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Contextual factors and G6PD diagnostic testing: a scoping review and evidence and gap map

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Abstract

Background Testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency is an important consideration regarding treatment for malaria. G6PD deficiency may lead to haemolytic anaemia during malaria treatment and, therefore, determining G6PD deficiency in malaria treatment strategies is extremely important.

Methods This report presents the results of a scoping review and evidence and gap map for consideration by the Guideline Development Group for G6PD near patient tests to support radical cure of *Plasmodium vivax*. This scoping review has investigated common diagnostic tests for G6PD deficiency and important contextual and additional factors for decision-making. These factors include six of the considerations recommended by the World Health Organization (WHO) handbook for guideline development as important to determining the direction and strength of a recommendation, and included 'acceptability', 'feasibility,''equity,''valuation of outcomes,''gender' and 'human rights'. The aim of this scoping review is to inform the direction of future systematic reviews and evidence syntheses, which can then better inform the development of WHO recommendations regarding the use of G6PD deficiency testing as part of malaria treatment strategies.

Results A comprehensive search was performed, including published, peer-reviewed literature for any article, of any study design and methodology that investigated G6PD diagnostic tests and the factors of 'acceptability', 'feasibility,''equity,''valuation of outcomes,''gender' and 'human rights'. There were 1152 studies identified from the search, of which 14 were determined to be eligible for inclusion into this review. The studies contained data from over 21 unique countries that had considered G6PD diagnostic testing as part of a malaria treatment strategy. The relationship between contextual and additional factors, diagnostic tests for G6PD deficiency and study methodology is presented in an overall evidence and gap, which showed that majority of the evidence was for the contextual factors for diagnostic tests, and the 'Standard G6PD (SD Biosensor)' test.

Conclusions This scoping review has produced a dynamic evidence and gap map that is reactive to emerging evidence within the field of G6PD diagnostic testing. The evidence and gap map has provided a comprehensive depiction of all the available literature that address the contextual and additional factors important for decision-making, regarding specific G6PD diagnostic tests. The majority of data available investigating the contextual factors of interest relates to quantitative G6PD diagnostic tests. While a formal qualitative synthesis of this data as part of a systematic review is possible, the data may be too heterogenous for this to be appropriate. These results can now be used

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to inform future direction of WHO Guideline Development Groups for G6PD near patient tests to support radical cure of *P. vivax* malaria.

Keywords Malaria, G6PD, Contextual factors, Scoping review, Evidence, Gaps, Mapping

Background

Testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency is an important consideration in treatment for malaria. G6PD is an enzyme involved in the maintenance, stability and integrity of red blood cells (RBCs), where it serves to protect against oxidative stress [1, 2].G6PD deficiency is an X-chromosomally transmitted disorder of RBCs, that often occurs in areas where malaria is or has been endemic [1]. G6PD deficiency causes RBCs to become susceptible to reactive oxygen species (such as hydrogen peroxide) leading to haemolytic anaemia and many other important healthcare concerns [1]. Most G6PD deficient individuals are asymptomatic [2], however G6PD deficiency can manifest clinically in three forms: (i) neonatal jaundice; (ii) rarely chronic non-spherocytic haemolytic anaemia (CNSHA) and, more commonly, as iii) acute haemolytic anaemia (AHA) triggered by fava beans, infection, or drugs (such as the 8- aminoquinolines, primaquine and tafenoquine) [1, 3]. The relationship between G6PD deficiency and primaquine is critically important in the context of treatment strategies for malaria, as primaquine is a commonly used anti-malarial for anti-relapse therapy of *Plasmodium vivax* malaria.

G6PD testing plays a critical role in strategies for the treatment of vivax malaria. Treatment strategies need to facilitate the appropriate identification of individuals with G6PD deficiency. Identification of G6PD deficiency can be achieved using a range of different diagnostic criteria and tests, the gold standards typically being quantitative tests that measure the total haemoglobin and G6PD enzymatic activity in fresh human blood. Appropriate identification of G6PD deficiency will enable healthcare providers to tailor treatment plans using appropriate anti-malarial medications at patient-specific dosages to minimize the risk of haemolytic reactions. By providing this patient-specific care, providers can ensure that malaria treatment strategies remain safe and efficient. The World Health Organization (WHO) Global Malaria Programme (GMP) is responsible for coordinating the global efforts to control, prevent and eliminate malaria. A key component of this service involves the development of guidelines and recommendations for G6PD testing.

As stipulated in the WHO handbook for guideline development [4], the WHO guideline development process requires Guideline Development Groups (GDGs) to consider eight factors that determine the direction and strength of a recommendation [4]. The first considerations include the certainty of the evidence and the trade-off between benefits (epidemiological impact) and harms, as determined through systematic review and synthesis of evidence for appropriately selected, patient-important outcomes [5]. The certainty of the evidence and this trade-off should then be balanced with other factors that are important for decision-making. These factors include; resource implications (is the intervention cost-effective?), priority (is the problem a priority as determined by its importance and frequency?), equity (will the intervention reduce or increase health inequities?), feasibility (is the intervention feasible to implement?), acceptability (is the intervention acceptable to key stakeholders?), and valuation of the outcomes (are the health outcomes considered important by key stakeholders?) [4–6]. These factors should all be judiciously considered by a GDG in the development of each recommendation for or against an intervention that appears throughout a WHO guideline.

Ideally, a GDG would be well-informed of each of the factors listed above, with the synthesized evidence from a rigorous systematic review or at least high quality primary studies relevant to the population of interest being preferential [6]. However, this is rarely observed in practice, possibly due to the scarcity of systematic reviews available regarding these specific contextual factors and interventions of interest to guideline panels. There has been a concerted effort by the WHO GMP to develop guidelines on G6PD tests using systematically collected evidence regarding the contextual factors of acceptability, feasibility, and valuation of the outcomes, in addition to other factors important for decision making such as gender, equity and human rights. To-date however, a comprehensive mapping of the evidence regarding these six contextual factors has yet to occur.

This report details the conduct of a scoping review and an evidence and gap map, produced in order to provide the WHO with an overview of the amount and type of studies available that address the six factors listed above. The factor of 'priority' is often informed by studies or datasets reporting the prevalence/burden of disease and is often known prior to guideline development and given the considerations associated with the factor of 'resource implications' (e.g. costs, resources, cost-effectiveness) are specific to the site/study/time-point under investigation, both of these factors were omitted from this review.

The results of this scoping review will enable the WHO GMP to consider how much evidence exists for the contextual factors of 'feasibility', 'acceptability', 'equity' and 'valuation of the outcome' for G6PD deficiency testing, as well as the additional factors of 'gender' and 'human rights' and whether to commission future, targeted systematic reviews or primary studies in these areas.

Objectives

Main objectives

1. To systematically search the literature for all studies that addressed the contextual factors of 'feasibility', 'acceptability', 'equity' and 'valuation of the outcome' or the additional factors of 'gender' and 'human rights' relating to the use of diagnostic tests used for G6PD deficiency testing in the context of malaria treatment.
2. To produce an evidence and gap map, that details the number and type of studies that are available in the literature providing data regarding a contextual factor or additional factor of interest, and a specific diagnostic test used for G6PD deficiency testing, in the context of malaria treatment.

Review question

What evidence exists regarding the 'feasibility', 'acceptability', 'equity' and 'valuation of the outcome' regarding diagnostic tests used for G6PD deficiency testing to inform treatment of malaria, and what considerations have been made regarding 'gender' and 'human rights'?

Methods

This scoping review was conducted in accordance with the JBI methodology for scoping reviews [7, 8]. It has been reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension for scoping reviews (PRISMA-ScR)[9]. The evidence-gap map has been constructed following the guidance from the Campbell Collaboration [10] and has been presented both as a static image below (Fig. 1) and as a dynamic webpage, through the EppiReviewer and EppiMapper software [11]. This review is appropriate to be conducted as a scoping review, as it aligns to the indication to examine key characteristics or factors related to a concept and to identify the type of available evidence in a given field [12]. An a priori protocol for this work was developed prior to conducting this work.

Eligibility criteria

Eligibility criteria has been presented according to the PCC (population, concept, context) question framework suggested for use for scoping reviews [7, 8].

Participants

Studies were eligible for inclusion in this review where they investigated the concepts of this scoping review (as outlined below) in adults and children who are residents of a region with ongoing malaria transmission and/or investigated the concepts of this scoping review in relation to deliverers of G6PD tests (e.g., clinicians, technicians, and other stakeholders).

Concepts

There were two 'concepts' in which studies needed to have investigated to be eligible for inclusion in this review. Studies needed to assess both a "contextual factor" and a "G6PD diagnostic test", which are both further defined below.

Contextual factors

Studies were eligible for inclusion in this scoping review where they provided data regarding the contextual factors of feasibility, acceptability, equity, and valuation of the outcome (defined above) or the additional factors of 'gender' and 'human rights'. These contextual and additional factors were considered in relation to diagnostic tests for G6PD, detailed below.

G6PD diagnostic tests

Studies were eligible for this review where they have investigated the below G6PD tests, as informed by a Cochrane review on these tests [13].

Quantitative tests

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

Semi-quantitative test

- Fluorescent Spot Test

Qualitative tests

- G6PD Qualitative FST
- CareStart G6PD
- BinaxNOW G6PD

Fig. 1 Evidence and gap map for G6PD diagnostic tests and contextual/additional factors of interest, according to the methodology that the study employed

- WST8/1-methoxy PMS assay

The Cochrane review on this topic excluded the following tests, which will also be excluded as part of this review.

- The brilliant cresyl blue decolouration test
- The methaemoglobin reduction test
- The formazan ring method
- The ephadex gel MTT-PMS method from the review.

Context

This scoping review only considered the above concepts if they were investigated as part of, or alongside G6PD testing to inform malaria treatment. Where these tests have been used for other purposes, these studies were not considered eligible. Finally, the contextual factors related to other interventions utilized for malaria prevention or treatment (e.g. vaccination, education programmes) were also not considered, only studies that have provided data regarding G6PD tests were eligible for this review.

Types of documents

This scoping review only considered peer-reviewed research articles. Due to the nature of contextual factors research, studies may utilize diverse methods in their data collection and no restriction was placed on the types of studies considered eligible. There were no exclusions based on language or publication status (i.e., published, unpublished, in press, in progress, pre-print). There were no limitations to the date when studies were conducted or published. Conference abstracts with no associated full text and expert opinion or letters to the editor were excluded from this review.

Search strategy

The search strategy aimed to locate both published and unpublished studies and was developed with the input of a medical librarian. An initial limited search of PubMed via NCBI was undertaken to identify relevant articles on this topic. The terminology contained in the titles and abstracts of relevant articles, including related subject headings, were used to develop a full search strategy. The search strategy, including all identified keywords and subject headings, was adapted for each included database and/or information source, by using Polyglot [14]. The databases searched included PubMed (NCBI [contains MEDLINE]), Embase (Elsevier), Cochrane Database of Systematic Reviews (CDSR; Wiley), Scopus (Elsevier) and WHO Global Index Medicus. The search strategies for each database were then peer-reviewed using the Peer Review of Electronic Search Strategies Guideline Statement [1]. The full search strategy has been made available as Appendix 1.

Study selection and screening

Following the search, all identified records were collated and uploaded into EndNote™ [15]. Duplicates were removed via the 'Deduplicator' software, available from the Systematic Review Accelerator [16]. Records were imported into Covidence [17] screened on their titles and abstracts by two independent screeners (THB and GMM) for assessment against the eligibility criteria for the review. Any disagreements that arose between the screeners at any stage of the selection process were resolved through discussion. Potentially relevant records were then exported from Covidence, where the full text of each record was retrieved and then imported into EppiReviewer [11]. The full text of each relevant record was then assessed in detail against the eligibility criteria by the same two independent screeners (THB and GMM), and conflicts were managed in the previously described manner. For reports that did not meet the eligibility criteria after being screened in full, the reasons for their exclusion have been documented and reported as Appendix 2. Reasons for exclusion at the full text included the following:

- Conference abstract with no associated full text
- Expert opinion or letter to the editor
- Not G6PD diagnostic test
- Not contextual factor of interest

The results of the search and screening process have been reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020) flow diagram [18].

