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Glucose-6-phosphate dehydrogenase deficiency near-patient tests for tafenoquine or primaquine use with Plasmodium vivax malaria (Protocol)

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[Diagnostic Test Accuracy Protocol]

Glucose-6-phosphate dehydrogenase deficiency near-patient tests for tafenoquine or primaquine use with Plasmodium vivax malaria

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (diagnostic). The objectives are as follows:

To assess the diagnostic accuracy of near-patient tests for G6PD deficiency in people undergoing treatment or prophylaxis with primaquine or tafenoquine for malaria; or in people at risk of or susceptible to malaria.

Secondary objectives

- To investigate sources of heterogeneity, namely the following.
  - Age: adults versus children
  - Sex: male versus female
  - Reported prevalence of G6PD (high versus low)
  - Malaria endemicity (endemic versus non-endemic)
  - Geographic location (continent of residence; that is, Africa, Asia, or other continent)
  - Reference standard used (adjusted male median, median G6PD, laboratory standard)
  - Type of blood used (venous versus capillary)
- To compare the accuracy of each type of test.

BACKGROUND

Glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency is one of the most common genetic disorders, affecting an estimated 500 million people worldwide (Luzzatto 2020). Deficiency of this enzyme leads to damage of the red cell membrane when the body is exposed to oxidative stress due to medication, certain food items (for example, fava beans), or infection. Spontaneous haemolysis in the absence of a trigger is also known to occur in some cases. G6PD deficiency is relatively common in malaria-endemic countries, especially in sub-Saharan Africa and Southeast Asia (Nkhoma 2009). It has an average prevalence of 8%, but ranges up to 15% in most countries, with peaks of up to 30% in certain areas (Nkhoma 2009). In these countries, testing and diagnosing of G6PD deficiency has important clinical implications in malaria treatment. People with G6PD deficiency are at risk of acute haemolytic anaemia when exposed to two important drugs used in malaria treatment and prophylaxis, primaquine and tafenoquine. Hence, screening for G6PD deficiency is recommended before these drugs are administered.

Target condition being diagnosed

G6PD deficiency

G6PD is an enzyme that is essential in responding to oxidative stress (Beutler 2008; Capellini 2008). The gene for this enzyme is encoded on the X chromosome. More than 217 mutations associated with decreased enzymatic activity (G6PD deficiency) have been described (Gómez-Manzo 2016). Haemolysis is triggered in individuals with G6PD deficiency when they are exposed to circumstances that increase cellular oxidative stress.

These circumstances include infections, certain food items such as fava beans, and the antimalarial drugs primaquine and tafenoquine, as well as other medications such as dapsone and rasburicase (Luzzato 2016). G6PD testing has become an integral part of clinical decision-making on the use of primaquine and tafenoquine in the treatment and prophylaxis of malaria. The World Health Organization (WHO) also recommends screening neonates for G6PD deficiency in all settings where G6PD deficiency is observed in 3% to 5% or more of the male population (WHO 2018a).

A diagnosis of G6PD deficiency is made when a patient's G6PD enzyme activity is less than 30% that of the reference standard. However, as the disease is an X chromosome-linked disorder, females can have a state of deficient, intermediate or normal G6PD activity. This is because heterozygous females with one normal X chromosome and one chromosome with a mutated G6PD gene can have different levels of G6PD activity, due to the presence of G6PD-normal and G6PD-deficient red cells at varying ratios. This is due to random inactivation of one X chromosome during embryonic life. For the purposes of this review, we define intermediate G6PD activity as 30% to 70% that of the reference standard. The rationale for clinical trials to use this threshold was based on studies on the haemolytic potential of tafenoquine in female volunteers heterozygous for G6PD deficiency (Rueangweerayut 2017), and is primarily based on safety concerns.

Importance of testing for G6PD deficiency in patients with malaria

Malaria is a febrile illness caused by *Plasmodium* (*P*) parasites. Five different species of *P* can cause malaria in humans. Of these, *P vivax* accounts for 20% of cases worldwide (Baird 2003), and is responsible for almost half of all the cases of malaria outside of Africa (WHO 2019). Even though vivax malaria is characterised by a relatively low amount of parasites circulating during the blood stage, compared to other species, it has been shown to relapse within weeks to months following the primary infection. This is mainly due to reactivation of dormant parasitic forms in the liver (hypnozoites). Hypnozoites are also seen in patients with malaria due to *P ovale*. Relapses increase the overall morbidity and mortality of the disease (Chu 2016). Relapses can represent up to 80% of all *P vivax* infections, and contribute to onward transmission of the disease.

In order to achieve radical cure (that is, cure and prevention of relapses) in patients with vivax and ovale malaria, relapses originating from hypnozoites must be prevented. The only drugs that have activity against hypnozoites are the 8-aminoquinolines. This drug class includes primaquine and tafenoquine (Chu 2018). The US Food and Drug Administration (FDA) approved tafenoquine for use in 2018. Tafenoquine and primaquine are also used for prophylaxis against malaria (Chu 2019). They also eradicate the reproductive forms of the parasite (gametocytes), which are necessary for the completion of the parasite life cycle, and disease transmission. Eradication of these gametocytes reduces transmission of the disease.

