Methods to Assess Adult and Adolescent Patients’ Adherence to Antimalarial Treatment: A Systematic Review

Heloísa Ferreira Pinto Santos¹, Lusiele Guaraldo¹, Renata Saraiva Pedro², Luana Santana Damasceno¹, Cláudio Tadeu Daniel-Ribeiro³,4 and Patrícia Brasil¹,4*

¹Clinical Research Laboratory on Acute Febrile Illnesses, Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz (Fiocruz), Rio de Janeiro, Brazil, ²Clinical Advice, Instituto de Tecnologia em Imunobiológicos, Fiocruz, Rio de Janeiro, Brazil, ³Malaria Research Laboratory, Instituto Oswaldo Cruz, Fiocruz, Rio de Janeiro, Brazil, ⁴Centro de Pesquisa, Diagnóstico e Treinamento em Malária, Fiocruz and Secretaria de Vigilância em Saúde, Ministério da Saúde, Rio de Janeiro, Brazil

Malaria is a curable disease for which early diagnosis and treatment, together with the elimination of vectors, are the principal control tools. Non-adherence to antimalarial treatment may contribute to therapeutic failure, development of antimalarial resistance, introduction or resurgence of malaria in non-endemic areas, and increased healthcare costs. The literature describes several methods to directly or indirectly assess adherence to treatment, but no gold standard exists. The main purpose of this review is to systematize the methods used to assess patient adherence to antimalarial treatment. A systematic review was performed, in accordance with the PRISMA statement, of the following databases: LILACS, EMBASE, PUBMED, COCHRANE, GOOGLE SCHOLAR, WEB OF SCIENCE, SCOPUS, and OPENGREY, through 14 December 2021. A snowball search was also performed by screening the references of the included studies as well as those cited in relevant reviews. Inclusion criteria were reporting assessment of the patient’s adherence to antimalarials in individuals with laboratory diagnosis of malaria, the description of antimalarials prescribed, and adherence estimates. Exclusion criteria were studies exclusively about directly observed therapy, studies of populations ≤12 yo and guidelines, commentaries, reviews, letters, or editorials. Study quality was assessed using MINORS and the Cochrane Risk of Bias Tool. Proportions were calculated to measure frequencies considering the number of articles as the denominator. Twenty-one studies were included in this review. Most of them (76.5%) assessed adherence to *falciparum* malaria treatment. Seventeen studies (80.9%) used a combination of methods. The methods described were pill counts, self-reports, biological assays, use of electronic pillboxes, and clinical cure. It was possible to identify different adherence classifications for all the methods used. Our review found that indirect methods

Abbreviations: AS, Artesunate; AQ, Amodiaquine; AL, Artemether + Lumefantrine; AM, Arthemeter; MQ, Mefloquine; CQ, Chloroquine; DHA, Dihidroartemisinine; DOX, Doxycycline; G6PD, Glucose 6 Phosphate Dehydrogenase; DOT, Directly Observed Therapy, MEMS, Medication Event Monitoring System; MINORS, Methodological Index for Non-randomized Studies; PIP, Piperaquine; PQ, Primaquine; Pf, Plasmodium Falciparum; Pv, Plasmodium vivax; QN, Quinine; TET, Tetra-cycline; WHO, World Health Organization.
INTRODUCTION

Malaria is a treatable disease endemic in several countries of Africa, Asia, and South America. The World Health Organization (WHO) estimates (World Health Organization, 2020) that 229 million cases and 409,000 deaths occurred worldwide in 2019. Prompt diagnosis and treatment are the principal tools for the control of malaria. WHO recommendations for antimalarial treatment vary according to the species responsible for the infection: artemisinin-based combination therapy (ACT) for uncomplicated Plasmodium falciparum malaria; chloroquine plus primaquine for Plasmodium vivax or P. ovale, and chloroquine for P. malariae (World Health Organization and Global Malaria Programme, 2015).

Non-adherence to antimalarial treatment is thought to be one of the main causes of failure and may contribute to the maintenance of malaria transmission in a given area, development of antimalarial resistance, inadequate control of the disease, and increased healthcare costs (Duarte and Gyorkos, 2003; World Health Organization and Global Malaria Programme, 2015).

Medication adherence, defined by WHO as “the extent to which a person’s behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider”, is a multidimensional phenomenon determined by the interaction of factors such as access to medication, patient behavior, socioeconomic status, the pathology of the disease, and the treatment complexity (Sabate, 2003). Methods for measuring medication adherence are classified as direct or indirect (Cramer, 1991). Direct methods are biological assays that measure the concentrations of drugs, metabolites, or biomarkers in blood, hair, or urine. Indirect methods include self-reports (interviews and questionnaires), medication measurement (pill count), and electronic monitoring devices (Medication Event Monitoring System, MEMS), which record the opening of a medicine bottle.

Adherence to antimalarials has been reviewed previously, with a focus on the effectiveness of interventions to improve adherence and effects on therapeutic response (Yeung and White, 2005), patterns of adherence and associated factors (Bruxvoort et al., 2014; Ahluwalia et al., 2020) on ACT exclusively (Banek et al., 2014; Yakasai et al., 2015). To date, no method for measuring medication adherence has been validated for malaria treatment. The present review aimed to systematize the information about the methods used to assess adherence to antimalarial therapy.