Translations

For studies published in languages other than English that were included for eligibility assessment at the full-text level, Deep L [19] and/or Google Translate was used to determine whether the study met eligibility criteria. Google Translate has recently demonstrated increased fidelity as a tool for translating research articles into English for the purposes of abstracting data for systematic reviews [20]. Where studies were published in a language other than English that met the eligibility criteria, translations were to be reviewed by a person fluent in the language. However, no study that required translation were included in this review.

Data extraction and coding

All studies that met eligibility criteria following screening at the full text level underwent data extraction within EppiReviewer. Data was extracted from all eligible studies by two independent reviewers (THB and GMM) and any discrepancies were resolved through discussion. A data dictionary of terms was produced and was iteratively updated to guide extractors during this process, this data dictionary has been provided as Appendix 3 and provides detailed context as to the definitions used to categorize each item during the coding. The data was extracted according to the demographic characteristics of the study itself and include the following items:

- Author names
- Year of publication
- Country in which the study took place

Following this, the studies were then coded within EppiReviewer. Each study was 'coded' where they were considered to be relevant to the below criteria, as presented in the coding framework. For example, a study

that employed either questionnaires/surveys, and investigated the Standard G6PD test by SD Biosensor on Acceptability for the public, would be coded as: [1. Standard G6PD by SD Biosensor; 2. Acceptability—The public; 3. Questionnaires/surveys (both closed and open-ended)]. This framework was structured to generate the evidence and gap map (described below).

1. *G6PD test used*

- Standard G6PD by SD Biosensor
- CareStart G6PD Biosensor by AccessBio
- Fluorescent Spot Test
- G6PD Qualitative FST
- CareStart G6PD (Qualitative)
- BinaxNOW G6PD
- WST8/1-methoxy PMS assay

2. *Contextual and additional factors*

- Acceptability (of the intervention(s) of interest) from the perspective of:

o The public
o The deliverer

- Feasibility (of the intervention(s) of interest) from the perspective of:

o The public
o The deliverer

- Equity
- Valuation of the outcomes of interest
- Gender
- Human rights

3. *Study methods*

- Experimental studies
- Observational studies
- Utility/health status value studies
- Questionnaires/surveys (both closed and open-ended)
- Focus groups/interviews
- Evidence reviews

Data analysis and presentation

All extracted data have been presented as frequency counts in column graphs. The data has also been narratively synthesized according to the following:

- When and where these studies were conducted.
- What tests for G6PD deficiency were investigated.
- What contextual factors were investigated.
- What where the types and methods of the bodies of evidence identified.

Evidence and gap map

The results of the study coding have been presented as an evidence and gap map developed using the EppiMapper software [21]. The map has been organized according to the data coding hierarchy as presented above. The map will be presented as both a static image as well as a dynamic, filterable and interactive HTML file.

Ethics and dissemination

The search conducted for the scoping review does not require ethics approval as it is a review of primary studies. No identified individual level participant data was collected.

Results

Results of the search

The systematic search was performed on August 25th, 2023, across the databases specified above. The results of the entire search strategy have been provided as Appendix 1. There were 1524 records identified as part of these searches. Of these, 372 were identified as duplicate records leaving 1152 available for screening at the title and abstract level (Fig. 2). There were 1106 records identified as irrelevant following screening at the title and abstract level, leaving 46 reports to be screened at the full-text level. Of these, 5 reports were irretrievable and subsequently not assessed for eligibility, the citation details for these reports have been provided as Appendix 4.

Of the 41 reports remaining to be assessed for eligibility, three were duplicate reports of the same study and were merged into the single unit [22–24]. This left 39 individual reports to be screened at the full text level. Of these, five were required to be translated, two in Portuguese [25, 26], one in Thai [27], one in French [28] and one in Spanish [29]. All of these studies that required translation were excluded from the study for not meeting the eligibility criteria following translation.

Of the 39 reports screened at the full text level, 14 individual studies met the inclusion criteria and have been included in the scoping review and evidence and gap map. There were 25 excluded with their reasons for exclusion detailed in Appendix 2. Finally, one included study was provided to the review team following direct correspondence [30]. The entire study selection process

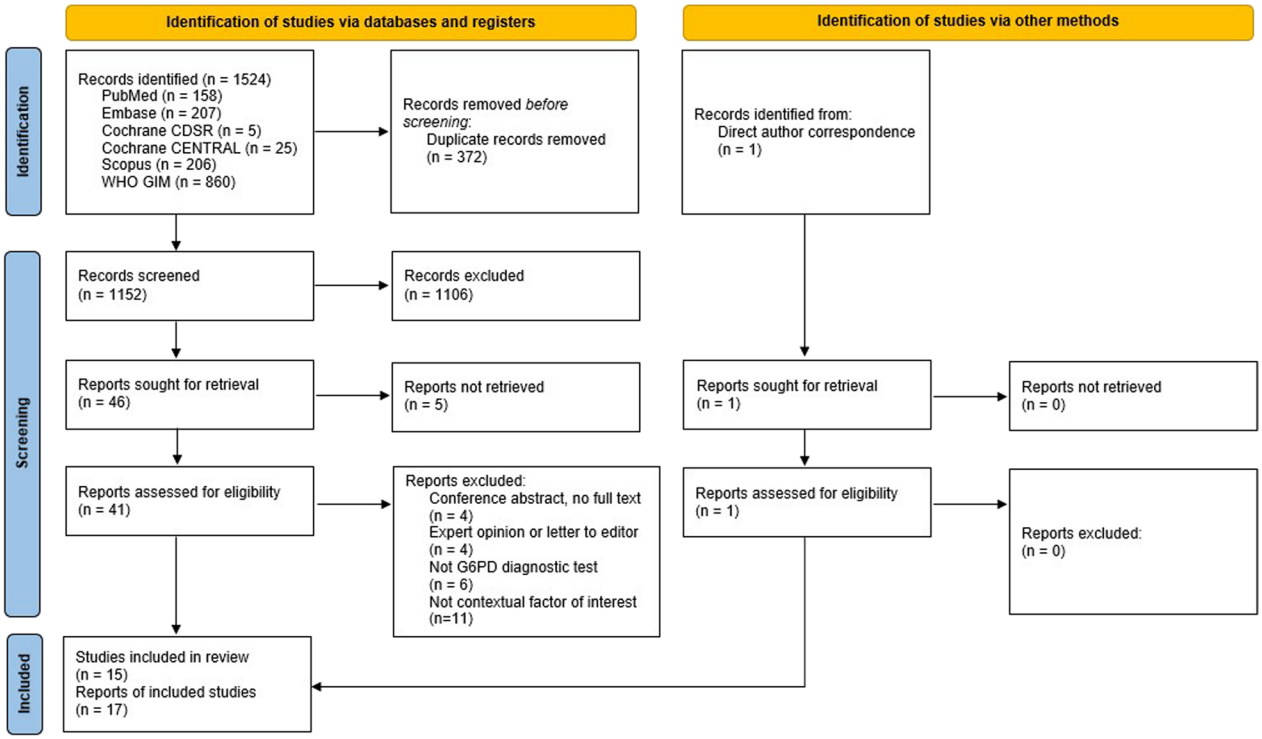

Fig. 2 PRISMA 2020 flow diagram

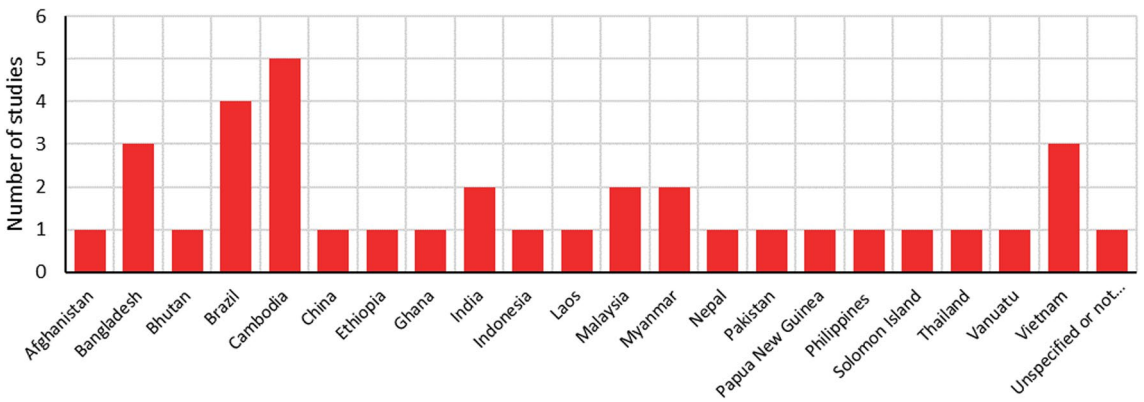

Fig. 3 Number of studies that provided data related to a G6PD test and a contextual factor or additional factor of interest, according to the studies country of origin

has been summarized in the PRISMA flow diagram (Fig. 1).

Characteristics of the included studies.

Study design, country of origin and time period

Of the 15 studies [23, 31–43] included in this review, data was available from 21 different countries (Fig. 3). It is worthwhile to note that three studies [31, 37, 41] provided data from multiple different countries, and one study did not specify what country their data has been sourced from [35]. Cambodia was the most represented country, with five studies [23, 31, 32, 39, 41] providing data. Bangladesh [31, 36, 41], Brazil [33, 34, 37] and Vietnam were the next most represented countries [31, 38, 42] with three studies each providing data. India [31, 37], Malaysia [31, 41] and Myanmar [31, 43] were the remaining countries represented by more than one study, with the remaining countries only being represented by a single included study. Most of these studies were published recently, with only three studies [35, 41, 43] published

before 2020, two published in 2020 [23, 40], five published in 2021 [31, 34, 36, 37, 42], three published in 2022 [32, 33, 39] and only one study published in 2023 [38].

Contextual factors and additional factors assessed

Acceptability, feasibility, and valuation of the outcomes were the most prominent contextual factors assessed in the included studies. Acceptability and feasibility were assessed from different perspectives, being that of the public (i.e., the persons in which the G6PD diagnostic test is being administered) and that of the deliver (i.e., a person involved in the delivery or management of the G6PD diagnostic test being administered). Of these levels, most studies preferentially provided data regarding the deliverer, with 12 studies providing feasibility data [23, 30–32, 34, 36–39, 41–43] and 10 studies providing acceptability data for deliverers of the G6PD diagnostic test [23, 31–34, 36, 38, 39, 41, 42]. Fewer studies provided data related to the public, with only six studies [33–35, 38, 39, 42] providing data regarding acceptability of the public, and even fewer [35, 39, 40] providing data regarding feasibility of the public. Ten included studies that provided data for the contextual factor of valuation of the outcomes [23, 31–34, 36, 38, 39, 41, 42] and four provided data for the contextual factor of equity [32, 36, 40, 41]. The additional factors considered were only reported sparingly in the literature, with only four studies providing data regarding gender [23, 30, 35, 39] and no studies were included that provided data regarding human rights (Fig. 4).

Diagnostic tests for G6PD deficiency assessed

There were six included studies that provided data regarding the 'Standard G6PD (SD Biosensor)' diagnostic test (Fig. 5) [30, 32, 36–39] while only one study provided data regarding the 'CareStart G6PD Biosensor (AccessBio)' diagnostic test [39]. Only one study reported on the semi-quantitative 'Fluorescent Spot Test' [43], and the qualitative 'G6PD Qualitative FST' [34], and three studies provided data regarding the qualitative 'CareStart G6PD (Qualitative)' diagnostic test [23, 39, 43]. There were no included studies that provided data toward the qualitative 'BinaxNOW G6PD' or the 'WST8/1-methoxy PMS assay' tests. Finally, five studies provided data but did not specify what diagnostic test for G6PD deficiency was under investigation, or the results were broader and were generalized to multiple G6PD deficiency testing methods [31, 35, 40–42].

