheral storage facilities*. Geneva: World Health Organization; 2009, available at http://.who.int/malaria/publications/atoz/rapid_diagnostic_tests_storage_central/en/ [18].

9.5 Quality assurance and control

It is important to monitor the quality control of G6PD tests along the supply chain from the manufacturer to end user. Manufacturers are responsible for their own quality checks prior to lot release. Some manufacturers of quantitative G6PD tests also provide product-specific controls.

10. Using a G6PD RDT

The basic workflow for using a qualitative G6PD deficiency RDT is described below (Figure 6). A small sample of whole blood is collected from the patient and placed on the RDT test strip, followed by the assay buffer. After a short period of time, the tests are read visually on the test cartridge by observing any change in colour in the reader window, which indicates whether the patient has normal or deficient G6PD activity.

FIGURE 6
Basic workflow for a qualitative G6PD deficiency RDT

Step 1: Materials

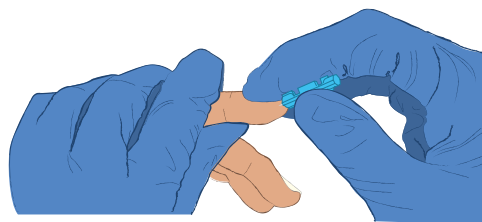
- Collect materials needed to perform the test. These include the test kit (which includes instructions, test cartridge, assay buffer, and sample pipette); lancet; alcohol swab; surgical gloves; and timer.
- Write patient's name or ID on the RDT cassette.



Collect materials for the test.

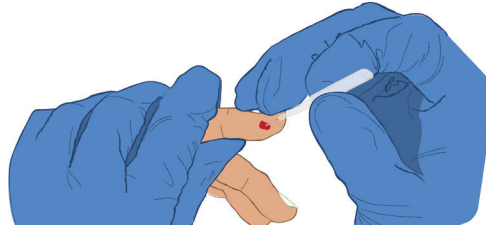
Step 2: Specimen collection

- Clean the fingertip to be lanced with an alcohol swab.
- Squeeze the end of the fingertip and pierce with a sterile lancet.
- Wipe away the first drop of blood with sterile gauze or cotton.
- Take the blood transfer device provided with the product, in this case a pipette, and while gently squeezing the tube, immerse the open end in the blood drop and then gently release the pressure to draw blood into the pipette until the correct volume is obtained. This is usually indicated by a line on the pipette.



Pierce fingertip with sterile lancet.

Not pictured: Whole blood can also be collected via venipuncture in a collection tube containing EDTA, citrate or heparin. Specimens should be stored at 2–8°C for up to 3 days, and brought to room temperature prior to use. Freezing specimens for more than 3 days may result in a non-specific reaction.



Draw blood into pipette.

Step 3.

Squeeze the sample pipette to add the volume of whole blood specified in the instructions to the sample well (well marked by an “S”).



Add blood to sample well.

Step 4.

Immediately after the application of blood, add the number of drops of assay buffer specified in the instructions to the buffer well (well marked by an “A”).



Add assay buffer to buffer well.

Step 5.

Set the timer based on instructions. Note that if blood takes more than the number of minutes specified in the instructions to reach the top of the test, the test is invalid and should be repeated.



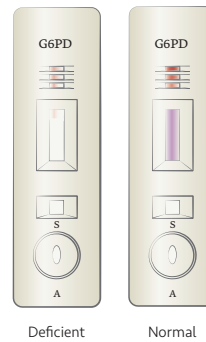
Set timer to time specified in instructions



Step 6.

Read results within the time specified in the instructions. Colour change in the reading window (in this case purple) = normal G6PD activity. No colour change in reading window = deficient G6PD activity.

A faint colour change in the reading window (borderline result) should be interpreted as deficient.



Read results within specified time. Coloured window = normal. White window = deficient. Light colour (borderline result) = interpret as deficient.

Step 7

Discard lancet into a sharps safety box, and the RDT, swab, capillary tube or pipette, and gloves into an infectious bin.



Discard materials safely.

10.1 Precautions

1. For *in vitro* diagnostic use only.
2. Open the test kit immediately before performing the test. Do not expose the test to sunlight or fluorescent light for more than 10 minutes because reagents on the test strips are often light-sensitive.
3. Allow test kits to come to room temperature (18–30 °C) before use.
4. Do not mix items from different lots of test kits.
5. Use disposable gloves when handling potentially infectious material and performing the test. Wash hands thoroughly afterwards.
6. Do not use the test kit beyond its expiration date.
7. Do not eat or smoke when handling specimens.
8. Clean up spills using a disinfectant.