The use of these medications depend on the G6PD enzyme status of the patient, as both tafenoquine and primaquine cause an increase in the oxidative stress in the red blood cell, which triggers haemolysis. This can lead to life-threatening anaemia in individuals with G6PD deficiency (Chu 2019). Due to the risk of this significant adverse event, the WHO recommends testing for G6PD deficiency before using these drugs in patients with malaria (WHO 2014).

Index test(s)

A range of near-patient diagnostic tests are available for the diagnosis of G6PD deficiency. This includes both qualitative and quantitative assays for G6PD. Qualitative tests determine whether a patient is above or below a given threshold of G6PD activity, whereas a quantitative test can determine the exact level of G6PD enzyme activity. Both types of tests are used in clinical practice. Technical details of these index tests are provided in Appendix 1.

The important diagnostic threshold for qualitative tests is less than 30% of reference G6PD activity (G6PD-deficient). A quantitative test should additionally be able to detect individuals with the full spectrum of G6PD activity, including females with intermediate activity.

Qualitative tests

Qualitative tests can be used to determine whether an individual is above or below a threshold predetermined by the diagnostic test for G6PD activity. This is usually less than 30% of reference G6PD activity (WHO 2018b). Results denoting deficiency indicate that the tested individual has G6PD activity below this threshold and should be considered G6PD-deficient. Normal results mean that the tested individual has G6PD activity above the specified threshold.

G6PD qualitative fluorescent spot test (FST)

The fluorescent spot test (FST) is the most widely used method for qualitative detection of G6PD deficiency (Beutler 1968). For several decades, FST has been recommended as a qualitative test for G6PD deficiency screening. This test has been used extensively in operational settings to guide patient treatment and to determine which patients should be included in clinical trials. It uses venous or capillary blood to catalyse a reaction that generates a fluorescent product. The level of florescence is used for analysis. A moderate or strong fluorescence indicates normal G6PD, whereas a weak or absent fluorescence indicates G6PD deficiency (less than 30% of reference activity).

Although the FST cannot be used as a point-of-care (POC) test, it can economically be customized for in-house use.

Lateral flow tests

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. The CareStart G6PD (CSG) (Adu-Gyasi 2015) and BinaxNOW G6PD (Osorio 2015) are qualitative lateral flow diagnostic tests. In these two tests, results are presented in binary form, with G6PD deficiency diagnosed on a single activity threshold of less than or equivalent to 30% of reference activity. This is based on a clinician's visual read of colour change. In the BinaxNOW test, persistence of red colour in the sample front indicates G6PD deficiency (less than 30% of reference activity). Similarly, in the CSG, lack of colour change in the solution indicates G6PD deficiency (less than 30% of reference activity). Unlike the FST, lateral flow tests can be used as POC tests in clinical and field settings.

WST8/1-methoxy phenazine methosulfate (PMS) method

The principle of the chemical reactions for detection of G6PD activity is that the hydrogen of nicotinamide adenine dinucleotide phosphate (NADPH) (produced by G6PD) converts water-soluble tetrazolium salt-8 (WST-8) to WST-8 formazan in the presence of a hydrogen carrier, 1-methoxy phenazine methosulfate (PMS). This gives an easily detectable orange colour, with colour intensity directly proportional to G6PD activity. Samples with normal G6PD activity show strong orange colour and deficient samples show a faint colour (moderate deficiency likely to represent heterozygotes) or no colour (severe deficiency and negative controls) (Niz 2013).

Quantitative tests

The general disadvantage of the above-mentioned qualitative tests is that they can only distinguish between patients with normal G6PD activity and patients whose G6PD activity is below 30% of the reference standard. Normal results mean that the tested individual has G6PD activity above the 30% threshold, but as one would expect, this has a wide variation, from 30% to 99%. Subjects on the lower end of this normal range (that is, heterozygous women with intermediate enzymatic activity) are still susceptible to haemolysis when treated with oxidative drugs. Therefore, in women a 'normal' diagnosis by qualitative testing does not correspond to absence of haemolytic risk during treatment with oxidative drugs (Chu 2017).

During clinical trials, G6PD-heterozygous women with intermediate G6PD activity defined as 30% to 70% of the reference standard, who tested normal by a qualitative test, underwent significant haemoglobin drops with certain primaquine and tafenoquine regimens (Chu 2018). Therefore, the important diagnostic thresholds to inform treatment with primaquine and tafenoquine in females for quantitative G6PD tests would be less than 70% of reference G6PD activity, which would indicate intermediate activity; and less than 30%, which would indicate deficiency.

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. Quantitative tests normalize the G6PD activity per red blood cell count or haemoglobin concentration in order to account for varying individual hematocrit ranges at the time of sampling, and correct for the influence of temperature on enzymatic activity. Most importantly, quantitative tests can detect heterozygous female individuals with intermediate G6PD activity.

Standard G6PD by SD Biosensor (Pal 2019) and the CareStart G6PD Biosensor (Bancone 2018) by AccessBio are tests that provide a quantitative reading of G6PD activity. Both of these tests provide results within minutes, and can be used at the POC.

The CareStart G6PD Biosensor combines a haemoglobin measurement device with a G6PD activity measurement device. It then calculates the G6PD activity, normalized for haemoglobin concentration, based on the two measurements.