Only two studies provided data for more than one diagnostic test for G6PD deficiency [39, 43]. Kheang et al.[39] provided data for both the 'Standard G6PD (SD Biosensor)' and the 'CareStart G6PD Biosensor (AccessBio)' quantitative tests as well as data regarding the qualitative 'CareStart G6PD (Qualitative)' diagnostic test. Oo et al. [43] provided data for the semi-quantitative 'Fluorescent Spot Test' and the 'CareStart G6PD (Qualitative)' test.

Study methodology employed

There were a variety of methodologies employed by the included studies, with five studies [32–34, 39, 42] employing multiple different methodologies to collect diverse forms of data. Adhikari et al. [32] employed both close-ended and

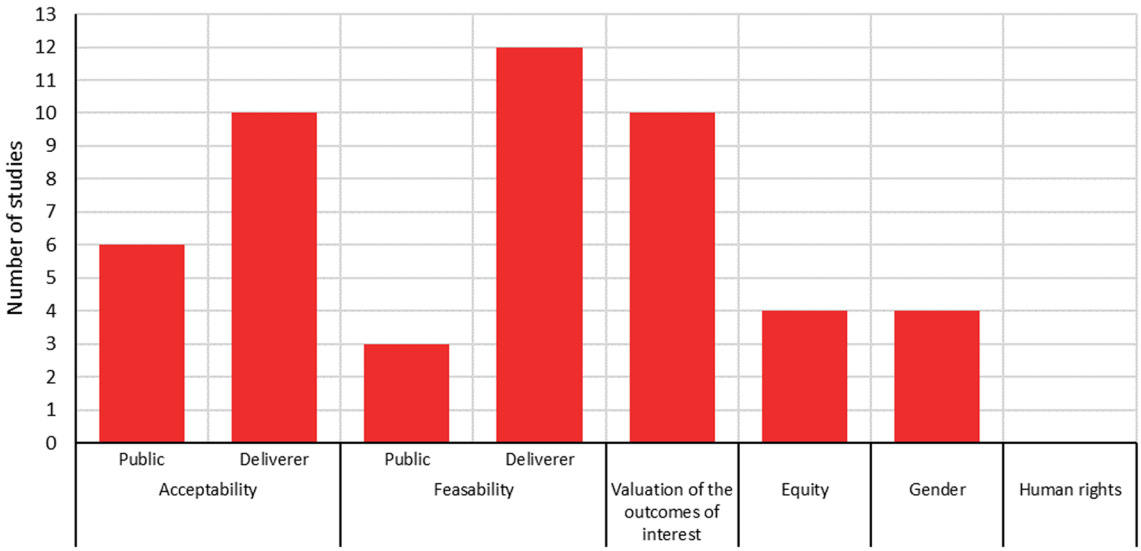

Fig. 4 Number of studies that provided data for a specific contextual factor or additional factor of interest

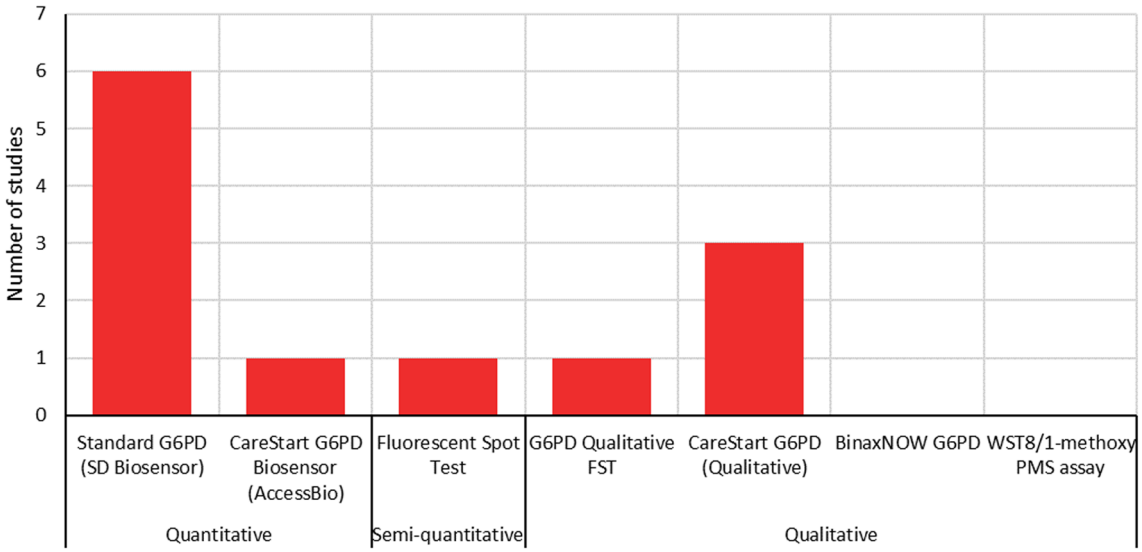

Fig. 5 Number of studies that provided data for a specific diagnostic test for G6PD deficiency

open-ended questionnaires/surveys in addition to 1-on-1 interviews. Both studies authored by Brito-Sousa et al. [33, 34] utilized an experimental study design in addition to focus groups and interviews, and Kheang et al. [39] similarly employed both focus groups and interviews but coupled these with observational study methods. Only one study [42] utilized more than two different study methods to collect their data. Nguyen et al. [42] employed observational study methods in addition to both open-ended and close-ended questionnaires/surveys as well as both focus groups and interviews. Overall, of the included studies three were experimental studies or utilized experimental methodology [33, 34, 43], four were observational studies or utilized observational methodology [30, 39, 40, 42], four studies utilized questionnaires/surveys (both closed and open-ended) [23, 32, 37, 42], nine studies utilized focus groups and/or interviews [31–34, 36, 38, 39, 41, 42], and one study was considered an evidence review, specifically a literature review [35]. None of the included studies were coded as being a utility/health status value study.

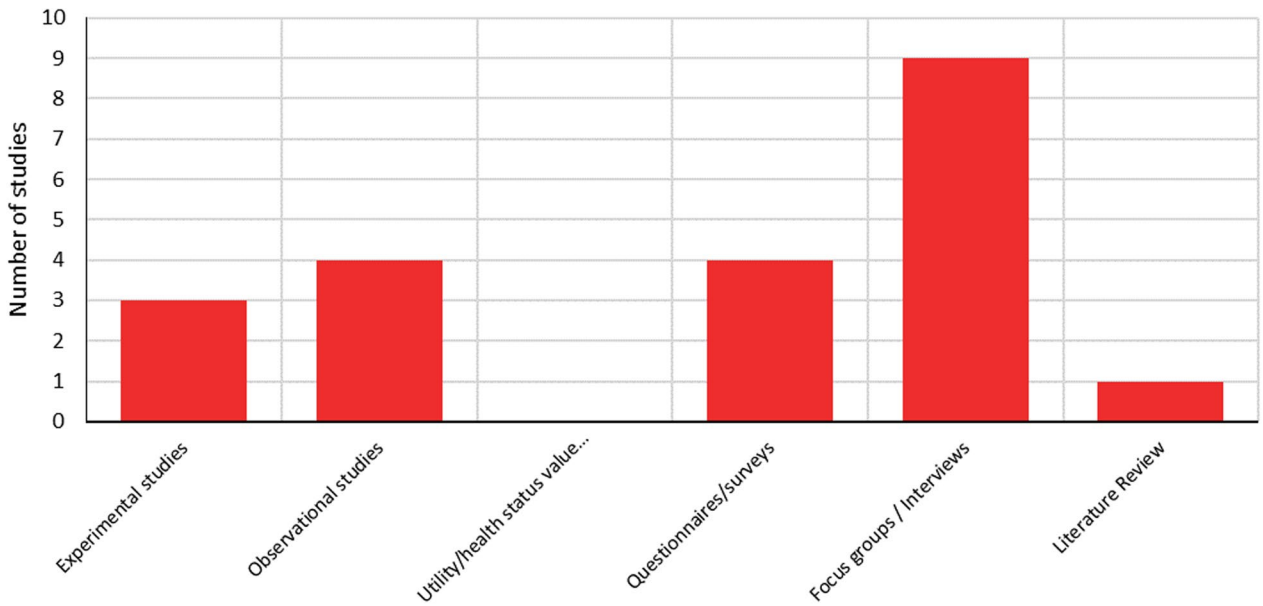

Fig. 6 Number of studies according to the study methodology they employed to collect their data

Of the four studies that utilized questionnaires/surveys two studies utilized only close-ended questions [23, 37] and two used a combination of both closed- and open-ended questions in their design [32, 42]. No study utilized only open-ended questions when employing questionnaires or surveys (Fig. 6).

Of the nine studies that utilized focus groups and/or interviews three studies [31, 32, 41] only utilized 1-on-1 interviews and the remaining six studies [33, 34, 36, 38, 39, 42] utilized a combination of both focus groups and interviews. No included study employed only the use of focus groups (Fig. 7).

Evidence and gap map

The relationship between contextual and additional factors, diagnostic tests for G6PD deficiency and study methodology is presented in the overall evidence and gap map (Fig. 1). This evidence and gap map also exists as a dynamic, filterable, and interactive HTML file.

Overall, the evidence and gap map clearly indicates that the majority of evidence regarding contextual factors for diagnostic tests for G6PD deficiency testing exists for the quantitative 'Standard G6PD (SD Biosensor)' test. Of this evidence, data is available, collected via multiple different methods regarding each contextual or additional factor except for human rights (which no data was available for any diagnostic test). The map also shows that data exists, collected from various methods, regarding all contextual factors of interest (sans human rights) that are applicable across any G6PD diagnostic test, or are applicable to G6PD diagnostic testing as a general consideration in the context of malaria treatment.

Less data is available for the qualitative 'G6PD qualitative FST' and 'CareStart G6PD (Qualitative)' diagnostic tests. However, where they were available, most of the contextual factors were of interest were considered, except for equity and human rights, and in the additional case for the 'G6PD qualitative FST', feasibility to the public and gender. The semi-quantitative 'Fluorescent Spot Test' was only the subject of one included study, in which the contextual factors of interest assessed were related to the feasibility of the deliverer. There were no studies identified that reported data for contextual or additional factors related to the qualitative 'BinaxNOW G6PD' or 'EST8/1-methoxy PMS assay' and there were no studies identified that investigated the additional factor of human rights. A summary of the characteristics of each individual, included study has been provided as Table 1, and the main findings for the studies that provided data regarding the quantitative 'Standard G6PD (SD Biosensor)' diagnostic test have been summarized in the following section.

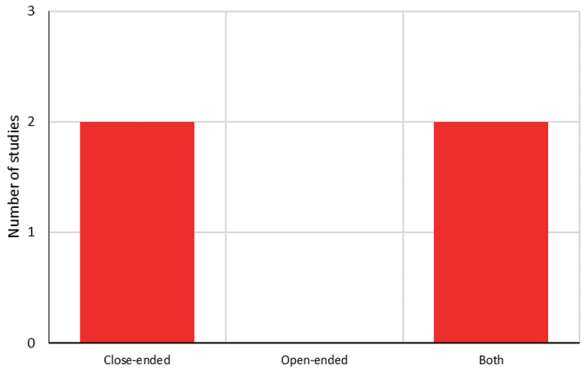

Fig. 7 Number of questionnaires or surveys that employed close- or open-ended questions

Standard G6PD by SD Biosensor.

Acceptability

Public Brito-Sousa et al. [33] performed a mixed-methods study evaluating the operational aspects of the diagnostic test. Patients were provided with a malaria card that included information regarding G6PD status. While many patients approved of the card in general, the G6PD results section received little or no attention.

Gerth-Guyette et al. [38] performed key informant interviews and focus groups discussions with patients. All patients expressed reluctance to go to the district health centres for G6PD testing, however this was primarily associated with the time required to travel.