10.2 Limitations

1. The test procedure, precautions and interpretations of results as specified in the manufacturer's instructions for the test must be followed when testing.
2. An RDT provides a qualitative result and cannot provide a quantitative measure of the patient's G6PD activity levels.
3. RDTs cannot distinguish heterozygous females with intermediate levels of G6PD enzyme activity from heterozygous females with normal levels, and this may result in a woman with intermediate activity being categorized as normal based on a qualitative screening test result.
4. Variation in individual haematocrit levels can affect the test result. Abnormally low haematocrit blood can cause a false-deficient result; abnormally high haematocrit blood can increase the risk of a false-normal result.

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APPENDICES



Appendix 1: Drugs and foods with risk of haemolysis in G6PD-deficient individuals

DRUGS WITH DEFINITE RISK OF HAEMOLYSIS IN MOST G6PD-DEFICIENT INDIVIDUALS

- Dapsone and other sulfones (higher doses for dermatitis herpetiformis more likely to cause problems)
- Methylthionium chloride
- Niridazole
- Nitrofurantoin
- Pamaquin
- Primaquine (30mg weekly for 8 weeks has been found to be without undue harmful effects in African and Asian people)
- Quinolones (including ciprofloxacin, moxifloxacin, nalidixic acid, norfloxacin, and ofloxacin)
- Rasburicase
- Sulfonamides (including co-trimoxazole; some sulfonamides, e.g. sulfadiazine, have been tested and found not to be haemolytic in many G6PD-deficient individuals)

DRUGS WITH POSSIBLE RISK OF HAEMOLYSIS IN SOME G6PD-DEFICIENT INDIVIDUALS

- Aspirin (acceptable up to a dose of at least 1g daily in most G6PD-deficient individuals)
- Chloroquine (acceptable in acute malaria and malaria chemoprophylaxis)
- Menadion, water, soluble derivatives (e.g. menadol sodium phosphate)
- Quinidine (acceptable in acute malaria)
- Quinine (acceptable in acute malaria)
- Sulfonylureas
- Naphthalene in mothballs also causes haemolysis in individuals with G6PD deficiency.

Source: British National Formulary 73: 2017 March–September: 923.

Appendix 2: Content to guide development of G6PD counselling forms

This includes pre-G6PD test counselling, post-test counselling for those who test as G6PD deficient, and primaquine-related counselling for patients with G6PD deficiency.

The messages in this document have been created to guide the development of *country-specific* materials for counselling patients on G6PD testing as part of *P. vivax* and *P. ovale* malaria case management.

Patients should receive counselling from their health care provider on both the rationale for G6PD testing and the treatment options for *P. vivax* and *P. ovale* malaria. Health care providers should have materials about G6PD deficiency and primaquine side effects that can be provided to patients in the local language and for non-literates.

PRE-TEST COUNSELLING - PRIOR TO CONDUCTING G6PD TEST

Questions

What test is being performed? Why is it being performed?

- We are testing you for G6PD deficiency.
- We will collect a small sample of blood and test it to determine the levels of G6PD enzyme activity in your blood.
- We are conducting this test today as a routine part of your care for malaria.

When and how will the test results be delivered?

- This is a rapid test – the results will be delivered within 30 seconds to 3 minutes (depending on the diagnostic tool used).
- If you would like to know your test results, they can be provided to you during this clinic session.

Why is it important to determine if I have G6PD deficiency?

- Your treatment provider needs to know if you have G6PD deficiency before prescribing certain medications, such as primaquine, to treat malaria.
- It will be helpful for you to know if you have G6PD deficiency because if you are G6PD deficient, you may need to avoid specific foods and medications that may cause illness.

POST-TEST COUNSELLING FOR PATIENTS WHO TEST AS G6PD DEFICIENT (G6PD ACTIVITY \leq 30%)

Questions

Is G6PD deficiency treatable or curable? What should I do to prevent illness?

- G6PD deficiency is not curable, but you can stay healthy by avoiding certain foods and medications.
- <Provide patient with a list of these foods and medications >

How do you become G6PD deficient?

- G6PD activity is genetically inherited from one's parents. G6PD deficiency is a genetically inherited trait caused by a mutation of the X-chromosome-linked G6PD gene.

POST-TEST COUNSELLING FOR PATIENTS WHO TEST AS G6PD DEFICIENT (G6PD ACTIVITY \leq 30%)



What are the harmful effects of G6PD deficiency?