MATERIALS AND METHODS

Search

This review was developed according to the recommendations of the PRISMA statement (Page et al., 2021), and the protocol was registered in international prospective register of systematic reviews (PROSPERO, CRD42020148054) (Santos et al., 2020). A systematic search for the identification of studies about measurement of adherence to antimalarials was conducted through 14 December 2021 in the following databases: LILACS, EMBASE, MEDLINE (Medical Literature Analysis and Retrieval System Online, interface PUBMED), COCHRANE, GOOGLE SCHOLAR, WEB OF SCIENCE, SCOPUS, and OPENGREY. Additionally, a snowball search was performed by screening the references of the studies included in this review for eligibility, as well as references of other reviews (Yeung and White, 2005; Banek et al., 2014; Bruxvoort et al., 2014; Yakasai et al., 2015).

The search queries were developed using the PECO strategy. The PECO of this review is: P: participants with a laboratory diagnosis of malaria at least 13 years of age; E: malaria treatment; C: Not applicable; O: Methods to assess adherence to treatment. The search descriptors used were malaria, treatment, drug therapy, antimalarials, adherence (medication, patient), compliance (medication, patient) and humans. The search strategy was adapted to each database as necessary. The complete search strategy is available (Supplementary Table S1). There were no language or year restrictions on the searches of the databases.

Selection

References were imported to the reference manager Zotero (Zotero, 2020) and duplicates were removed. The selection was performed by pairs of independent reviewers (HFPS and RSP, HFPS and LSD) using the web application Rayyan (Ouzzani et al., 2016). Studies were included if reporting assessment of patients’ adherence to antimalarials in individuals with laboratory diagnosis of malaria, adherence estimates, and the antimalarials prescribed. We excluded studies exclusively about directly observed therapy (DOT) and studies of populations ≤12 years...
old. DOT studies were excluded as they do not assess but ensure adherence. Children depend on their parents or caregivers to administer their medications, making the evaluation of adherence more complex (Santer et al., 2014; El-Rachidi et al., 2017). Guidelines, commentaries, reviews, letters, and editorials were also excluded. Titles and abstracts were screened for relevance then full text reading was performed. Discrepancies were reviewed and resolved by consensus between two other reviewers (LG and PB).

Data Extraction and Quality Assessment
Data were extracted independently by the same pairs reviewers who selected the studies (HFPS and RSP, HFPS and LSD). Discrepancies were reviewed and resolved by consensus. A standardized data extraction form was developed for the review using the software Epidata v. 3.1, including the following sections: identification of the study (authors, journal, year of publication, and language); study characteristics (design and duration); study population (total number of patients, age, sex, inclusion of pregnant women, and the plasmodial species responsible for the infection); treatment prescribed (drugs and duration of treatment); assessment of the patient’s adherence (method for measuring patient adherence to treatment, adherence classification, adherence criteria, estimate of adherence thereby obtained); and other miscellaneous information such as factors posited to explain nonadherence, and any caveats that the authors made about the estimates of adherence or limitations of the study.

Study quality was assessed using the Methodological Index for Non-randomized Studies (MINORS) for observational studies (Slim et al., 2003) and the Cochrane Risk of Bias Tool for Randomized Controlled Trials for clinical trials (Higgins and Green, 2011). Two reviewers (HFPS and LG) evaluated each article independently and discrepancies were resolved by consensus.

Data Synthesis and Analysis
A description of the studies regarding the year of publication, study design, population (country, sample size, sex, and age), type of infection, antimalarial treatment described with treatment duration, adherence assessment methods (description, assessment day, and adherence categories) and the resulting estimates were performed. Proportions were calculated to measure frequencies of variables considering the number of articles as the denominator.

RESULTS
The search strategy returned 1721 studies (Figure 1). After the exclusion of duplicates and application of inclusion criteria, 19 studies were deemed suitable for inclusion in this review. Two additional studies were included after snowball search. Thus, a total of 21 studies were selected for this review.

Characteristics of the included studies (country, design, population, infection/treatment, adherence methods, estimates and quality) are outlined in Supplementary Table S2. The included studies were published between 1997 and 2020, and
FIGURE 2 | Quality assessment of the studies included in the systematic review according to the Methodological Index for Non-randomized Studies (Sim et al., 2003). (A), quality items for all observational studies; (B), quality items for observational studies with a control group.