Kheang et al. [39] have provided data regarding both quantitative diagnostic tests but have not separated these tests in their analysis. Following key informant interviews and focus group discussions, the care pathway was widely perceived as very beneficial and manageable. Although attending sessions and some follow-up was difficult for some patients due to considerations around travel, patients were highly motivated to receive testing. Treated patients encouraged peers to participate in diagnostic testing (Fig. 8).

Deliverer

Adhikari et al. [32] conducted semi-structured interviews with village malaria and mobile malaria workers. These workers reported enthusiasm about using the diagnostic test and did not see the integration of the test into their routine work as an additional burden.

Brito-Sousa et al. [33] found that despite the extensive and repeated training, some healthcare providers (HCPs) felt that implementation of the G6PD test could be challenging, and these challenges resulted in some HCPs leaving the training.

Engel et al. [36] performed semi-structured interviews and focus-group discussions of laboratory personnel,

Table 1 Summary characteristics of included studies

Author (year published)	Country of origin	G6PD diagnostic tests assessed	Contextual / additional factors assessed	Methods
Adhikari (2021)	Afghanistan Bangladesh Bhutan Cambodia India Indonesia Laos Malaysia Myanmar Nepal Pakistan Papua New Guinea Philippines Solomon Island Thailand Vanuatu Vietnam	Unspecified and/or can be applied to multiple tests	Acceptability—Public Feasibility—Deliverer Valuation of the outcomes of interest	Interviews
Adhikari (2022)	Cambodia	Standard G6PD (SD Biosensor)	Acceptability—Deliverer Feasibility—Deliverer Valuation of the outcomes of interest Gender	Open-ended questionnaire/ surveys Close-ended questionnaire/ surveys Interviews
Brito (2023) [Submitted for publication]	Brazil	Standard G6PD (SD Biosensor)	Feasibility—Deliverer Gender	Observational studies
Brito-Sousa (2021)	Brazil	G6PD Qualitative FST	Acceptability—Public Acceptability—Deliverer Feasibility—Deliverer Valuation of the outcomes of interest	Experimental studies Focus groups Interviews
Brito-Sousa (2022)	Brazil	Standard G6PD (SD Biosensor)	Acceptability—Public Acceptability—Deliverer Valuation of the outcomes of interest	Experimental studies Focus groups Interviews
Domingo (2019)	Unspecified or not applicable	Unspecified and/or can be applied to multiple tests	Acceptability—Public Feasibility—Public Gender	Literature review
Engel (2021)	Bangladesh	Standard G6PD (SD Biosensor)	Acceptability—Deliverer Feasibility—Deliverer Valuation of the outcomes of interest Equity	Focus groups Interviews
Gerth-Guyette (2021)	Brazil Ethiopia India	Standard G6PD (SD Biosensor)	Feasibility—Deliverer	Close-ended questionnaire/ surveys
Gerth Guyette (2023)	Vietnam	Standard G6PD (SD Biosensor)	Acceptability—Public Acceptability—Deliverer Feasibility—Deliverer Valuation of the outcomes of interest	Focus groups Interviews
Kheang (2022)	Cambodia	Standard G6PD (SD Biosensor) Carestart G6PD Biosensor (AccessBio) CareStart G6PD (Qualitative)	Acceptability—Public Acceptability—Deliverer Feasibility—Public Feasibility—Deliverer Valuation of the outcomes of interest Gender	Observational studies Focus groups Interviews
Kuupiel (2020)	Ghana	Unspecified and/or can be applied to multiple tests	Feasibility—Public Equity	Observational studies

Table 1 (continued)

Author (year published)	Country of origin	G6PD diagnostic tests assessed	Contextual / additional factors assessed	Methods
Ley (2017)	Bangladesh Cambodia China Malaysia	Unspecified and/or can be applied to multiple tests	Acceptability—Deliverer Feasibility—Deliverer Valuation of the outcomes of interest Equity	Interviews
Nguyen (2021)	Vietnam	Unspecified and/or can be applied to multiple tests	Acceptability—Public Acceptability—Deliverer Feasibility—Deliverer Valuation of the outcomes of interest	Observational studies Open-ended questionnaire/ surveys Close-ended questionnaire/ surveys Focus groups Interviews
Oo (2016)	Myanmar	Fluorescent Spot Test CareStart G6PD (Qualitative)	Feasibility—Deliverer	Experimental studies
Wojnarski (2020)	Cambodia	CareStart G6PD (Qualitative)	Acceptability—Deliverer Feasibility—Deliverer Valuation of the outcomes of interest Gender	Close-ended questionnaire/ surveys

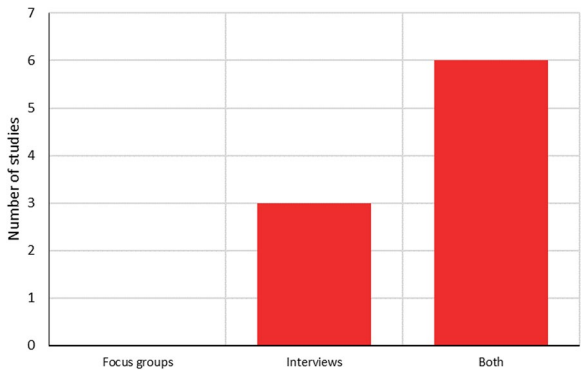

Fig. 8 Number of studies that employed focus groups, 1-on-1 interviews, or both in their design

doctors, nurses and 'decision-makers'. The laboratory personnel appreciated the usefulness of the results of the test, however expressed concerns compared to qualitative tests, which required fewer 'steps' to utilize appropriately.

Gerth-Guyette et al. [38] reported that following key informant interviews and focus group discussions, the overall willingness to use the diagnostic tests from HCPs was high.

Kheang et al. [39] discuss that when asked through key informant interviews and focus group discussions, healthcare staff were willing, where possible to monitor the use of G6PD tests. Overall, staff preferred quantitative tests over qualitative tests. It was noted these tests could present ambiguous results that were difficult to interpret and were inadequate for females.

Feasibility

Public Kheang et al. [39] have reported that some patients found that travelling to attend a session was difficult.

Deliverer

Adhikari et al. [32] have described that workers reported constraints related to the use of the test, including the use of two pipettes, poor visibility of black lines, hole was too small in the test, insertion of chip code being difficult, among others.

Brito et al. [30] have performed a retrospective review of patient data, to investigate whether *P. vivax* patients were treated appropriately following G6PD diagnostic testing. The authors report that 99.7% of patients were treated appropriately in accordance with their G6PD activity. The authors conclude that G6PD testing is necessary before 8-aminoquinoline administration for *P. vivax* radical cure.

Engel et al. [36] reported that laboratory personnel interviewed were concerned over potential misuse of the test, with some participants reporting the test to be 'fiddly'. There were also concerns raised over electricity interruptions, battery replacements, humidity, storage conditions, maintaining cold chains and temperature, and shelf life.

Gerth-Guyette et al. [37] conducted a multiple-choice questionnaire of malaria field supervisors, malaria field workers and malaria microscopists. The results indicated that the weakest point of user comprehension to the use of the diagnostic test was related to the appropriate

operating temperature in which the test can be utilized, with only half operating the device at the appropriate temperatures. However, the remaining questions regarding intended use and safety were answered correctly by more than 85% of participants.

Gerth-Guyette et al. [38] collected cost data throughout the intervention period to estimate the incremental financial costs to the National Institute of Malariology, Parasitology, and Entomology. Total commodity purchase cost for the diagnostic test was $18,089 (USD). HCP proficiency with the diagnostic test was also considered, with nearly all HCPs assessed (30/31) passing the proficiency test immediately following training on administration of the test. One HCP reported confusion in performing the diagnostic test, and some believed the test was difficult to perform.

Kheang et al. [39] reported that deliverers of the test noted that attendance, follow-up, and non-adherence served as barriers, and the use of mobile phones and tablets to track patients was well received. Some healthcare workers expressed concerns in other workers performing the tests correctly, due to a wide variation in skills, and a lack of reliable cold storage in villages.

Valuation of the outcomes of interest

Adhikari et al. [32] discussed that most workers expressed that the use of these diagnostic tests could aid in their routine responsibilities, particularly for *vivax* malaria management in their communities.

Brito-Sousa et al. [33] reported that many of the HCPs involved in the training to use the diagnostic test openly admitted to leaving the training, and did not understand why the test is done and would not be able to perform the test in the field.

Engel et al. [36] have provided data from laboratory technicians who expressed concerns that only a few patients are diagnosed with *vivax* malaria, with much of the burden concentrated in remote, border or conflict regions. This will complicate selecting the diagnostic testing sites and whether it is conducted.

Gerth-Guyette et al. [38] reported that following key informant interviews and focus group discussions, all HCPs agreed that the risks associated with G6PD deficiency should be prioritized in their facilities.

Kheang et al. [39] reported that the reasons for willingness of patients to get tested included the economic impacts of malaria infection and preventing relapse.

Gender

Brito et al. [30] reported G6PD deficiency prevalence was 7.0% in males and 7.7% in females.

Kheang et al. [39] discussed that healthcare staff reported that initially, only males were referred for G6PD testing and radical cure, then only after 5 months and additional training were females also included.

Equity

Adhikari et al. stated that some workers asked whether these "machines" can be deployed in health centres at the village or community level as some expressed that doing so may mitigate barriers that patients may have in seeking care at distant health centres or hospitals.

As above, Engel et al. [36] have provided data from laboratory technicians who expressed concerns that only a few patients are diagnosed with *vivax* malaria, with much of the burden concentrated in remote, border or conflict regions. This will complicate selecting the diagnostic testing sites and whether it is conducted.

Discussion

Summary of main findings

This scoping review has produced a dynamic evidence and gap map that demonstrates the evidence within the field of G6PD diagnostic testing. The evidence and gap map, in its current iteration as presented within this document, has provided a comprehensive depiction of all the available literature that address the contextual and additional factors important for decision making, regarding specific G6PD diagnostic tests, and G6PD diagnostic testing in general. The aim of this scoping review was to provide direction towards the most optimal route for the future synthesis of data regarding these contextual or additional factors, to better inform WHO guideline development groups in their decision-making. According to this scoping review and evidence and gap map, there appears to be sufficient evidence to perform formal systematic reviews regarding the standard G6PD (SD Biosensor) diagnostic test for most contextual factors of interest. A benefit of the evidence and gap map is that conducting a future systematic review on this topic can be achieved with comparative ease, as only updated searches need to be run, building on the studies already identified as part of this work.

In terms of the SD Biosensor test itself, the results above can be used almost immediately by guideline development groups to assist in their decision-making making for any recommendations that involve this test. However, it is worth noting, that additional methodological components may still be required (discussed below). In summary, the SD Biosensor test appeared to be largely acceptable to patients, however there were some acceptability and feasibility concerns identified related to the

need to travel to receive the test. Regarding the deliverer of the diagnostic test, acceptability appeared to be mixed and there were some feasibility concerns raised regarding the test design, storage of the test and conditions to operate the test appropriately. There is also inconclusive data regarding how users of the test (both patients and deliverer) valued the use of the test, and the intended outcome for a diagnosis regarding G6PD deficiency, with some individuals demonstrating they see the value, others not. Data regarding gender was sparse and inconclusive. The consideration of equity was made in relation to how this test can be performed in remote villages, and in areas that *vivax* malaria is most common. It is critical to note that these findings are derived from studies that have not been assessed for risk of bias and have not been formally synthesized together, these findings should be carefully considered and contextualized by a well-informed guideline panel.

As the primary data sources available for this diagnostic test involved focus groups, interviews, and questionnaires/surveys, the ideal systematic review for this data may likely be a systematic review of qualitative evidence [44]. However, while there may be sufficient evidence available to conduct these hypothetical reviews, there is likely to be substantial heterogeneity of the data. The included studies provided data from 21 different countries, with data from only seven countries available across more than one study and different methods for data collection including focus groups, interviews, and questionnaires/surveys.