- Some forms of G6PD deficiency can cause serious illness and others only cause mild symptoms.
- The most serious effect of G6PD deficiency is called haemolysis. Haemolysis is caused by damage to your red blood cells. The red blood cells of people with G6PD deficiency are vulnerable to damage from certain types of foods and medications <see list>.
- The symptoms of haemolysis include: dark-coloured urine or blood in the urine, paleness, jaundice, shortness of breath, dizziness, weakness, and back and/or abdominal pain.
- **If you experience any of these symptoms, you should notify your health care provider immediately.**

How does this diagnosis affect my family?

- G6PD deficiency is not spread by touch, food, sex, clothing, or other contact with people.
- Children may inherit G6PD deficiency from their parents while they are in the womb.
- Not all children born to G6PD-deficient parent(s) will have G6PD deficiency, but some might.
- Therefore, your children and any newborn babies in your family should be tested for G6PD deficiency.

PRIMAQUINE-RELATED COUNSELLING FOR PATIENTS WITH G6PD DEFICIENCY

Where close medical supervision is available, patients with G6PD deficiency \leq 30% may be given weekly primaquine at 0.75mg/kg bodyweight for 8 weeks.

Common questions

What do I need to know about taking primaquine because I am G6PD deficient?

- Primaquine is a drug that can cause haemolysis in people with G6PD deficiency. However, it is very important for you to receive treatment with primaquine to completely cure your malaria.
- Once you begin taking primaquine, carefully observe if you have any of the following symptoms: dark-coloured urine or blood in the urine, pallor (paleness), jaundice, shortness of breath, dizziness, weakness, enlarged spleen, and back and/or abdominal pain.
- If you experience any of these symptoms, stop taking primaquine and immediately notify your health care provider.
- Primaquine is quickly passed through your body once you stop taking it, so these symptoms will stop after you discontinue taking the drug.

Is there another way to cure malaria other than treatment with primaquine?

- Certain types of malaria such as *Plasmodium vivax* and *Plasmodium ovale* can only be completely cured using primaquine. If you do not take the drug, it is possible you will experience more illness from malaria, and it is also possible for mosquitoes to transmit the disease from you to other members of your family and community.
- By testing you for G6PD deficiency, we know that it is important for you and your health care provider to monitor you for symptoms of haemolysis during your treatment for malaria.

Appendix 3: Information card for patients

About G6PD deficiency and treatment with primaquine

Glucose-6-phosphate dehydrogenase (G6PD) is an important enzyme involved in the body's metabolism. This enzyme plays a key role in the production of energy as well as protection against cell damage. This enzyme is very important in red blood cells. Individuals with G6PD deficiency experience higher than normal rates of haemolysis (the destruction of red blood cells), which can cause haemolytic anaemia. Haemolytic anaemia is due to the destruction of red blood cells at a rate that is faster than the generation of new red blood cells. The most common symptoms of haemolytic anaemia are: pallor (paleness), jaundice, shortness of breath, dizziness, dark-colored urine, weakness, and back and/or abdominal pain. Depending on its severity, haemolytic anaemia can cause mild symptoms or if massive and not recognized and treated rapidly with blood transfusions, can lead to death. Individuals with G6PD deficiency may experience haemolytic anaemia when exposed to oxidative substances or during certain bacterial or viral infections, as they are unable to replenish G6PD; as a result, they have a reduced ability to protect red blood cells from damage and haemolysis.

G6PD-deficient individuals have lower than normal oxygen levels, as red blood cells are responsible for carrying oxygen throughout the body.

Individuals with G6PD deficiency should avoid certain substances that are known to cause oxidative damage. These include: drugs such as the antimalarials chloroquine and primaquine, fava beans, legumes, red wine, soya, and any other substance that is considered an oxidizing agent. It is very important for individuals with G6PD deficiency to avoid these substances and to tell their doctor that they have this enzyme deficiency.

It is important to note that G6PD deficiency is an X-chromosome-linked trait, which means that it is inherited from the female parent. Thus, this deficiency cannot be contracted—individuals with G6PD deficiency have this trait from birth—and there is no cure. Since males only have one X chromosome, G6PD deficiency is more common. However, women with one or more copies of the G6PD deficiency gene can still present with G6PD deficiency of varying severity and, of course, may pass the trait to their offspring.

G6PD deficiency is considered to be one of the most common enzyme deficiencies. Approximately 400 million people across the globe experience some variation of G6PD deficiency. G6PD deficiency is most commonly observed in individuals with Mediterranean, African, Asian, and/or Middle Eastern ancestry.

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