The Standard G6PD by SD Biosensor is designed to measure the quantitative concentration of total haemoglobin and G6PD enzymatic activity in capillary and venous blood using a colourimetric method. This means that the intensity of the colour change of the test reaction is translated into a numerical value.

Clinical pathway

Primaquine is indicated for achieving a radical cure for *P vivax* and *P ovale* malaria. This is due to the efficacy of the drug in eradicating the dormant forms within the liver (hypnozoites) and interrupting the life cycle of the parasite. A radical cure prevents relapses and reduces transmission of the disease. There is currently scientific interest in the use of tafenoquine for radical cure of *P vivax* malaria. The distinct advantage of tafenoquine is that is can be used as single-dose therapy, whereas Primaquine requires 14-day administration. In addition, tafenoquine is also licensed for use in malaria prophylaxis (Chu 2019). In contrast to a 14-day primaquine regimen that can be given safely to patients with greater than 30% G6PD activity, single-dose tafenoquine can be given safely only to patients with greater than 70% G6PD activity.

Decision-making pathway for primaquine in the treatment of malaria

The WHO's current recommendation is to test patients for G6PD deficiency whenever feasible, before administering primaquine in the management of *P vivax* and *P ovale* malaria. The decision pathway depends on the availability of G6PD testing in the clinical setting (WHO 2018a).

When testing for G6PD deficiency is unavailable

In cases where testing is not available, a decision for administration of the medication is made based on risk-benefit stratification. Aspects factored into the decision making process include 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. If a decision is made not to administer primaquine, the patient is advised on when to return to seek treatment for a suspected relapse.

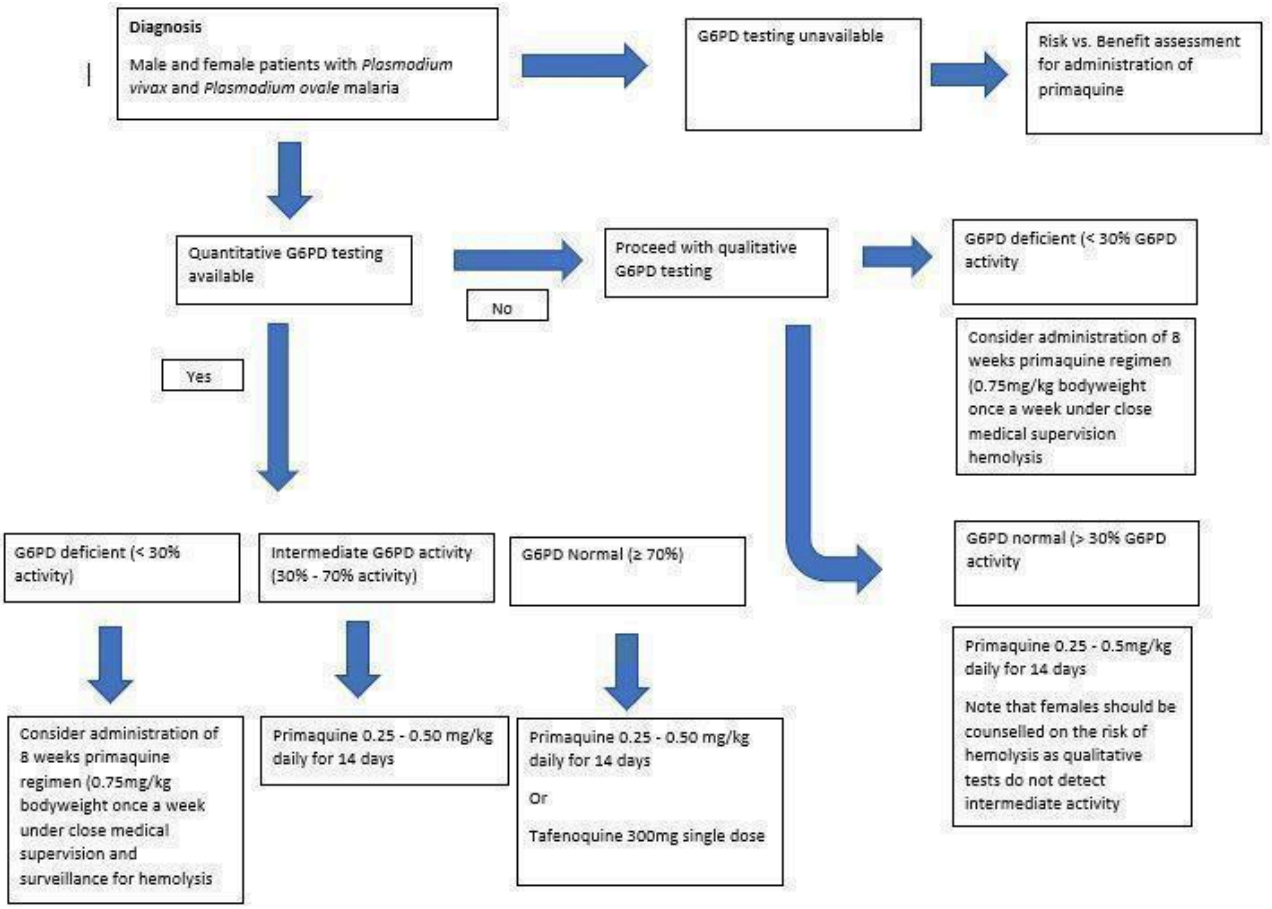
When testing for G6PD deficiency is available

If qualitative testing is available, and this testing detects possible G6PD deficiency (less than 30% of reference G6PD activity) patient counselling is performed. Following careful consideration of risks and benefits, a modified dose of primaquine (0.75 mg base/kg body weight once per week for a duration of eight weeks) can be considered for administration, under very strict medical surveillance.