Multiple included studies did not specify what G6PD diagnostic test they were investigating, and/or they specifically investigated any G6PD diagnostic test (i.e., asking stakeholder as to whether any G6PD testing should occur). The evidence and gap map appears to suggest that, for at least the contextual factors of acceptability and feasibility of the deliverer that a formal systematic review is similarly possible, following the methods described above.

Whilst the map identifies that multiple different methods were employed to collect data that addressed most of the contextual/additional factors of interest regarding the qualitative 'G6PD qualitative FST' and 'CareStart G6PD (Qualitative)' diagnostic tests, most of this data only came from a single study (for each test). The study of Brito-Sousa et al. [34] utilized both experimental methods as well as focus groups and interviews to collect their data and were the only study to provide data for the 'G6PD qualitative FST'. Similarly, while three studies provided data for the 'CareStart G6PD (Qualitative)' test the only contextual factors of interest in which these three studies all provided data was regarding feasibility of the deliverer. As one of these was an experimental study [43] and the others were observational studies that utilized questionnaires [23] or focus groups and interviews [39] it may not be appropriate to combine this data together in a formal synthesis.

The evidence and gap map has clearly indicated that significantly more primary research regarding both the semi-quantitative 'Fluorescent Spot Test' and all qualitative tests analysed is required before appropriate synthesis can occur. Similarly, only four individual studies [32, 36, 40, 41] provided data regarding the contextual factor of equity or the additional factor of human rights. Future research should likewise be directed that explicitly addresses these factors in relation to G6PD diagnostic testing. Finally, the evidence and gap map now exists in a dynamic format, where new evidence can be added to facilitate continued mapping (easily transitioning to a living mode if resources are available), which will better support the synthesis of this evidence that underpins the decision-making processes employed by WHO guideline development groups.

Limitations of the review process

This scoping review and evidence and gap map may be limited in its specificity to delineate the roles of a 'deliverer'. While some studies provided data from the perspective of healthcare professionals [32, 36, 38] other studies provided data from the perspective of policy makers and legislators [39]. As these nuances were not identified until after the coding process had begun, all of these studies have been coded and appear in the map as 'deliverers' when a more specific title may have been more appropriate.

As this was a scoping review, there has been no risk of bias assessment, or assessment of the methodological quality of the included studies. While this process falls outside the remit of a scoping review, it remains a limitation in terms of providing recommendations as to the suitability of combining the available data as depicted in the evidence and gap through a formal synthesis. Studies of varying quality may not be appropriate to synthesize together, and this is a further consideration that this scoping review cannot address.

Conclusion

This scoping review and evidence and gap map identified fourteen individual studies, taking place over 21 different countries that provided data regarding a G6PD diagnostic test and a contextual or additional factor of interest. The evidence and gap map demonstrates that there appears to be sufficient evidence available to support a comprehensive systematic review (likely of qualitative evidence). The evidence and gap map has also identified that there is not

sufficient data available to conduct a formal synthesis for the semi-quantitative or any of the qualitative diagnostic tests, and future primary research should be conducted on these types of tests, while also addressing the factors of equity and human rights, which were comparatively under-reported in the literature compared to the other factors of interest.

Appendices

Appendix 1

Search strategy

Databases	PubMed (NCBI), Embase (Elsevier), Cochrane CDSR (Wiley), Cochrane CENTRAL (Wiley), Scopus (Elsevier), WHO Global Index Medicus
Date Run	August 25, 2023
Some Terminology from	KilleeKilleen GF, Masalu JP, Chinula D, Fotakis E., Kavishe DR, Malone D, Okumu F. (2017). Control of malaria vector mosquitoes by insecticide-treated combinations of window screens and eave baffles. *Emerging infectious diseases, 23(5), 782–789.* https://doi.org/https://doi.org/10.3201/eid2305.160662 Key Articles 19,497127 OR 24830448 OR 29566754 OR 27716420
Results – G6PD	- PubMed: 158 - Embase: 270 - Cochrane CDSR: 5 - Cochrane CENTRAL: 25 - Scopus: 206 - WHO GIM: 860 - TOTAL: 1524 - Duplicates Removed (Deduplicator): 372 - Duplicates Removed (Covidence): 0 - TOTAL UNIQUE: 1152
Run by	Carrie Price, MLS, Albert S. Cook Library, Towson University, Towson, Maryland, USA

PubMed (NCBI)		
1	"antimalarials"[mesh] OR "malaria"[mesh]	86,499
2	"antimalaria"[tw] OR "antimalarial"[tw] OR "antimalarial"[tw] OR "antimalarials"[tw] OR "antimalarials"[tw] OR "black water fever"[tw] OR "black water fevers"[tw] OR "blackwater fever"[tw] OR "blackwater fevers"[tw] OR "malarials"[tw] OR "malarial"[tw] OR "malaria"[tw] OR "marsh fever"[tw] OR "marsh fevers"[tw] OR "p falciparum"[tw] OR "p. falciparum"[tw] OR "paludism"[tw] OR "plasmodia"[tw] OR "plasmodial"[tw] OR "plasmodiosis"[tw] OR "plasmodium"[tw] OR "plasmodiums"[tw] OR "remittent fever"[tw] OR "remittent fevers"[tw] OR "swamp fever"[tw] OR "swamp fevers"[tw]	131,629
3/malaria	#1 OR #2	131,629
4	"data collection"[mesh:noexp] OR "document analysis"[mesh] OR "focus groups"[mesh] OR "forms as topic"[mesh] OR "hermeneutics"[mesh] OR "interrupted time series analysis"[mesh] OR "interviews as topic"[mesh] OR "qualitative research"[mesh] OR "surveys and questionnaires"[mesh:noexp] OR "population surveillance"[mesh:noexp]	834,652
5	"coding"[tw] OR "data collection"[tw] OR "decision aid*"[tw] OR "direct choice"[tw] OR "direct choices"[tw] OR "document analysis"[tw] OR "focus group"[tw] OR "focus groups"[tw] OR "form"[tw] OR "forms"[tw] OR "hermeneutic"[tw] OR "hermeneutics"[tw] OR "interview"[tw] OR "interviews"[tw] OR "qualitative method"[tw] OR "qualitative methods"[tw] OR "qualitative research"[tw] OR "qualitative study"[tw] OR "qualitative studies"[tw] OR "qualitative method"[tw] OR "questionnaire"[tw] OR "questionnaires"[tw] OR "surveillance"[tw] OR "survey"[tw] OR "surveys"[tw] OR "thematic"[tw] OR "thematics"[tw] OR "themes"[tw] OR "theme"[tw] OR "phenomenology"[tw] OR "phenomenological"[tw] OR "standard gamble"[tw] OR "top down"[tw] OR "time series"[tw] OR "time tradeoff"[tw] OR "time trade off"[tw] OR "visual analogue"[tw] OR "visual analog"[tw]	4,094,024
6/qualitative	#4 OR #5	4,094,024
7	"ethnology"[mesh] OR "ethnology"[sh] OR "health knowledge, attitudes, practice"[mesh:noexp] OR "patient acceptance of health care"[mesh:noexp] OR "treatment adherence and compliance"[mesh:noexp] OR "treatment refusal"[mesh:noexp]	347,018
8	"acceptabilities"[tw] OR "acceptability"[tw] OR "acceptable"[tw] OR "acceptance"[tw] OR "adherence"[tw] OR "adherent"[tw] OR "attitude"[tw] OR "attitudes"[tw] OR "belief"[tw] OR "beliefs"[tw] OR "choice"[tw] OR "choices"[tw] OR "choose"[tw] OR "choosing"[tw] OR "chosen"[tw] OR "compliance"[tw] OR "compliant"[tw] OR "contextual factor"[tiab] OR "contextual factors"[tiab] OR "ethnolog*"[tw] OR "feasibilities"[tw] OR "feasibility"[tw] OR "feasible"[tw] OR "feel"[tw] OR "feel"[tw] OR "feeling"[tw] OR "feelings"[tw] OR "feelings"[tw] OR "felt"[tw] OR "hesitancy"[tw] OR "hesitant"[tw] OR "hesitate"[tw] OR "hesitates"[tw] OR "hesitating"[tw] OR "impression"[tw] OR "impressions"[tw] OR "inclination"[tw] OR "inclinations"[tw] OR "influence"[tw] OR "influences"[tw] OR "influential"[tw] OR "intention"[tw] OR "intentions"[tw] OR "KAP"[tw] OR "knowledgable"[tw] OR "knowledge"[tw] OR "knowledgeable"[tw] OR "life quality"[tw] OR "non use"[tw] OR "nonadherence"[tw] OR "nonadherent"[tw] OR "noncompliance"[tw] OR "noncompliant"[tw] OR "nonuse"[tw] OR "non-use"[tw] OR "perception"[tw] OR "perceptions"[tw] OR "perspective"[tw] OR "perspectives"[tw] OR "persua*"[tw] OR "prefer"[tw] OR "preference"[tw] OR "preferences"[tw] OR "preferential"[tw] OR "preferentially"[tw] OR "quality of life"[tw] OR "quality of living"[tw] OR "refusal"[tw] OR "refuse"[tw] OR "refusing"[tw] OR "seek"[tw] OR "seeking"[tw] OR "sought"[tw] OR "think"[tw] OR "thought"[tw] OR "thoughts"[tw] OR "use"[tw] OR "uses"[tw] OR "using"[tw] OR "utilisation"[tw] OR "utilities"[tw] OR "utility"[tw] OR "utilization"[tw] OR "value"[tw] OR "valued"[tw] OR "valued"[tw] OR "values"[tw] OR "valuing"[tw] OR "willingness"[tw] OR "valuation"[tw] OR "valuations"[tw] OR "gender"[tw] OR "equity"[tw] OR "human right"[tw] OR "human rights"[tw]	14,667,211
9/contextual factors	#7 OR #8	14,667,211

PubMed (NCBI)

10	"glucosephosphate dehydrogenase deficiency"[mesh] OR "6 phosphate dehydrogenase"[tw] OR "6 phospho-glucose dehydrogenase"[tw] OR "6 phosphoglucoside dehydrogenase"[tw] OR "d glucose 6 phosphate"[tw] OR "dextro glucose 6 phosphate dehydrogenase"[tw] OR "e.c. 1.1.1.49"[tw] OR "g 6 pdh"[tw] OR "g6 pd"[tw] OR "g6 pdh"[tw] OR "g6pd"[tw] OR "g6pdh"[tw] OR "glucose 6 phosphate"[tw] OR "glucose 6 phosphatedehydrogenase"[tw] OR "glucose 6 phosphodehydrogenase"[tw] OR "glucose phosphate dehydrogenase"[tw] OR "glucosephosphate dehydrogenase"[tw] OR "gpd deficiencies"[tw] OR "gpd deficiency"[tw] OR "hexose 6 phosphate dehydrogenase"[tw] OR "hexose monophosphate dehydrogenase"[tw] OR "hexose phosphate dehydrogenase"[tw] OR "hexosemonophosphate dehydrogenase"[tw] OR "hexosemonophosphate shunt dehydrogenase"[tw] OR "robison ester dehydrogenase"[tw] OR "zwischenferment"[tw]	32,528
11	#3 AND #6 AND #9 AND #10	158

Embase (Elsevier)