FIGURE 3 | Quality assessment of the studies included in the systematic review according to the Cochrane Risk of Bias Tool for Randomized Controlled Trials for clinical trials (Higgins and Green, 2011).
66.7% (14/21) were published after 2011. They were carried out in countries that included malaria-endemic areas in Africa, Asia, and the Americas. In the Americas, all studies were conducted in Brazil. Regarding study design of the 21 studies included in this review, 14 (66.7%) were observational, six (28.5%) experimental, and one quasi-experimental (4.8%). The sample size described in the studies varied from 27 to 300 participants for the observational/quasi-experimental studies and from 50 to 324 participants for the experimental ones. The patient populations were children and adults, and nine (42.9%) studies excluded pregnant women (Fungladda et al., 1998; Lemma et al., 2011; Ferreira et al., 2014; Minzi et al., 2014; Osorio-de-Castro et al., 2015; Souza et al., 2016; Saravu et al., 2018; Oduro et al., 2019; Rosa et al., 2020). The eligible studies assessed adherence to antimalarials prescribed for the treatment of malaria caused by \( P. \) vivax\(^{7} \) (10/21, 47.6%) and \( P. \) falciparum\(^{7} \) (16/21, 76.2%). The drugs for vivax malaria were chloroquine or ACT and primaquine, and treatment duration ranged from 7–14 days. In the studies on \( falciparum \) malaria, the treatment regimen prescribed was ACT, with a single exception (Fungladda et al., 1998).

The quality assessment of the studies is summarized in \textit{Supplementary Table S2} and \textit{Figure 2 and Figure 3}. Most of the observational/quasi-experimental studies (13/15, 86.6%) collected data prospectively and reported appropriate endpoints. About half (8/15, 53.3%) of them reported adequately low to follow up less than 5% and the prospective calculation of study size (7/15, 46.6%). The same was observed for the quasi-experimental study, which is the only one that has comparative groups. Of the six clinical trials included in this review, five were considered of high quality (Fungladda et al., 1998; Qingjun et al., 1998; Asante et al., 2009; Saravu et al., 2018; Bagchi et al., 2020), and one fair quality (Steury, 2016) according to the Cochrane Risk of Bias tool. None of the trials reported whether blinding was used either when assigning patients to treatment arms or when measuring endpoints.

Quantitative estimates of antimalarial adherence varied among treatments and methods used to assess adherence (\textit{Supplementary Table S2}). Estimates of the rate of adherence to \( P. \) vivax treatment differed considerably depending upon the method used to measure adherence. When adherence was measured based on a biological assay, the estimated adherence rate was 95.3% (Cheoymang et al., 2015) versus 71.1–100% based on pill counts (Almeida et al., 2014; Cheoymang et al., 2015; Osorio-de-Castro et al., 2015), 50–100% (Rocha, 2008; Cheoymang et al., 2015; Osorio-de-Castro et al., 2015) based on interviews, and 63.8–83% based on questionnaires (Qingjun et al., 1998; Almeida et al., 2014). When adherence was measured using a combination of different methods, the estimated rate of adherence varied from 44.1 to 75% (Souza et al., 2016; Saravu et al., 2018; Rosa et al., 2020). Studies of \( P. \) falciparum treatment also reported a wide range of adherence rates: 45.4–92.6% by pill count (Asante et al., 2009; Amponsah et al., 2015; Osorio-de-Castro et al., 2015), 66.7–100% by interview (Rocha, 2008; Minzi et al., 2014; Osorio-de-Castro et al., 2015; Takahashi et al., 2018), 16.7% by electronic pillbox (Steury, 2016), and 86.8–100% by biological assays (Na-Bangchang et al., 1997; Minzi et al., 2014). The rate of adherence based on a combination of methods varied from 60 to 94.4% (Takahashi et al., 2018; Oduro et al., 2019; Bagchi et al., 2020).

The studies included in the review assessed adherence by indirect and direct methods. The indirect methods described were self-reports, pill counts, MEMS, and clinical cure. To measure adherence to antimalarial treatment, 76.2% (16/21) of the studies used a combination of methods, the most frequent of which were self-reported adherence and pill counts (Fungladda et al., 1998; Lemma et al., 2011; Tun et al., 2012; Almeida et al., 2014; Ferreira et al., 2014; Osorio-de-Castro et al., 2015; Souza et al., 2016; Saravu et al., 2018; Takahashi et al., 2018; Oduro et al., 2019; Bagchi et al., 2020) (\textit{Supplementary Table S2} and \textit{Table 1}).

Five studies included detailed descriptions of the questionnaires/interviews (Rocha, 2008; Almeida et al., 2014; Ferreira et al., 2014; Souza et al., 2016; Rosa et al., 2020). Two studies used a single question to assess adherence. The question was “Could you take the prescribed medications?” and patients who answered “yes” were considered adherent and those responding “no”, non-adherent (Ferreira et al., 2014; Souza et al., 2016). Another study (Almeida et al., 2014) developed a 5-item questionnaire by adding the following question to Morisky’s 4-item instrument (Morisky et al., 1986): “Do you replicate the dose when you are feeling sick?” The patients’ responses to this question were evaluated using both a dichotomous yes/no scale and a Likert scale (“all the time”, “nearly always”, “usually”, “sometimes”, “once a while”, and “never”). One study used the Morisky Medication Adherence Scale 8-item (MMAS-8) (Morisky et al., 2008) questionnaire with dichotomous responses (Rosa et al., 2020); however, study did not include a definition of adherence. Seven studies (Fogg et al., 2004; Lemma et al., 2011; Tun et al., 2012; Minzi et al., 2014; Amponsah et al., 2015; Osorio-de-Castro et al., 2015; Souza et al., 2016; Steury, 2016; Takahashi et al., 2018; Oduro et al., 2019; Bagchi et al., 2020) reported that the questionnaire applied included the time and date of the medication used by the patient (\textit{Table 2}).