If qualitative testing is normal (greater than 30% of reference G6PD activity), the patient is prescribed a 14-day primaquine regimen at a dose of 0.25 to 0.5 mg base/kg body weight daily. The most important problem with qualitative testing, as discussed above, is that it may classify patients with intermediate G6PD activity as normal. This is especially relevant in the case of heterozygous females. Due to this, all females with normal qualitative testing are counselled on the possibility that they may have intermediate G6PD activity, before administration of primaquine (WHO 2018a). This constraint could potentially be overcome by the use of quantitative G6PD testing,

This pathway is summarized in Figure 1.

Figure 1.



Clinical pathway for tafenoquine in the treatment of malaria

Current recommendations for tafenoquine indicate that the drug should only be prescribed to those with G6PD activity that is greater than 70% of the local population median (reference activity). This requires all females being considered for tafenoquine to undergo quantitative testing for G6PD. The rationale for requiring quantitative G6PD testing is that heterozygous females with intermediate G6PD activity are also at risk for tafenoquine-induced haemolysis. This risk is further compounded by the fact that tafenoquine has a longer half-life, compared to primaquine. This means that drug-related haemolyses are harder to manage, as the drug exposure cannot be stopped at the first signs of haemolysis (Rueangweerayut 2017).

To date, published studies using tafenoquine have included only G6PD-normal individuals. Some studies specifically included only those participants with a G6PD activity that was greater than 70% of the population median (reference activity), which for safety reasons is therefore proposed as the upper limit of the intermediate threshold (Chu 2019).

This pathway is summarized in Figure 1

Tafenoquine for prophylaxis of malaria

Tafenoquine is licensed for use in the prophylaxis of malaria. This is primarily due to its effects on the transmission of *P falciparum* gametocytes. Primaquine has a similar effect, but is not in widespread use due to its impractical daily dosing schedule. Due to the risk of haemolysis, all individuals considered for prophylaxis with tafenoquine should undergo G6PD testing prior to administration.

Alternative test(s)

Genetic tests

Genetic tests use deoxyribonucleic acid (DNA) analysis methods to detect mutations within the G6PD gene. These tests are predominantly used in large population studies and have poor utility in clinical practice. Genetic tests detect single nucleotide polymorphisms and may miss detection of patients with G6PD deficiency with mutations not included in the reference panel. They may also detect novel mutations that require subsequent phenotypic confirmation. Neither DNA sequencing nor polymerase chain reaction can measure the relative proportion of G6PD-deficient to G6PD-normal red blood cell populations in heterozygous females (WHO 2018a).

Cytochemical assay methods

These methods provide information on intracellular G6PD levels and could be utilized for observation of the relative proportions of deficient to normal cells in heterozygous females. However, most of these methods are used only in research, and are not widely used in clinical practice.

Rationale

Effective treatment of *P vivax* and *P ovale* malaria is dependent on gametocidal activity and radical cure against hypnozoites. The 8-aminoquinolines, primaquine or tafenoquine, are currently indicated for this purpose. It is notable that evidence accumulated over the years demonstrates that the failure to prevent relapse through achieving radical cure incurs risk of serious illness and death with *P vivax* malaria (Baird 2015). As discussed above, these medications have a propensity to trigger haemolysis in patients with G6PD deficiency. The current gold standard tests for diagnosis of G6PD deficiency is quantitative spectrophotometry. However, this is an expensive technique that requires optimum laboratory conditions and equipment. Furthermore, the results of the test may not be available in time to guide clinical decisions. Most populations with high prevalence of G6PD deficiency live in tropical countries where this test is available only in specialized hospitals, or is not available at all. Qualitative tests provide valuable information in differentiating individuals at a level of 30% G6PD activity, which in most cases is the threshold for treatment with standard dose primaquine. Over the years, several rapid diagnostic qualitative tests have been introduced to clinical practice for diagnosis of G6PD deficiency. A comparative analysis of these qualitative tests would be instrumental in the development of guidelines on test choices in clinical practice.

The recent FDA approval of tafenoquine may place more importance on quantitative G6PD assay methods, as administration of the drug requires demonstration of G6PD activity that is greater than 70% of the local population median (reference activity). In this light, it is imperative that a diagnostic accuracy analysis be performed for rapid diagnostic quantitative tests for G6PD deficiency. Based on the justification presented above, the findings of this review are perceived to have high impact in informing management decisions in *P vivax* and *P ovale* malaria. Furthermore, direct comparative analyses among available qualitative and quantitative tests would also have clear implications for practice recommendations.

OBJECTIVES

To assess the diagnostic accuracy of near-patient tests for G6PD deficiency in people undergoing treatment or prophylaxis with primaquine or tafenoquine for malaria; or in people at risk of or susceptible to malaria.