1	'antimalarial agent'/de OR 'malaria'/de	108,686
2	'antimalaria':ti,ab,de,kw OR 'antimalarial':ti,ab,de,kw OR 'antimalarial':ti,ab,de,kw OR 'antimalarials':ti,ab,de,kw OR 'antimalarials':ti,ab,de,kw OR 'black water fever':ti,ab,de,kw OR 'black water fevers':ti,ab,de,kw OR 'blackwater fever':ti,ab,de,kw OR 'blackwater fevers':ti,ab,de,kw OR 'malarials':ti,ab,de,kw OR 'malarial':ti,ab,de,kw OR 'malaria':ti,ab,de,kw OR 'marsh fever':ti,ab,de,kw OR 'marsh fevers':ti,ab,de,kw OR 'p falciparum':ti,ab,de,kw OR 'p. falciparum':ti,ab,de,kw OR 'paludism':ti,ab,de,kw OR 'plasmodia':ti,ab,de,kw OR 'plasmodial':ti,ab,de,kw OR 'plasmodiosis':ti,ab,de,kw OR 'plasmodium':ti,ab,de,kw OR 'plasmodiums':ti,ab,de,kw OR 'remittent fever':ti,ab,de,kw OR 'remittent fevers':ti,ab,de,kw OR 'swamp fever':ti,ab,de,kw OR 'swamp fevers':ti,ab,de,kw	175,920
3/malaria	#1 OR #2	176,174
4	'data collection method'/de OR 'document analysis'/de OR 'hermeneutics'/de OR 'interview'/de OR 'audio interview'/de OR 'semi structured interview'/de OR 'structured interview'/de OR 'unstructured interview'/de OR 'video interview'/de OR 'qualitative research'/de OR 'questionnaire'/de OR 'population surveillance'/de	1,236,349
5	'coding':ti,ab,de,kw OR 'data collection':ti,ab,de,kw OR 'decision aid*':ti,ab,de,kw OR 'direct choice':ti,ab,de,kw OR 'direct choices':ti,ab,de,kw OR 'document analysis':ti,ab,de,kw OR 'focus group':ti,ab,de,kw OR 'focus groups':ti,ab,de,kw OR 'form':ti,ab,de,kw OR 'forms':ti,ab,de,kw OR 'hermeneutic':ti,ab,de,kw OR 'hermeneutics':ti,ab,de,kw OR 'interview':ti,ab,de,kw OR 'interviews':ti,ab,de,kw OR 'qualitative method':ti,ab,de,kw OR 'qualitative methods':ti,ab,de,kw OR 'qualitative research':ti,ab,de,kw OR 'qualitative study':ti,ab,de,kw OR 'qualitative studies':ti,ab,de,kw OR 'qualitative method':ti,ab,de,kw OR 'questionnaire':ti,ab,de,kw OR 'questionnaires':ti,ab,de,kw OR 'surveillance':ti,ab,de,kw OR 'survey':ti,ab,de,kw OR 'surveys':ti,ab,de,kw OR 'thematic':ti,ab,de,kw OR 'thematics':ti,ab,de,kw OR 'themes':ti,ab,de,kw OR 'theme':ti,ab,de,kw OR 'phenomenology':ti,ab,de,kw OR 'phenomenological':ti,ab,de,kw OR 'standard gamble':ti,ab,de,kw OR 'top down':ti,ab,de,kw OR 'time series':ti,ab,de,kw OR 'time tradeoff':ti,ab,de,kw OR 'time trade off':ti,ab,de,kw OR 'visual analogue':ti,ab,de,kw OR 'visual analog':ti,ab,de,kw	5,801,308
6/qualitative	#4 OR #5	5,801,308
7	'ethnology'/de OR 'attitude to health'/de OR 'acceptability'/de OR 'patient compliance'/de OR 'treatment refusal'/de	372,995

Embase (Elsevier)

8	'acceptabilities':ti,ab,de,kw OR 'acceptability':ti,ab,de,kw OR 'acceptable':ti,ab,de,kw OR 'acceptance':ti,ab,de,kw OR 'adherence':ti,ab,de,kw OR 'adherent':ti,ab,de,kw OR 'attitude':ti,ab,de,kw OR 'attitudes':ti,ab,de,kw OR 'belief':ti,ab,de,kw OR 'beliefs':ti,ab,de,kw OR 'choice':ti,ab,de,kw OR 'choices':ti,ab,de,kw OR 'choose':ti,ab,de,kw OR 'choosing':ti,ab,de,kw OR 'chosen':ti,ab,de,kw OR 'compliance':ti,ab,de,kw OR 'compliant':ti,ab,de,kw OR 'contextual factor':ti,ab OR 'contextual factors':ti,ab OR 'ethnolog*':ti,ab,de,kw OR 'feasibilities':ti,ab,de,kw OR 'feasibility':ti,ab,de,kw OR 'feasible':ti,ab,de,kw OR 'feel':ti,ab,de,kw OR 'feel':ti,ab,de,kw OR 'feeling':ti,ab,de,kw OR 'feelings':ti,ab,de,kw OR 'feelings':ti,ab,de,kw OR 'felt':ti,ab,de,kw OR 'hesitancy':ti,ab,de,kw OR 'hesitant':ti,ab,de,kw OR 'hesitate':ti,ab,de,kw OR 'hesitates':ti,ab,de,kw OR 'hesitating':ti,ab,de,kw OR 'impression':ti,ab,de,kw OR 'impressions':ti,ab,de,kw OR 'inclination':ti,ab,de,kw OR 'inclinations':ti,ab,de,kw OR 'influence':ti,ab,de,kw OR 'influences':ti,ab,de,kw OR 'influential':ti,ab,de,kw OR 'intention':ti,ab,de,kw OR 'intentions':ti,ab,de,kw OR 'KAP':ti,ab,de,kw OR 'knowledgable':ti,ab,de,kw OR 'knowledge':ti,ab,de,kw OR 'knowledgeable':ti,ab,de,kw OR 'life quality':ti,ab,de,kw OR 'non use':ti,ab,de,kw OR 'nonadherence':ti,ab,de,kw OR 'nonadherent':ti,ab,de,kw OR 'noncompliance':ti,ab,de,kw OR 'noncompliant':ti,ab,de,kw OR 'nonuse':ti,ab,de,kw OR 'non-use':ti,ab,de,kw OR 'perception':ti,ab,de,kw OR 'perceptions':ti,ab,de,kw OR 'perspective':ti,ab,de,kw OR 'perspectives':ti,ab,de,kw OR 'persua*':ti,ab,de,kw OR 'prefer':ti,ab,de,kw OR 'preference':ti,ab,de,kw OR 'preferences':ti,ab,de,kw OR 'preferential':ti,ab,de,kw OR 'preferentially':ti,ab,de,kw OR 'quality of life':ti,ab,de,kw OR 'quality of living':ti,ab,de,kw OR 'refusal':ti,ab,de,kw OR 'refuse':ti,ab,de,kw OR 'refusing':ti,ab,de,kw OR 'seek':ti,ab,de,kw OR 'seeking':ti,ab,de,kw OR 'sought':ti,ab,de,kw OR 'think':ti,ab,de,kw OR 'thought':ti,ab,de,kw OR 'thoughts':ti,ab,de,kw OR 'use':ti,ab,de,kw OR 'uses':ti,ab,de,kw OR 'using':ti,ab,de,kw OR 'utilisation':ti,ab,de,kw OR 'utilities':ti,ab,de,kw OR 'utility':ti,ab,de,kw OR 'utilization':ti,ab,de,kw OR 'value':ti,ab,de,kw OR 'valued':ti,ab,de,kw OR 'valued':ti,ab,de,kw OR 'values':ti,ab,de,kw OR 'valuing':ti,ab,de,kw OR 'willingness':ti,ab,de,kw OR 'valuation':ti,ab,de,kw OR 'valuations':ti,ab,de,kw OR 'gender':ti,ab,de,kw OR 'equity':ti,ab,de,kw OR 'human right':ti,ab,de,kw OR 'human rights':ti,ab,de,kw	18,965,194
9/contextual factors	#7 OR #8	14,466,823
10	'glucose 6 phosphate dehydrogenase'/de OR '6 phosphate dehydrogenase':ti,ab,de,kw OR '6 phosphoglucose dehydrogenase':ti,ab,de,kw OR '6 phosphoglucoside dehydrogenase':ti,ab,de,kw OR 'd glucose 6 phosphate':ti,ab,de,kw OR 'dextro glucose 6 phosphate dehydrogenase':ti,ab,de,kw OR 'e.c. 1.1.1.49':ti,ab,de,kw OR 'g 6 pdh':ti,ab,de,kw OR 'g6 pd':ti,ab,de,kw OR 'g6 pdh':ti,ab,de,kw OR 'g6pd':ti,ab,de,kw OR 'g6pdh':ti,ab,de,kw OR 'glucose 6 phosphate':ti,ab,de,kw OR 'glucose 6 phosphatedehydrogenase':ti,ab,de,kw OR 'glucose 6 phosphodehydrogenase':ti,ab,de,kw OR 'glucose phosphate dehydrogenase':ti,ab,de,kw OR 'glucosephosphate dehydrogenase':ti,ab,de,kw OR 'gpd deficiencies':ti,ab,de,kw OR 'gpd deficiency':ti,ab,de,kw OR 'hexose 6 phosphate dehydrogenase':ti,ab,de,kw OR 'hexose monophosphate dehydrogenase':ti,ab,de,kw OR 'hexose phosphate dehydrogenase':ti,ab,de,kw OR 'hexosemonophosphate dehydrogenase':ti,ab,de,kw OR 'hexosemonophosphate shunt dehydrogenase':ti,ab,de,kw OR 'robison ester dehydrogenase':ti,ab,de,kw OR 'zwischenferment':ti,ab,de,kw	41,315
11	#3 AND #6 AND #9 AND #10	270

Cochrane CENTRAL and CDSR (Wiley)		
1	[mh "antimalarials"] OR [mh "malaria"]	4,279
2	"antimalaria":ti,ab,kw OR "antimalarial":ti,ab,kw OR "anti-malarial":ti,ab,kw OR "antimalarials":ti,ab,kw OR "anti-malarials":ti,ab,kw OR "black water fever":ti,ab,kw OR "black water fevers":ti,ab,kw OR "blackwater fever":ti,ab,kw OR "black-water fevers":ti,ab,kw OR "malarials":ti,ab,kw OR "malarial":ti,ab,kw OR "malaria":ti,ab,kw OR "marsh fever":ti,ab,kw OR "marsh fevers":ti,ab,kw OR "p falciparum":ti,ab,kw OR "p. falciparum":ti,ab,kw OR "paludism":ti,ab,kw OR "plasmodia":ti,ab,kw OR "plasmodial":ti,ab,kw OR "plasmodiosis":ti,ab,kw OR "plasmodium":ti,ab,kw OR "plasmodiums":ti,ab,kw OR "remittent fever":ti,ab,kw OR "remittent fevers":ti,ab,kw OR "swamp fever":ti,ab,kw OR "swamp fevers":ti,ab,kw	8,012
3/malaria	#1 OR #2	8,012
4	[mh ^"data collection"] OR [mh "document analysis"] OR [mh "focus groups"] OR [mh "forms as topic"] OR [mh "hermeneutics"] OR [mh "interrupted time series analysis"] OR [mh "interviews as topic"] OR [mh "qualitative research"] OR [mh ^"surveys and questionnaires"] OR [mh ^"population surveillance"]	37,743
5	"coding":ti,ab,kw OR "data collection":ti,ab,kw OR "decision aid":ti,ab,kw OR "decision aide":ti,ab,kw OR "decision aids":ti,ab,kw OR "decisions aides":ti,ab,kw OR "direct choice":ti,ab,kw OR "direct choices":ti,ab,kw OR "document analysis":ti,ab,kw OR "focus group":ti,ab,kw OR "focus groups":ti,ab,kw OR "form":ti,ab,kw OR "forms":ti,ab,kw OR "hermeneutic":ti,ab,kw OR "hermeneutics":ti,ab,kw OR "interview":ti,ab,kw OR "interviews":ti,ab,kw OR "qualitative method":ti,ab,kw OR "qualitative methods":ti,ab,kw OR "qualitative research":ti,ab,kw OR "qualitative study":ti,ab,kw OR "qualitative studies":ti,ab,kw OR "qualitative method":ti,ab,kw OR "questionnaire":ti,ab,kw OR "questionnaires":ti,ab,kw OR "surveillance":ti,ab,kw OR "survey":ti,ab,kw OR "surveys":ti,ab,kw OR "thematic":ti,ab,kw OR "thematics":ti,ab,kw OR "themes":ti,ab,kw OR "theme":ti,ab,kw OR "phenomenology":ti,ab,kw OR "phenomenological":ti,ab,kw OR "standard gamble":ti,ab,kw OR "top down":ti,ab,kw OR "time series":ti,ab,kw OR "time tradeoff":ti,ab,kw OR "time trade off":ti,ab,kw OR "visual analogue":ti,ab,kw OR "visual analog":ti,ab,kw	395,465
6/qualitative	#4 OR #5	2,653,895
7	[mh "ethnology"] OR [mh ^"health knowledge, attitudes, practice"] OR [mh ^"patient acceptance of health care"] OR [mh ^"treatment adherence and compliance"] OR [mh "treatment refusal"]	11,304