More than half of the studies that utilized pill counts (12/18, 66.6%) classified the patient as adherent if there were no tablets remaining upon study completion (Fungladda et al., 1998; Fogg et al., 2004; Lemma et al., 2011; Tun et al., 2012; Minzi et al., 2014; Amponsah et al., 2015; Osorio-de-Castro et al., 2015; Souza et al., 2016; Steury, 2016; Takahashi et al., 2018; Oduro et al., 2019; Bagchi et al., 2020). Four studies compared self-reports to pill counts as a validationary step. In Fogg et al.’s (2004) and Osorio-de-Castro et al.’s (2015) studies, there was a substantial concordance between methods (Kappa coefficients 0.81 and 0.74). In Almeida et al.’s (2014) and Minzi et al.’s (2014) studies, the concordance was almost perfect (Kappa 0.94 and 0.96).

Adherence was measured directly by biological assays quantifying lumefantrine (Fogg et al., 2004; Minzi et al., 2014), mefloquine (Na-Bangchang et al., 1997), and primaquine (Cheoymang et al., 2015) in blood. The assessment required defining a threshold concentration above which the patient was considered adherent. The reference threshold varied among studies. In one study, the threshold was the median concentration of antimalarials in hospitalized patients (Na-Bangchang et al., 1997). Another
utilized a pre-established concentration from a previous study (Minzi et al., 2014). The two remaining studies utilized a different method to determine the threshold (Fogg et al., 2004; Cheoymang et al., 2015). Fogg et al. (2004) correlates lumefantrine concentrations with the results of indirect methods assessed; Cheoymang et al. (2015) describes minimum, maximum and outliers primaquine plasma concentrations (Table 1).

The timing of the assessment of adherence differed somewhat among the studies. Most studies (17/21, 80.9%) measured adherence 1 day after treatment ended and two studies measured it on the final day of treatment (Na-Bangchang et al., 1997; Asante et al., 2009). In other two studies, adherence was assessed more than once (Minzi et al., 2014; Cheoymang et al., 2015). Finally, a single study (Osorio-de-Castro et al., 2015) evaluated adherence in the course of

| Author, Year | Biological methods | Adherence methods description |
|--------------|--------------------|------------------------------|
| Na-Bangchang et al. (1997) | Biological Assay | Blood Mefloquine concentrations on day 2 compared with reference profiles from hospitalized patients under supervisioned treatment |
| Fungladda et al. (1998) | 1. Self-reported Measure 2. Pill count | 1. Interview on day 5 for AS and day 7 for QN+TET* 2. The blister pack was examined on day 5 for AS and day 7 for QN+TET for remaining tablets |
| Ongun et al. (1998) | Self-reported Measure | Questionnaire applied on day 8* |
| Fogg et al. (2004) | 1. Self-reported Measure 2. Pill count 3. Biological assay | 1. Open questionnaire - a structured interview concerning the time and method of taking each dose, applied on day 3 2. The blister pack was examined on day 3 for remaining tablets 3. Blood Lumefantrine concentrations correlated with the results of indirect methods assessed* |
| Rocha (2008) | Self-reported Measure | 1. Interview asking if the participant took the medication as prescribed by the healthcare professional and describing how it was taken applied on day 7 |
| Asante et al. (2009) | Pill count | The blister pack was examined on day 2 for remaining tablets |
| Lemma et al. (2011) | 1. Self-reported Measure 2. Pill count | 1. Questionnaire applied on day 3* 2. The blister pack was examined on day 3 for remaining tablets |
| Tun et al. (2012) | 1. Self-reported Measure 2. Pill count | 1. Questionnaire applied on day 3* 2. The blister pack was examined on day 3 for remaining tablets |
| Almeida et al. (2014) | 1. Self-reported Measure 2. Pill count | 1. A 5 item self-reported questionnaire adding one question to Morisky’s 4-item questionnaire (Dichotomous and Likert scale) applied on day 7 2. The blister pack was examined on day 7 for remaining tablets |
| Ferreira et al. (2014) | 1. Self-reported Measure 2. Pill count | 1. Interview with one question - “Could you take the prescribed medications?” applied on day 3 for Pf and day 6 for Pv* 2. The blister pack was examined on day 3 for Pf and day 6 for Pv for remaining tablets |
| Minzi et al. (2014) | 1. Self-reported Measure 2. Pill count | 1. Interview - A structured interview to determine how the regimen was taken, the time and method of taking each dose was then conducted, applied on day 3 2. The blister pack was examined on day 3 for remaining tablets 3. Blood Lumefantrine concentrations on day 7, that corresponds to 24 hours after 7 days of AL intake |
| Ampoonsah (2015) | Pill count | The blister pack was examined on day 3 for remaining tablets |
| Cheoymang et al. (2015) | 1. Self-reported Measure 2. Pill count 3. Biological assay | 1. Interview without questionnaire applied on days 3, 7, and 14* 2. The blister pack was examined on days 3, 7, and 14 for remaining tablets 3. Blood Primaquine concentrations collected about 2–4 h after dosing on days 3, 7, and 14 of the initial treatment for the determination of primaquine concentrations, describing the minimum, maximum and outliers of plasma concentrations |
| Osorio-de-Castro et al. (2015) | 1. Self-reported Measure 2. Pill count | 1. Interview applied on day 2 for Pf and day 5 for Pv* 2. The blister pack was examined on day 2 for Pf and day 5 for Pv for remaining tablets |
| Souza et al. (2016) | 1. Self-reported Measure 2. Pill count | 1. Interview with one question: “Could you take the prescribed medications?” 2. The blister pack was examined for remaining tablets |
| Steury (2016) | MEMS 2. Pill count | 1. The MEMS cap on the pillbox containing the ACT electronically recorded the time of each opening of the medication bottle beginning with the first dose on day 3 to 1 week 2. The blister pack was examined on day 3 to 1 week for remaining tablets |
| Saravu et al. (2018) | Self-reported Measure 2. Pill count | 1. Interview applied on day 6* 2. The blister pack was examined on day 6 for remaining tablets |
| Takahashi et al. (2018) | Self-reported Measure 2. Pill count | 1. Interview (home visit or telephone) applied on day 3 or 4* 2. The blister pack was examined on day 3 or 4 for remaining tablets |
| Oduro et al. (2019) | Self-reported Measure 2. Pill count | 1. Interview - The in-depth interview included a day-by-day account of the number of doses taken, number of tablets taken during each dose, time of each dose, reasons for any leftover or missed dose, and whether or not there was vomiting, applied on day 3 2. The blister pack was examined on day 3 for remaining tablets |
| Bagchi et al. (2020) | Self-reported Measure 2. Self-reported Measure 3. Pill count | 1. Interview applied on day 3* 2. Subject’s self-reported compliance asked on day 3* 3. The blister pack was examined on day 3 for remaining tablets |
| Rosa et al. (2020) | Self-reported Measure | 1. Morisky Medication Adherence Scale (MMAS-8) questionnaire |