Secondary objectives

- To investigate sources of heterogeneity, namely the following.
  - Age: adults versus children
  - Sex: male versus female
  - Reported prevalence of G6PD (high versus low)
  - Malaria endemicity (endemic versus non-endemic)
  - Geographic location (continent of residence; that is, Africa, Asia, or other continent)
  - Reference standard used (adjusted male median, median G6PD, laboratory standard)
  - Type of blood used (venous versus capillary)
- To compare the accuracy of each type of test.

METHODS

Criteria for considering studies for this review

Types of studies

Diagnostic accuracy studies are typically cross-sectional in design (Deeks 2013). This review will include cross-sectional studies that compare the index test to the current diagnostic gold standard test, as well as studies that perform comparative analyses between different index tests. Diagnostic test accuracy studies performed at the baseline of randomised trials are also considered cross-sectional, and will therefore be included. Within the cross-sectional design, a diagnostic test accuracy study may be conducted in a 'single-gate' or 'two-gate' orientation. In the single-gate orientation, a single set of inclusion criteria is used for inclusion of participants. In the 'two-gate' orientation, different sets of criteria are used for those with and those without the target condition. This review will include studies with both single-gate and two-gate orientations, though the latter are prone to overestimation of accuracy (Rutjes 2005). We will assess the effect of 'two gate' studies on the risk of bias using the "Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies" (QUADAS-2) (Whiting 2011). We will also assess their effect on the overall accuracy estimates through a sensitivity analysis.

Participants

This review will include participants who are eligible to be considered for treatment or prophylaxis of malaria with primaquine and tafenoquine. Although the final analysis and interpretation of this review will mostly be instrumental in management decisions in malaria, the diagnostic accuracy studies

evaluating the selected index tests will not be restricted to patients with malaria or to populations in malaria-endemic areas. This is because valid data on the diagnostic accuracy of the index tests can be extracted irrespective of the population characteristics.The inclusion of data from testing in healthy volunteers is also relevant for use of primaquine and tafenoquine as prophylaxis against the disease.

We will exclude studies providing data on diagnostic accuracy of the index tests in neonates. This is because G6PD activity is higher in the neonatal period compared to other age groups, and may also vary by ethnicity. This generates unique reference ranges and reference standards for diagnosis of G6PD deficiency in this population. Furthermore, performance of the index tests in neonates is likely to be different in comparison to studies in older populations (Kaplan 2005; Keihanian 2017).

Index tests

The index tests included in the review are as follows.Technical details of these tests are provided in Appendix 1

Qualitative tests

- G6PD Qualitative FST
- CareStart G6PD
- BinaxNOW G6PD
- WST8/1-methoxy PMS assay

We will exclude the brilliant cresyl blue decolouration test, the methaemoglobin reduction test, the formazan ring method, and the ephadex gel MTT-PMS method from the review, as they are not used in routine clinical practice.

Quantitative tests

- Standard G6PD by SD Biosensor
- CareStart G6PD Biosensor by AccessBio

Target conditions

The target condition is G6PD deficiency. We will determine the sensitivity and specificity of the index tests to detect the presence of two target conditions: G6PD activity less than 30% that of the reference standard (G6PD deficiency); and G6PD activity less than 70% that of the reference standard (the threshold for diagnosis of intermediate G6PD activity).

For both quantitative and qualitative index tests

1) G6PD activity that is less than 30% that of the reference standard, classified as G6PD deficient, wherein are found all hemizygous G6PD-deficient males and all homozygous G6PD-deficient females. This is the WHO-defined threshold for informing treatment decisions for primaquine.

For quantitative tests

2) G6PD activity that is less than 70% that of the reference standard, the threshold established in clinical trials for tafenoquine-eligibility. This is based on the upper cutoff level for intermediate G6PD activity. The rationale for clinical trials to use this threshold was based on studies on the haemolytic potential of tafenoquine in female volunteers heterozygous for G6PD deficiency (Rueangweerayut 2017).

Reference standards

Reference standards will be based on the spectrophotometric assay for G6PD, the gold standard quantitative test for level of G6PD activity. This provides a quantitative value for G6PD enzyme activity. We will base our spectrophotometry reference standard definitions on the following considerations.

Domingo 2013 recommended that the reference standard value should be based on the median value of G6PD activity for the entire male population in a given study. If purposive or biased recruitment were used, the median G6PD value of the G6PD-normal males recruited for the study should be used as the definition of normal. If this is not available, an adjusted male median (AMM) could be used as the reference standard. AMM is calculated by exclusion of all males with G6PD activity equal to or less than 10% of the male median and determining a new median G6PD activity. This can be used as the 100% G6PD activity value from which cut-off levels are defined. For example, a 30% value of the AMM is classified as G6PD-deficient. We also appreciate that in studies prior to Domingo 2013, the reference standard used might have been a test manufacturer-specified value, or a laboratory value determined from male subjects with known normal G6PD status.

For studies where the AMM is not reported, we will consider calculating it, if the relevant data are available. We would then define the thresholds for these studies based on the AMM. This approach was used in a recent meta-analysis by Ley 2019. Due to the variation in reference standards, we will perform a heterogeneity analysis, based on the utilized reference standard.

Search methods for identification of studies

We prepared the search strategy with the assistance of the CIDG Information Specialist.

We will attempt to identify all relevant studies regardless of language, publication status, or publication date limit.