Cochrane CENTRAL and CDSR (Wiley)		
8	"acceptabilities":ti,ab,kw OR "acceptability":ti,ab,kw OR "acceptable":ti,ab,kw OR "acceptance":ti,ab,kw OR "adherence":ti,ab,kw OR "adherent":ti,ab,kw OR "attitude":ti,ab,kw OR "attitudes":ti,ab,kw OR "belief":ti,ab,kw OR "beliefs":ti,ab,kw OR "choice":ti,ab,kw OR "choices":ti,ab,kw OR "choose":ti,ab,kw OR "choosing":ti,ab,kw OR "chosen":ti,ab,kw OR "compliance":ti,ab,kw OR "compliant":ti,ab,kw OR "contextual factor":ti,ab OR "contextual factors":ti,ab OR "ethnology":ti,ab,kw OR "ethnologies":ti,ab,kw OR "feasibilities":ti,ab,kw OR "feasibility":ti,ab,kw OR "feasible":ti,ab,kw OR "feel":ti,ab,kw OR "feel":ti,ab,kw OR "feeling":ti,ab,kw OR "feelings":ti,ab,kw OR "feelings":ti,ab,kw OR "felt":ti,ab,kw OR "hesitancy":ti,ab,kw OR "hesitant":ti,ab,kw OR "hesitate":ti,ab,kw OR "hesitates":ti,ab,kw OR "hesitating":ti,ab,kw OR "impression":ti,ab,kw OR "impressions":ti,ab,kw OR "inclination":ti,ab,kw OR "inclinations":ti,ab,kw OR "influence":ti,ab,kw OR "influences":ti,ab,kw OR "influential":ti,ab,kw OR "intention":ti,ab,kw OR "intentions":ti,ab,kw OR "KAP":ti,ab,kw OR "knowledgable":ti,ab,kw OR "knowledge":ti,ab,kw OR "knowledgeable":ti,ab,kw OR "life quality":ti,ab,kw OR "non use":ti,ab,kw OR "nonadherence":ti,ab,kw OR "nonadherent":ti,ab,kw OR "noncompliance":ti,ab,kw OR "noncompliant":ti,ab,kw OR "nonuse":ti,ab,kw OR "non-use":ti,ab,kw OR "perception":ti,ab,kw OR "perceptions":ti,ab,kw OR "perspective":ti,ab,kw OR "perspectives":ti,ab,kw OR "persuade":ti,ab,kw OR "prefer":ti,ab,kw OR "preference":ti,ab,kw OR "preferences":ti,ab,kw OR "preferential":ti,ab,kw OR "preferentially":ti,ab,kw OR "quality of life":ti,ab,kw OR "quality of living":ti,ab,kw OR "refusal":ti,ab,kw OR "refuse":ti,ab,kw OR "refusing":ti,ab,kw OR "seek":ti,ab,kw OR "seeking":ti,ab,kw OR "sought":ti,ab,kw OR "think":ti,ab,kw OR "thought":ti,ab,kw OR "thoughts":ti,ab,kw OR "use":ti,ab,kw OR "uses":ti,ab,kw OR "using":ti,ab,kw OR "utilisation":ti,ab,kw OR "utilities":ti,ab,kw OR "utility":ti,ab,kw OR "utilization":ti,ab,kw OR "value":ti,ab,kw OR "valued":ti,ab,kw OR "valued":ti,ab,kw OR "values":ti,ab,kw OR "valuing":ti,ab,kw OR "willingness":ti,ab,kw OR "valuation":ti,ab,kw OR "valuations":ti,ab,kw OR "gender":ti,ab,kw OR "equity":ti,ab,kw OR "human right":ti,ab,kw OR "human rights":ti,ab,kw	1,217,386
9/contextual factors	#7 OR #8	1,205,961

Cochrane CENTRAL and CDSR (Wiley)

10	[mh "glucosephosphate dehydrogenase deficiency"] OR "6 phosphate dehydrogenase":ti,ab,kw OR "6 phosphoglucose dehydrogenase":ti,ab,kw OR "6 phosphoglucoside dehydrogenase":ti,ab,kw OR "d glucose 6 phosphate":ti,ab,kw OR "dextro glucose 6 phosphate dehydrogenase":ti,ab,kw OR "e.c. 1.1.1.49":ti,ab,kw OR "g 6 pdh":ti,ab,kw OR "g6 pd":ti,ab,kw OR "g6 pdh":ti,ab,kw OR "g6pd":ti,ab,kw OR "g6pdh":ti,ab,kw OR "glucose 6 phosphate":ti,ab,kw OR "glucose 6 pho sphatedehydrogenase":ti,ab,kw OR "glucose 6 phosphodehydrogenase":ti,ab,kw OR "glucose phosphate dehydrogenase":ti,ab,kw OR "glucosephosphate dehydrogenase":ti,ab,kw OR "gpd deficiencies":ti,ab,kw OR "gpd deficiency":ti,ab,kw OR "hexose 6 phosphate dehydrogenase":ti,ab,kw OR "hexose monophosphate dehydrogenase":ti,ab,kw OR "hexose phosphate dehydrogenase":ti,ab,kw OR "hexosemonophosphate dehydrogenase":ti,ab,kw OR "hexosemonophosphate shunt dehydrogenase":ti,ab,kw OR "robison ester dehydrogenase":ti,ab,kw OR "zwischenferment":ti,ab,kw	523
11	#3 AND #6 AND #9 AND #20	30 • 5 CDSR • 25 CENTRAL

Scopus (Elsevier)

1/malaria	TITLE-ABS-KEY([antimalaria] OR [antimalarial] OR [anti-malarial] OR [antimalarials] OR [anti-malarials] OR [black water fever] OR [black water fevers] OR [blackwater fever] OR [blackwater fevers] OR [malarials] OR [malarial] OR [45] OR [marsh fever] OR [marsh fevers] OR [p falciparum] OR [p. falciparum] OR [paludism] OR [plasmodia] OR [plasmodial] OR [plasmodiosis] OR [plasmodium] OR [plasmodiums] OR [remittent fever] OR [remittent fevers] OR [swamp fever] OR [swamp fevers])	177,755
2/qualitative	TITLE-ABS-KEY([coding] OR [data collection] OR "decision aid*" OR [direct choice] OR [direct choices] OR [document analysis] OR [focus group] OR [focus groups] OR [form] OR [forms] OR [hermeneutic] OR [hermeneutics] OR [interview] OR [interviews] OR [qualitative method] OR [qualitative methods] OR [qualitative research] OR [qualitative study] OR [qualitative studies] OR [qualitative method] OR [questionnaire] OR [questionnaires] OR [surveillance] OR [survey] OR [surveys] OR [thematic] OR [thematics] OR [themes] OR [theme] OR [phenomenology] OR [phenomenological] OR [standard gamble] OR [top down] OR [time series] OR [time tradeoff] OR [time trade off] OR [visual analogue] OR [visual analog])	10,941,389

Scopus (Elsevier)

3/contextual factors	TITLE-ABS-KEY([acceptabilities] OR [acceptability] OR [acceptable] OR [acceptance] OR [adherence] OR [adherent] OR [attitude] OR [attitudes] OR [belief] OR [beliefs] OR [choice] OR [choices] OR [choose] OR [choosing] OR [chosen] OR [compliance] OR [compliant] OR [contextual factor] OR [contextual factors] OR "ethnolog*" OR [feasibilities] OR [feasibility] OR [feasible] OR [feel] OR [feel] OR [feeling] OR [feelings] OR [feelings] OR [felt] OR [hesitancy] OR [hesitant] OR [hesitate] OR [hesitates] OR [hesitating] OR [impression] OR [impressions] OR [inclination] OR [inclinations] OR [influence] OR [influences] OR [influential] OR [intention] OR [intentions] OR [46] OR [knowledgable] OR [knowledge] OR [knowledgeable] OR [life quality] OR [non use] OR [nonadherence] OR [nonadherent] OR [noncompliance] OR [noncompliant] OR [nonuse] OR [non-use] OR [perception] OR [perceptions] OR [perspective] OR [perspectives] OR "persua*" OR [prefer] OR [preference] OR [preferences] OR [preferential] OR [preferentially] OR [quality of life] OR [quality of living] OR [refusal] OR [refuse] OR [refusing] OR [seek] OR [seeking] OR [sought] OR [think] OR [thought] OR [thoughts] OR [47] OR [uses] OR [48] OR [utilisation] OR [utilities] OR [utility] OR [utilization] OR [value] OR [valued] OR [valued] OR [values] OR [valuing] OR [willingness] OR [valuation] OR [valuations] OR [gender] OR [equity] OR [human right] OR [human rights])	41,529,832
4	#1 AND #2 AND #3	19,334
5	TITLE-ABS-KEY([glucosephosphate dehydrogenase deficiency] OR [6 phosphate dehydrogenase] OR [6 phosphoglucose dehydrogenase] OR [6 phosphoglucoside dehydrogenase] OR [d glucose 6 phosphate] OR [dextro glucose 6 phosphate dehydrogenase] OR [e.c. 1.1.1.49] OR [g 6 pdh] OR [g6 pd] OR [g6 pdh] OR [g6pd] OR [g6pdh] OR [glucose 6 phosphate] OR [glucose 6 phosphatedehydrogenase] OR [glucose 6 phosphodehydrogenase] OR [glucose phosphate dehydrogenase] OR [glucosephosphate dehydrogenase] OR [gpd deficiencies] OR [gpd deficiency] OR [hexose 6 phosphate dehydrogenase] OR [hexose monophosphate dehydrogenase] OR [hexose phosphate dehydrogenase] OR [hexosemonophosphate dehydrogenase] OR [hexosemonophosphate shunt dehydrogenase] OR [robison ester dehydrogenase] OR [zwischenferment])	35,868
16	#4 AND #15	206

WHO Global Index Medicus, all indexes

1/malaria	tw:("antimalaria" OR "antimalarial" OR "anti-malarial" OR "antimalarials" OR "anti-malarials" OR "black water fever" OR "black water fevers" OR "blackwater fever" OR "blackwater fevers" OR "malarials" OR "malarial" OR "malaria" OR "marsh fever" OR "marsh fevers" OR "p falciparum" OR "p. falciparum" OR "paludism" OR "plasmodia" OR "plasmodial" OR "plasmodiosis" OR "plasmodium" OR "plasmodiums" OR "remittent fever" OR "remittent fevers" OR "swamp fever" OR "swamp fevers")	12,169