The authors did not provide a brief description of the method. ACT, Artemisinin-based Combination Therapy; AL, Artemether + Lumefantrine; AS, Artesunate; MEMS, Medication Event Monitoring System; PI, Plasmodium falciparum; Pv, Plasmodium vivax; QN, Quinine; TET, Tetracycline.
| Method                              | Categories                | Definition                                                                                           | Study                                                                 |
|------------------------------------|---------------------------|------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Self-reports                       | Adherent                  | Report of taking the medicines as prescribed                                                         | Rocha, (2008)                                                        |
|                                     | Adherent                  | values > median*                                                                                    | Almeida et al. (2014)                                               |
|                                     | Adherent                  | Report no missed doses during treatment period                                                       | Osorio-de-Castro et al. (2015)                                       |
|                                     | Adherent                  | adherent report and no tablets remaining                                                             | Fungladda et al. (1998)                                             |
| Self-report and pill count          | Definitely non-adherent   | tablets remaining                                                                                    | Fogg et al. (2004), Lemma et al. (2011), Tun et al. (2012)           |
|                                     | Probably non-adherent     | empty or missing blister and report not following the scheme (taking all doses at the correct time on the correct day and correct amount) |                                                                     |
|                                     | Probably adherent         | empty or missing blister and report following the scheme (taking all doses at the correct time on the correct day and correct amount) |                                                                     |
|                                     | Adherent                  | answered “yes” and 100% pills taken of CQ, and 70% pills taken of PQ or 70% pills taken of AL     | Ferreira et al. (2014)                                             |
|                                     | Definitely non-adherent   | Tablets unfinished                                                                                    | Minzi et al. (2014)                                               |
|                                     | Probably non-adherent     | empty or missing blister and wrong dose/incorrect time                                               |                                                                      |
|                                     | Definitely adherent       | empty or missing blister and correct dose/correct time                                               |                                                                      |
|                                     | Definitely non-adherent   | tablets remaining                                                                                    | Takahashi et al. (2018)                                            |
|                                     | Probably non-adherent     | empty or missing blister and the patient answered “having not taken all doses”.                     |                                                                      |
|                                     | Probably non-adherent     | if the patient answered “having not taken all the doses.” – telephone                                |                                                                      |
|                                     | Adherent                  | if the patient answered “having taken all of the doses” and “taken on each day of the regimen.” – telephone |                                                                      |
|                                     | Complete adherence        | reported taking all doses as recommended and no pill left in the pack.                              | Oduro et al., (2019)                                               |
|                                     | Incomplete adherence      | reported that they did not take all the doses as recommended and a greater than or less than the expected number of pills. |                                                                      |
|                                     | Definitely non-adherent   | did not take the tablets at all or as recommended and a greater than expected number of pills       |                                                                      |
|                                     | Adherent                  | when all the doses of study medications were taken at the correct time on the correct day and in the correct amount. | Blagchi et al. (2020)                                             |
|                                     | Non-adherent              | if tablets remained in the blister pack or when reporting inadequate intake of dose and/or timing of tablets |                                                                      |
| Pill count                          | Adherent                  | >70% of pills taken                                                                                   | Almeida et al. (2014)                                              |
|                                     | Fully adherent            | 100% of pills taken                                                                                   | Amponsah et al. (2015)                                             |
|                                     | Partially adherent        | 70–<100% of pills taken                                                                               |                                                                      |
|                                     | Non-adherent              | <70% of pills taken                                                                                   |                                                                      |
|                                     | Adherent                  | quantity received as proxy of quantity consumed                                                      | Osorio-de-Castro et al. (2015)                                      |
|                                     | Non-adherent              | remaining medication tablets or stated any irregularity in adherence to the treatment regimen        | Souza et al. (2016)                                               |
| Biological assay                   | Fully adherent            | concentrations within or above reference interval of MQ (1587-2572 µg/L)                            | Na-Bangchang et al. (1997)                                         |
|                                     | Partially adherent        | concentrations below reference interval of MQ (1587-2572 µg/L)                                      |                                                                      |
|                                     | Non-adherent              | concentrations undetectable                                                                           |                                                                      |
|                                     | Adherent                  | concentration of Lumefantrine ≥175 ng/mL                                                              | Minzi et al. (2014)                                               |
| MEMS and pill count                | Probably adherent         | recorded bottle opening times according to the designated ranges (bottle opening within 1 hour of the prescribed time for the second dose (8 h after initial dose), and a recorded bottle opening within 2 h of the prescribed time for the next 2 days’ doses (8 a.m. and 8 p.m. on each day) and no tablets remaining | Steury, (2016)                                                    |
|                                     | Probably non-adherent     | requirement was not satisfied                                                                         |                                                                      |