Electronic searches

We will search the following databases, using the search terms and strategy described in Appendix 2: the Cochrane Central Register of Controlled Trials (CENTRAL, published in the Cochrane Library), MEDLINE (via OVID), Embase (accessed via Ovid), and Science Citation Index (Web of Science). We will also search the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov, to identify trials in progress.

Searching other resources

We will also check the reference lists of relevant studies. We will search for articles citing our included studies in the Science Citation Index-Expanded (Web of Science). We will also use the “Related articles” feature in PubMed to identify additional references.

Data collection and analysis

Selection of studies

Two review authors (SP and JT) will independently determine study eligibility for inclusion by examining the title and abstract of each article identified by the literature search. A third review author (PW) will resolve conflicts if necessary. Two review authors (SP and JT) will subsequently obtain the full-text articles for the selected abstracts and assess them against the prespecified inclusion and

exclusion criteria, as defined in the protocol. The two review authors and a third review author (PW) will resolve any conflicts by discussion. If the review authors still cannot reach consensus, a fourth review author (EO) will make the final decision.

Data extraction and management

Two review authors (SP and JT) will perform data extraction and management, with the assistance of PW and GB. We will develop a standardized data extraction form, which will include the following themes.

- Details of study: first author, publication year, journal, study design, inclusion/exclusion criteria
- Characteristics of study population: age, gender (percentage of males and females in the study population), malaria-endemicity of setting, prevalence of G6PD
- Reference standard: Spectrophotometeric assay conditions and interpretation standards
- Index test used: quantitative, qualitative, mixed; type of assay method used; cutoff used for determination of G6PD activity
- Details of outcome: number of indeterminate, missing or unavailable test results; number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) results

Inconsistencies and conflicts in data extraction will be resolved by discussion within the review team.

Assessment of methodological quality

Two review authors will independently assess the quality of each individual study using a modified QUADAS-2 tool (Whiting 2011). The tool will be utilized in line with the review question Table 1. Two review authors (SP and JT) will independently assess all included studies using a pre-designed and pre-tested form. This will be performed under the supervision of PW and EO. Disagreements will be resolved based on discussion and consensus between the two authors and in consultation with the whole review team, where consensus between the two denoted authors cannot be reached.

Statistical analysis and data synthesis

We will enter two-by-two data (the number of TP, TN, FP, and FN results) for each study into Review Manager 5 (RevMan 2020). We will summarize estimates of sensitivity and specificity from each individual study on forest plots and plot these estimates with summary receiver operating characteristics (SROC) plots. If meta-analysis is appropriate, given the number of studies, we will pool results from the included studies. We will pool data from quantitative and qualitative tests separately. For each type of test (qualitative or quantitative), we will select a common threshold and use the bivariate model to obtain pooled estimates of sensitivity and specificity at the common threshold (Macaskill 2010). For example, selected thresholds will be less than 30% for qualitative tests and less than 30% and less than 70% for quantitative tests. We will fit the bivariate model using the 'xtmelogit' commands in Stata version 14 (Stata 2017). We will plot the pooled estimates of sensitivity and specificity using SROC plots in Review Manager 5.

If studies permit, we will compare the accuracy of qualitative tests with the accuracy of quantitative tests. We will initially perform an indirect comparison analysis of diagnostic tests in all included studies, and then proceed to direct comparison in studies that used the test in the same individuals. We will compare the accuracy of qualitative and quantitative tests by adding a covariate for test type to the bivariate model. We will assess model fit by performing likelihood ratio tests, and we will profile the likelihood of the correlation coefficient to determine whether this parameter has been poorly estimated.

Investigations of heterogeneity

We will first visually examine the forest plots and SROC plots for heterogeneity. We will analyze the potential determinants or sources of heterogeneity as covariates in the bivariate model. Where possible and appropriate, we will assess the following categorical covariates for heterogeneity;

- Age: adults versus children
- Sex: male versus female
- Reported prevalence of G6PD (high versus low)
- Malaria-endemic versus non-endemic: endemic areas will be extracted from maps generated using model-based geostatistics methods (Gosoniu 2006)
- Geographic location (based on continent of residence; for example, Africa, Asia)
- Reference standard used (AMM/median G6PD/laboratory standard)
- Type of blood used (venous versus capillary)

Sensitivity analyses

If there are sufficient data, we will perform sensitivity analyses to examine the influence of risk of bias. We will examine the impact of risk of bias in each of the four QUADAS-2 domains (patient selection, index test, reference standard, and flow and timing) (Table 1) by excluding studies at high risk of bias from the main analyses. We will also perform a sensitivity analysis for the included 'two gate' studies to assess the influence of these studies on the risk of bias. We will also assess their effect on the overall accuracy estimates.

Assessment of reporting bias

We will not assess reporting bias in this review.