WHO Global Index Medicus, all indexes		
2/qualitative	tw:("coding" OR "data collection" OR "decision aid*" OR "direct choice" OR "direct choices" OR "document analysis" OR "focus group" OR "focus groups" OR "form" OR "forms" OR "hermeneutic" OR "hermeneutics" OR "interview" OR "interviews" OR "qualitative method" OR "qualitative methods" OR "qualitative research" OR "qualitative study" OR "qualitative studies" OR "qualitative method" OR "questionnaire" OR "questionnaires" OR "surveillance" OR "survey" OR "surveys" OR "thematic" OR "thematics" OR "themes" OR "theme" OR "phenomenology" OR "phenomenological" OR "standard gamble" OR "top down" OR "time series" OR "time tradeoff" OR "time trade off" OR "visual analogue" OR "visual analog")	434,624
3/contextual factors	tw:("acceptabilities" OR "acceptability" OR "acceptable" OR "acceptance" OR "adherence" OR "adherent" OR "attitude" OR "attitudes" OR "belief" OR "beliefs" OR "choice" OR "choices" OR "choose" OR "choosing" OR "chosen" OR "compliance" OR "compliant" OR "contextual factor"OR "contextual factors" OR "ethnolog*" OR "feasibilities" OR "feasibility" OR "feasible" OR "feel" OR "feel" OR "feeling" OR "feelings" OR "feelings" OR "felt" OR "hesitancy" OR "hesitant" OR "hesitate" OR "hesitates" OR "hesitating" OR "impression" OR "impressions" OR "inclination" OR "inclinations" OR "influence" OR "influences" OR "influential" OR "intention" OR "intentions" OR "KAP" OR "knowledgable" OR "knowledge" OR "knowledgeable" OR "life quality" OR "non use" OR "nonadherence" OR "nonadherent" OR "noncompliance" OR "noncompliant" OR "nonuse" OR "non-use" OR "perception" OR "perceptions" OR "perspective" OR "perspectives" OR "persua*" OR "prefer" OR "preference" OR "preferences" OR "preferential" OR "preferentially" OR "quality of life" OR "quality of living" OR "refusal" OR "refuse" OR "refusing" OR "seek" OR "seeking" OR "sought" OR "think" OR "thought" OR "thoughts" OR "use" OR "uses" OR "using" OR "utilisation" OR "utilities" OR "utility" OR "utilization" OR "value" OR "valued" OR "valued" OR "values" OR "valuing" OR "willingness" OR "valuation" OR "valuations" OR "gender" OR "equity" OR "human right" OR "human rights")	652,279
3	#1 AND #2 AND #3	860

Appendix 2

Studies excluded at full-text screening and reasons for exclusions

Author (year published)	Reason for exclusion
Abdullah (2019)	Conference abstract
Adhikari (2023)	Not contextual factor
Adu-Gyasi (2015)	Not contextual factor
Anand (2001)	Full text irretrievable
Assefa (2018)	Not contextual factor
Aung (2023)	Not contextual factor
Baird (2015)	Expert opinion
Carneiro (1985)	Full text irretrievable
Cerutti (2007)	Not G6PD
Chakrabarti (1993)	Not G6PD
Chocontá (2019)	Not G6PD
Couto (1991)	Full text irretrievable
Duarte (2002)	Conference abstract
Earl (2020)	Conference abstract
Genzen (2022)	Not contextual factor
Hassan (2002)	Expert opinion
Henriques (2018)	Not contextual factor
Incardona (2020)	Conference abstract
Jalloh (2004)	Not contextual factor
Khantikul (2018)	Not contextual factor
Kumar (2022)	Expert opinion
Lek (2020)	Full text irretrievable
Marasini (2020)	Not contextual factor
Narain (2019)	Expert opinion
Okoko (2005)	Not G6PD
Palacios (2005)	Not G6PD
Sea (2018)	Full text irretrievable
Sottile (2009)	Not G6PD
Tabatabaei (2015)	Not contextual factor
Weppelmann (2017)	Not contextual factor

Appendix 3

Data dictionary

Term	Definition
G6PD and relevance to malaria	New blood-stage infections of malaria can occur many months after the original infection due to *Plasmodium vivax* having a long-lasting "liver stage". Relapse such as this causes transmission to be difficult to interrupt. 8-aminoquinoline drugs, including primaquine and tafenoquine, can clear the liver stage parasites, known as radical cure [45]. However, primaquine and tafenoquine cause oxidative stress in red blood cells and can precipitate potentially life-threatening acute haemolysis in individuals with low levels of the enzyme Glucose-6-Phosphate Dehydrogenase (G6PD) [47, 49, 50]
G6PD Deficiency (G6PD-d)	G6PD deficiency (G6PD-d) is a x-lined congenital disorder that particularly impacts residents of tropical and subtropical zones in the Eastern Hemisphere and commonly occurs in regions where malaria is (or has been) endemic. G6PD-d can cause neonatal jaundice, acute haemolytic anaemia triggered by fava beans, infection, or drugs, and chronic non-spherocytic haemolytic anaemia (CNSHA). In 1989, WHO recommended G6PD screening of all newborn babies in areas with a prevalence of G6PD deficiency of 3–5% or more in males [51]

Term	Definition
G6PD-d Testing	G6PD tests are based on the biochemical activity of G6PD in a sample of blood. Tests can be quantitative, semiquantitative or qualitative. Access to quantitative testing is limited in most LMICs because it requires highly trained staff, expensive and electricity dependent equipment and a controlled laboratory environment
Quantitative tests	Quantitative tests allow a specific readout of activity across the full spectrum and are generally reported in IU or units per gram of haemoglobin. The gold standard for G6PD activity testing is a quantitative temperature controlled spectrophotometric assay whereby the formation of nicotinamide adenine dinucleotide phosphate (NADPH) from nicotinamide adenine dinucleotide phosphate (NADP) is measured based on a difference in absorbance at 340 nm during 10 min at a controlled temperature, generally 30˚C [46] Quantitative tests include: • Standard G6PD by SD Biosensor CareStart G6PD Biosensor by AccessBio
Semi-quantitative tests	Semi-quantitative tests, such as the longstanding fluorescent spot test (FST), also known as the Beutler test aim to assign G6PD activity as deficient, intermediate, or normal based on thresholds of G6PD activity e.g., < 30%, ~ 30% and ~ 60–70% and ~ > 60–70% of normal activity, respectively. The test was considered 'perfectly adequate' for normal and deficient males (and homozygous females) but not reliable for the detection of heterozygous females. Nonetheless, the test has been used widely for screening in populations, in males and female babies
Qualitative tests	Include Rapid Diagnostic Tests and can be tested from a finger prick sample. These tests do not require any specialised equipment and can be performed at point of care, to allow for prompt determination of G6PD deficiency. However, they are considered 'qualitative' as the output needs to be qualitatively determined, often by a trained professional Qualitative tests include: • G6PD Qualitative FST • CareStart G6PD • BinaxNOW G6PD WST8/1-methoxy PMS assay
Tests to exclude	The Cochrane review on this topic excluded the following tests, and which will be repeated in this study: • The brilliant cresyl blue decolouration test • The methaemoglobin reduction test • The formazan ring method ephadex gel MTT-PMS method

Term	Definition
Acceptability	Is the option acceptable to key stakeholders? [6]. Acceptability might reflect who benefits (or is harmed) and who pays (or saves); and when the benefits, adverse effects, and costs occur (and the discount rates of key stakeholders; e.g. politicians may have a high discount rate for anything that occurs beyond the next election). Unacceptability may be due to; • Not accepting the distribution of the benefits, harms, and costs • Not accepting costs or undesirable effects in the short term for desirable effects (benefits) in the future • Attaching more value (relative importance) to the undesirable consequences than to the desirable consequences or costs of an option (because of how they might be affected personally or because of their perceptions of the relative importance of consequences for others) Morally disapproving (i.e., in relationship to ethical principles such as autonomy, non maleficence, beneficence or justice)
Feasibility	Is the option feasible to implement? [6]. Can the option be accomplished or brought about? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e., the more barriers there are that would be difficult to overcome). Feasibility can overlap with values and preferences, resource considerations, existing infrastructure, equity, cultural norms, legal frameworks, and many other considerations [4, 6]
Valuation of the outcomes of interest	This described the relative importance assigned to health outcomes by those affected by them, how such importance varies within and across populations, and whether this importance or variability is surrounded by uncertainty [4]. When used generically as in "values and preferences" we refer to the collection of goals, expectations, predispositions, and beliefs that individuals have for certain decisions and their potential outcomes [52]
Gender	Gender is considered when studies look at specific contextual factors of testing relative to gender differences. This can relate to the acceptability of tests between men and women, or the accuracy/feasibility of tests across males and females. Testing has been shown to be less accurate in females, who more often have an intermediate level of deficiency [35]
Equity	Health inequity is defined as avoidable differences in health that are considered unfair or unjust. Special consideration should be made in healthcare decision making to disadvantaged populations that are at a higher risk of health inequities [53]. Health equity can related to specific characteristics, including economic status, employment or occupation, education, place of residence, gender or ethnicity. Does implementation of the chosen intervention increase or decrease health equity? [53]

Term	Definition
Experimental studies	Include randomised controlled trials and their derivatives (cluster-randomised controlled trials, cross-over trials etc.), pseudo-randomised controlled trials and quasi-experimental studies [54]
Observational studies	Include prospective and retrospective cohort studies, case–control studies and case series/case reports [55]
Utility/health status value studies	Include the following types of studies: standard gamble, time trade off, discrete choice, visual analogue scale, multi-attribute instruments, utility or health status values transformed from quality of life measurements [56]
Close-ended questionnaires/surveys	Include surveys/questionnaires in which questions are presented that have an explicit/discrete/guided answer that is to be selected by the participants [57]
Open-ended questionnaire/surveys	Include surveys/questionnaires in which questions are presented with no explicit/discrete/guided answer associated, and allow the participant to reflect personally on the question being asked [57]
Focus groups	Include group interviews that capitalise on communication between research participants and the researcher to generate data [58]
Interviews	Include semi-structured or unstructured communication between a single research participant and the researcher to generate data [59]
Literature review	Traditional literature reviews are useful for describing an issue and its underlying concepts and theories. However, they rely heavily on the author's knowledge and experience and provide a limited presentation of a topic. Such reviews are often based on references chosen selectively from the evidence available, resulting in a review inherently at risk for bias or systematic error [60]
Systematic review	Systematic reviews seek to collate evidence that fits pre-specified eligibility criteria to answer a specific research question. They aim to minimise bias by using explicit, systematic methods documented in advance with a protocol [61]
Scoping review	Scoping reviews may be conducted where the purpose of the review is to identify knowledge gaps, scope a body of literature, clarify concepts or to investigate research conduct. While useful in their own right, scoping reviews may also be helpful precursors to systematic reviews and can be used to confirm the relevance of inclusion criteria and potential questions [12]

Appendix 4

Citation details of reports that were irretrievable and not assessed for eligibility

1. Anand, A. C. (2001). "Malarial liver failure: myth or reality?".
2. Carneiro, C. S. (1985). "Tratamento da malária por Plasmodium falciparum com cloroquina e quinina: estudo da cardiotoxidade e resposta terapêutica." Rev. patol. trop 14(1).
3. Couto, R. C. d. S. (1991). "Buscando ouro, perdendo saúde: um estudo sobre as condiçoes de saúde no garimpo do Cumaru—Pará."
4. Lek, D., et al. (2020). "Implementing primaquine radical cure in Cambodia: Evaluating impact on plasmodium vivax infection and relapse, identifying operational roadblocks and maximizing effectiveness." American Journal of Tropical Medicine and Hygiene 103(5 SUPPL).
5. Sea, D., et al. (2018). "Perception of G6PD deficiency and primaquine risk and benefit in a malaria risk population in northwest Cambodia." American Journal of Tropical Medicine and Hygiene 99(4).

Abbreviations

CINAHL	Cumulative index to nursing and allied health literature
FST	Fluorescent spot test
G6PD	Glucose-6-phosphate dehydrogenase
GDG	Guideline development group
GMP	Global malaria programme
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	International prospective register of systematic reviews
WHO	World health organization

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Author contributions

All authors developed the study protocol. CP completed the search strategy. THB and GMM screened and analysed studies for inclusion or exclusion and drafted the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

This work is funded by the World Health Organization, APW203270267. All rights in all work performed under this APW, including, without limitation, the report and database, shall be vested in WHO. The Contractual Partner can present and discuss work undertaken under this agreement in university seminars, tutorials, and lectures, but will need to inform WHO of any specific plans to do so and share the materials that will be presented.

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