(Continued on following page)
treatment. Furthermore, the articles utilized distinct models for following up with patient’s post-treatment. In the majority of studies (11/21, 52.4%), follow-up took the form of home visits (Fogg et al., 2004; Asante et al., 2009; Lemma et al., 2011; Tun et al., 2012; Almeida et al., 2014; Ferreira et al., 2014; Minzi et al., 2014; Osorio-de-Castro et al., 2015; Souza et al., 2016; Takahashi et al., 2018; Oduro et al., 2019). In six studies, the patient was required to return to the clinic (Na-Bangchang et al., 1997; Fungladda et al., 1998; Rocha, 2008; Cheoymang et al., 2015; Steury, 2016; Saravu et al., 2018), whereas three studies did not report where the follow up took place (Amponsah et al., 2015; Bagchi et al., 2020; Rosa et al., 2020). One study reported the use of telephone interview when home visits could not be conducted (Takahashi et al., 2018) and another used both telephone interviews and home visits (Qingjun et al., 1998) (Supplementary Table S2 and Table 1).

In total, sixteen studies classified adherence into categories. We identified five distinct systems for classifying adherence among these studies. In seven studies, participants were classified as “adherent” or “non-adherent” (Fungladda et al., 1998; Rocha, 2008; Almeida et al., 2014; Ferreira et al., 2014; Osorio-de-Castro et al., 2015; Souza et al., 2016; Bagchi et al., 2020); two studies used “fully adherent”, “partially adherent” and “non-adherent” (Na-Bangchang et al., 1997; Amponsah et al., 2015), five used “definitely non-adherent”, “probably non-adherent”, “probably adherent” (Fogg et al., 2004; Lemma et al., 2011; Tun et al., 2012; Minzi et al., 2014; Takahashi et al., 2018), one study used “probably perfectly adherent”, “probably adherent”, “probably non adherent”, and “probably not perfectly adherent” (Steury, 2016), and another study, which was the only study that utilized MEMS, classified participants as “complete adherent”, “incomplete adherent”, and “definitely non-adherent” (Oduro et al., 2019) (Supplementary Table S2). Twelve studies (Fungladda et al., 1998; Fogg et al., 2004; Lemma et al., 2011; Tun et al., 2012; Ferreira et al., 2014; Minzi et al., 2014; Souza et al., 2016; Steury, 2016; Saravu et al., 2018; Oduro et al., 2019; Bagchi et al., 2020; Rosa et al., 2020) used a combination of methods to classify the adherence (Table 2).

DISCUSSION

We reviewed a variety of methods for assessing adherence to antimalarials among patients whose infection was confirmed by parasitological examination. More than half of the studies (14/21, 66.7%) were published in the past decade, and one third (7/21, 33.3%) in the last 5 years, suggesting that concern about adherence has increased. Irrespective of the malaria species or drug regimen, the most frequently used methods to measure adherence were pill counts and self-reports. The widespread use of these methods can be attributed to their low cost (Gabarró, 1999), straightforward implementation, and suitability for any therapeutic regimen.