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ADDITIONAL TABLES

Table 1. QUADAS-2 tool application

Domain	Participant selection	Index test (IT)	Reference standard (RS)	Flow and timing
Description	Methods of patient selection	How index test was conducted and reported	How reference standard was conducted and reported	Describe patients that did not receive and time interval between index test or reference standard

Table 1. QUADAS-2 tool application *(Continued)*

Signalling questions (Yes, no, unclear)	Consecutive or random sample of patients? • Yes if the study reported consecutive enrolment or random sampling of patients. • No if patients were purposefully selected, for example based on previous test results (other tests or reference standard) • Unclear if the study did not explicitly state consecutive enrolment or random sampling, and it was unclear how patients were sampled	IT results interpreted without knowledge of the results of RS? • Yes if it was clear that the IT results were interpreted without knowledge of RS results • No if was apparent that the IT results were interpreted with knowledge of the RS results • Unclear if there was insufficient detail to judge	RS likely to correctly classify the target condition? • Yes if laboratory reference test was used at the thresholds determined by the AMM, median value of G6PD activity for the entire male population in a given study, or If purposive or biased recruitment was used, the median G6PD value of the G6PD-normal male recruited for the study • No if laboratory reference test used with un validated manufacturer data • Unclear if there was insufficient detail to judge	Appropriate interval between IT and RS? • Yes if samples for both the IT and RS were drawn at the same time or within an interval of 24 hours • No if samples for the IT and RS were drawn at an interval of more than 5 days. Unclear if there was insufficient detail to judge
	Was a case-control design avoided? • Yes if a case-control design was not used. • No if patients with known disease (cases) and patients without the disease (controls) were clearly enrolled (such that participants are unrepresentative of the spectrum of patients seen in clinical practice). • Unclear if the study design used was not clearly reported.	Prespecified threshold used? • Yes if threshold as per manufacturer's instructions were reported. Test results reported as positive or negative • No if threshold as per manufacturer's instructions was not used • Unclear if there was insufficient detail to judge	RS results interpreted without knowledge of the results of IT? • Yes if it was apparent that RS results were interpreted without knowing IT results • No if it was clear that RS results were interpreted while knowing IT results • Unclear if there was insufficient detail to judge.	Number of participants receiving RS/same RS, and included in the analysis? • Yes if all participants received a RS or the same RS regardless of IT results • No if only some participants received an RS or if different RS were used • Unclear if there was insufficient detail to judge.
	Did the study avoid inappropriate exclusions? - i.e. critically ill patients • Yes if no patients were excluded after inclusion in the study • No if specific populations were excluded			
Risk of bias High, low, unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation has introduced bias?	Could the patient flow have introduced bias?

Table 1. QUADAS-2 tool application *(Continued)*

Applicability	Were there concerns that the included participants did not match the review question? • High if the selected participants were from a non malarial endemic area • Low if the selected participants were from a malarial endemic area • Unclear if there was insufficient information to make a judgement	Were there concerns that the IT, its conduct, or interpretation differed from the review question? • High if the IT was a prototype, not commercially available, or conducted in a nearby laboratory • Low if the IT was commercially available or conducted in a field setting • Unclear if there was insufficient information to make a judgement	Were there concerns that the target condition as defined by the RS did not match the review question? Not applicable	Not applicable

Abbreviations: IT: index test; RS: reference standard.

APPENDICES

Appendix 1. Technical details of index tests

In the G6PD qualitative fluorescent spot test (FST), phenotypic determination is performed by incubating a few µL of venous or capillary blood with glucose-6-phosphate and NADP in the substrate reagent and spotting the residual on filter paper. The dried spots are then viewed under long-wave ultraviolet (UV) light to detect the florescent by product NADPH. Detected fluorescence is directly proportional to G6PD activity and lack of fluorescence signals G6PD deficiency (Beutler 1968).

Depending on the brand of FST, fluorescence is read at both 5 and 10 minutes or directly at 10 minutes. The following fluorescence levels are used for analysis:

- Normal G6PD activity: (moderate to strong fluorescence after 5 minutes) strong fluorescence after 10 minutes.
- Deficient G6PD activity: weak or no fluorescence after (5 and) 10 minutes.

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.

The CareStart G6PD and BinaxNOW G6PD are qualitative lateral flow diagnostic tests. In these two tests results are presented in binary form with deficiency diagnosed on a single activity threshold of $\lesssim$ 30%.

The BinaxNOW G6PD test device consists of a lateral flow test strip comprised of a white sample pad and a reaction pad. The reaction pad contains the reagents necessary for the G6PD enzymatic reaction and the subsequent reduction of a nitro blue tetrazolium dye into its concomitant blue formazan product. The resulting colour change on the strip indicates enough G6PD activity is present to presume the sample is not deficient.To perform the test, a whole venous blood sample is mixed with RBC lysing reagent in a sample preparation vial and then transferred to the test device sample pad. The lysed blood sample migrates up the test strip, reconstituting reagents in the reaction pad. Test results are read visually. If no change in the red colour of the sample front is observed at the test read time, the sample is presumed to be deficient in G6PD enzyme activity. Samples normal in G6PD activity produce a distinct colour change - the red sample colour changes to a brown/black colour on the upper half of the reaction pad (Osorio 2015; Tinley 2010).

The CareStart G6PD is a qualitative enzyme chromatographic test is based on the reduction of colourless nitro blue tetrazolium dye to dark coloured formazan (Adu-Gyasi 2015). This is qualitative enzyme chromatographic test is based on the reduction of colourless nitro blue tetrazolium dye to dark coloured formazan. Two µL of venous blood are added into the sample well with two drops of buffer into the buffer well. The G6PD deficiency status of an individual is read in 10 minutes. Samples with normal G6PD activity produce a distinct purple colour background in the result window while no colour change will be observed for samples with deficient G6PD activity (Kim 2011).