In eleven studies that used pill counts, home visits were realized to increase follow-up (Qingjun et al., 1998; Fogg et al., 2004; Asante et al., 2009; Lemma et al., 2011; Tun et al., 2012; Almeida et al., 2014; Minzi et al., 2014; Osorio-de-Castro et al., 2015; Souza et al., 2016; Takahashi et al., 2018; Oduro et al., 2019). Similar to studies of chronic diseases, most of these studies defined adherence as consumption of 70% of pills (Almeida et al., 2014; Ferreira et al., 2014; Amponsah et al., 2015). This cut-off may not be suitable for the treatment of an acute infectious disease like malaria, where the goal has to be completing a full therapeutic scheme. A limitation of pill counts is that the counts might not provide information on either the timing of consumption or reasons for non-adherence (Krousel-wood et al., 2004; Lam and Fresco, 2015). Furthermore, it is impossible to confirm whether missing pills were ingested rather than lost or discarded (social desirability bias). This bias can be reduced using unannounced visits, as performed by the studies of Fogg et al. (2004) and Minzi et al. (2014).

Self-reported methods differ in complexity. Interviews and questionnaires examine behavior, beliefs, attitudes toward symptoms, and the patient’s understanding of the drug regimen. Reasons for non-adherence reported in the literature include forgetfulness, adverse reactions, misunderstanding of medication instructions, and the patient’s belief of cure before the end of treatment (Fungladda et al., 1998; Fogg et al., 2004; Lemma et al., 2011; Ferreira et al., 2014; Amponsah et al., 2015; Cheoymang et al., 2015). However, self-reported reasons for non-adherence are subject to recall and social desirability bias if the patient deliberately or unintentionally withholds information (Garber et al., 2004; Cook et al., 2005). As methods of self-reporting varied among studies, it is difficult to assess the reliability between measures.

In the studies included in this review, MEMS and clinical cure were indirect methods that were always used together with other methods (Rocha, 2008; Steury, 2016). Electronic pillboxes are capable of recording the date and time when the bottle was opened, making it possible to recognize patterns of medication
use such as only opening the pillbox before the follow-up visits (“White Coat Adherence”) (Schwed et al., 1999; Ailinger et al., 2008). However, pillbox opening does not guarantee ingestion of the pills and, just as failure to open the pillbox does not mean the pills are not being taken. Due to their high cost, the use of electronic pillboxes has been restricted primarily to clinical trials involving a single drug. This tends to limit the utility of MEMS to malaria monotherapy. When electronic pillboxes cannot be used, adherence can be measured via self-reports, pill counts, or biological assays, with blinding of the possible follow up visit to minimize “White Coat Adherence” (Fogg et al., 2004; Minzi et al., 2014).

Clinical cure was defined as the absence of malaria symptoms 6 days after diagnosis (Rocha, 2008). A study in Brazil reported that although symptoms of vivax malaria disappeared on the second day of treatment, 22.5% of patients still had a positive smear (Abdon et al., 2001). This finding casts doubt on the accuracy of clinical cure as an indicator of adherence. In light of this, clinical cure should be combined with laboratory confirmation of cure.

Less than a quarter of the studies (4/21, 23.5%) used direct methods that measured drug concentrations in blood (Na-Bangchang et al., 1997; Fogg et al., 2004; Minzi et al., 2014; Cheoymang et al., 2015), which provide the strongest evidence that the patient ingested the medication (Farmer, 1999; de Achaval and Suarez-Almazor, 2010; Bent et al., 2012; Lam and Fresco, 2015). This is likely due to the fact that direct methods require specialized training and laboratory resources making them expensive and invasive. Furthermore, drug interactions and variations in drug pharmacokinetics may interfere with the evaluation of these methods. For instance, changes in the CYP 2D62C8 metabolic pathways can increase the risk of therapeutic failure of primaquine (Ingelman-Sundberg, 2005) and modify the kinetics of chloroquine (Kim et al., 2003), altering the perception of adherence. In addition, in the study of Fogg et al. (2004), the plasma concentration of lumefantrine was not used to classify adherence because the fraction absorbed is highly variable, and it was used only to assess the correlation with the indirect methods. These combination of factors impact on the feasibility of direct methods in clinical practice (Lam and Fresco, 2015).

Furthermore, the definition of the reference value of drug concentrations is a challenge. None of the studies included utilized the same reference value. Half of them (2/4, 50%) (Fogg et al., 2004; Cheoymang et al., 2015) calculated the mean concentration of the adherent and non-adherent patients. As treatments for malaria are based on combined therapy avoid the evolution of resistance, the assessment of adherence via biological assays should consider all of the drugs that are included in the treatment regimen.

The timing of assessment of adherence was appropriate in all included studies. The proximity of self-report to the completion of treatment is beneficial as it tends to reduce recall problems. In studies of MEMS, there was no risk of memory bias since the date and time when the pill bottle was opened were recorded electronically.