The principle of the WST8/1-methoxy PMS method is based on reduction of hydrogen from NADPH which converts WST8 to WST8-formazan in the presence of the hydrogen carrier 1-methoxy-PMS (Niz 2013). This reaction yields a strong easily detectable orange colour, with a colour intensity directly proportional to G6PD activity. Following a 2 hour incubation at room temperature, samples with normal G6PD

activity demonstrate a strong orange colour. Deficient samples can show a show faint orange colour which represents moderate deficiency or no colour which indicates severe deficiency.

Quantitative tests

Standard G6PD by SD Biosensor and the CareStart G6PD Biosensor by AccessBio are tests that provide a quantitative reading of G6PD activity.

The CareStart G6PD Biosensor consolidates a haemoglobin measurement device with a G6PD activity measurement device. The device consolidates a haemoglobin measurement device with a G6PD activity measurement device. This then calculates the G6PD activity normalized for haemoglobin concentration based on the two measurements. Requires 5 µL of whole blood for G6PD and 7 µL for Hb assessment (Bancone 2018). Results are presented in IU/gHb.

The Standard G6PD by SD Biosensor is designed to measure the quantitative concentration of total haemoglobin (g/dL) and G6PD enzymatic activity (IU/g Hb) in fresh human whole blood based on reflectometry assays. This requires 10 µL of capillary or venous blood. Results are presented in IU/gHb (Pal 2019).

The Standard G6PD test contains a flow through Standard G6PD test device treated membrane and mesh. The test is based on the colorimetric measuring and quantitative detection system for automatic calculation of the code chip on each test device. G6PD catalyzes the first step in the pentose phosphate pathway (PPP), oxidizing glucose-6-phosphate (G6P) to 6-phosphogluconolactone and reducing nicotinamide adenine dinucleotide phosphate (NADP) to reduced nicotinamide adenine dinucleotide phosphate (NADPH). When NADPH is generated by the Standard G6PD Test, 5-bromo-4-chloro-3-indolyl-phosphate (BCIP) and nitro blue tetrazolium (NBT) are reduced by the diaphorase reaction and then yield a violet colour, which is directly proportional to the concentration of G6PD present in the specimens. The colour intensity can be measured numerically by checking the specific absorbance of the reduced BCIP and NBT, and the test result is displayed on the Standard G6PD Analyzer's screen by processing the pre-programmed algorithm.

Appendix 2. Ovid MEDLINE search strategy

Database: Ovid MEDLINE and In-Process & Other Non-Indexed Citations <1946 to present

1 exp Glucosephosphate Dehydrogenase Deficiency/

2 ((glucose-6-phosphate-dehydrogenas* or glucose-phosphate-dehydrogenas* or G6PD or G-6-P-D or G-6-PD or GPD) adj3 (deficien* or lack)).tw. (4388)

3 (Glucosephosphate Dehydrogenase/ or (glucose-6-phosphate-dehydrogenas* or glucose-phosphate-dehydrogenas* or G6PD or G-6-P-D or G-6-PD or GPD).mp.) adj3 ((malaria* or Plasmodium or ovale or anemia or anaemia or hemolysis or antimalaria* or primaquine or tafenoquine).mp. or (Anemia, Sickle Cell/ or Sickle Cell Trait/))

4 1 or 2 or 3

5 qualitative test*.tw.

6 (fluorescent spot test* or FST).tw.

7 (diagnos* adj3 (assay* or test*)).tw,kf.

8 rapid diagnostic test*.tw,kf.

9 RDT*.tw,kf.

10 CareStart*.tw,kf.

11 BinaxNOW*.tw,kf.

12 exp Reagent Kits, Diagnostic/

13 G6PD-test*.tw,kf.

14 *Point-of-Care Systems/

15 *Point-of-Care Testing/

16 Diagnostic Tests, Routine/

17 *Clinical Chemistry Tests/

18 Clinical Enzyme Tests/

19 point of care.tw.

20 Histocytochemistry/

21 Histocytochemistry.tw.

22 Spectrophotometry/

23 spectrophotometr*.tw.

24 Sequence Analysis, DNA/

25 DNA sequenc*.tw.

26 Polymerase Chain Reaction/

27 ("Polymerase Chain Reaction" or PCR).tw.

28 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

or 23 or 24 or 25 or 26 or 27

29 4 and 28

This is the preliminary search strategy for MEDLINE (OVID). It will be adapted for other electronic databases. All search strategies will be reported in full in the final version of the review.

HISTORY

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CONTRIBUTIONS OF AUTHORS

JP and SP wrote the section on background and justification, PW, EO, MR, and GB collaborated in determination of methods and data analysis.

All author read and approved the final protocol version.

DECLARATIONS OF INTEREST

PV has no known conflicts of interest.

GB has authored and co-authored a number of manuscripts that will be probably used in the G6PD DTA review. The manuscripts were the results of diagnostic tests validation studies supported by PATH. GB does not have an affiliation with companies producing G6PD diagnostic tests.

EAO has no known conflicts of interest.

SP has no known conflicts of interest.

JT has no known conflicts of interest.

MC has no known conflicts of interest.

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