We found that rates of medication adherence were classified into a wide variety of qualitative categories, which were not standardized across the studies. While seven of the 21 studies adopted binary classification as “adherent” or “non-adherent” (Fungladda et al., 1998; Rocha, 2008; Almeida et al., 2014; Ferreira et al., 2014; Osorio-de-Castro et al., 2015; Souza et al., 2016; Bagchi et al., 2020), four other categorizations were also used in the studies included in this review (Na-Bangchang et al., 1997; Fogg et al., 2004; Lemma et al., 2011; Tun et al., 2012; Minzi et al., 2014; Amponsah et al., 2015; Steury, 2016; Takahashi et al., 2018; Oduro et al., 2019). Recent studies have described adherence as a “spectrum” of behaviors ranging from refusal of treatment, to partial conformity, to precisely following the prescription (Julius et al., 2009). Until standardized categories are adopted in the literature, it will remain difficult to compare data from different studies and assess the efficacy of adherence-increasing interventions.

In our view it is beneficial to use multiple, complementary techniques, as any given method for measuring adherence will have limitations. A high level of concordance between pill count and self-report methods was shown in four studies included in this review (Fogg et al., 2004; Almeida et al., 2014; Minzi et al., 2014; Osorio-de-Castro et al., 2015). However, only two studies (Fogg et al., 2004; Minzi et al., 2014) used announced visits to minimize the social desirability bias, common in both methods. It should be noted that subjective and objective methods assess different dimensions of adherence. While subjective methods are useful in ascertaining the beliefs or barriers to adherence, objective methods provide more accurate data on the way patients intake in their medication regimens. As a gold standard method is not currently available, like other authors (Brown et al., 2016; Anghel et al., 2019), we recommend that two or three approaches be used in parallel. Since the resources available for antimalarial treatment may vary considerably among treatment sites, the best method to be applied in one setting may not necessarily be the best in another. Methods that require specialized equipment and personnel, such as biological assays and MEMS, tend to be more difficult to apply in clinical practice than in research settings, while other indirect methods can be applied in both.

The duration, timing, and frequency of doses were reported in eight studies included in this review (Fogg et al., 2004; Lemma et al., 2011; Tun et al., 2012; Minzi et al., 2014; Souza et al., 2016; Steury, 2016; Oduro et al., 2019; Bagchi et al., 2020). We recommend that these variables should be measured whenever possible. The study that used MEMS (Steury, 2016) detected lower adherence (16.7%) than the others. As electronic pillboxes automatically record the timing and frequency of doses, they are able to detect suboptimal adherence with high sensitivity (El Alili et al., 2016).

Among the strengths of this review are that we searched eight databases and the grey literature, with no restrictions on language, publication date, or drug regimen and only included studies with confirmed parasitological diagnosis. The limitations include the lack of information about the instruments used for self-reports, and uncertainty about medication intake based on pill counts and the cut-off value for biological assays. Another
potential weakness of this review is that we did not request unpublished data from the authors of the eligible studies.

Future studies about adherence to antimalarial treatment should describe their methods in sufficient detail so that they can be replicated and utilize standardized categories of adherence to facilitate comparisons. Clinical outcomes such as clinical and radical cure can be used to define cut-off points that optimally stratifies the good versus poor adherence categories (Karve et al., 2009; O’Halloran Leach et al., 2021). A validation step should be considered for the methods, mainly for the indirect ones, but not for the direct adherence markers. For new instruments to be developed, self-reports should measure whether the patient was able to take the medications as prescribed, several times during the follow-up to test consistency in the response. Further, self-reports should assess if the patient ever missed a dose or experienced adverse events, as these data can be used to improve future therapies. Another suggestion is the development of studies that combine direct and indirect methods as a way to validate the different types of self-reports (Wilson et al., 2016). Studies designed to determine a range of cut-off values to assess drug metabolism should also be performed. The DOT can be used with direct methods for the definition of malaria drug concentration threshold, as well as assist in the development and validation of point-of-care tests to assess adherence (Gandhi et al., 2019). It is important to consider that using methods developed for chronic diseases might not be suitable for an acute disease like malaria, since the consequences of non-adherence are different. In antimalarial treatment, suboptimal medication adherence can cause relapses, severe malaria, death, development of antimalarial resistance, and spread of the disease (Duarte and Gyorkos, 2003; Bruxvoort et al., 2014; Siddiqui et al., 2015; World Health Organization and Global Malaria Programme, 2015).

Indirect methods for assessing adherence to antimalarial treatment have been used more frequently than direct ones and seem to be the most practical, irrespective of the malaria species or therapeutic scheme. In our view, the best approach for measuring treatment adherence is a combination of methods that evaluate adherence using different parameters and are feasible given local resources. Combining an objective method that gives solid proof of the ingestion of medication and a subjective method that complements the research with information regarding factors, beliefs or barrier of adherence seems to be the best approach. There is a need for methods that combine these approaches in a cost-effectiveness way.

Our review underscores the importance of developing an optimum adherence classification by methods and validating methods for assessing adherence to antimalarial treatment, including specific method for evaluating the causes of non-adherence, as it is a fundamental tool for improving the efficacy of therapy and control.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

LG, PB and HFPS conceived and designed the review. HFPS developed the search strategy. HFPS, LSD and RSP conducted the review and synthesized the findings. HFPS conducted the analysis and wrote the first draft of the manuscript. PB, LG, LSD, RSP and CTDR revised and edited the manuscript. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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