Statistical Analysis Plan

WWARN Vivax Haematology Study Group: Part 2: A pooled analysis investigating the effect of primaquine dose and recurrences on haematological recovery following treatment in patients with *Plasmodium vivax* malaria

Version 1.1

**WorldWide Antimalarial Resistance Network (WWARN)**

Suggested citation: Statistical Analysis Plan, WWARN Vivax Haematology Study Group: Part 2: A pooled analysis investigating the effect of primaquine dose and recurrences on haematological recovery following treatment in patients with *Plasmodium vivax* malaria

|  |  |  |
| --- | --- | --- |
| **Version History Version number**  | **Revision(s) & reason for amendment**  | **Release date**  |
| V1.1  |  |  |

WorldWide Antimalarial Resistance Network (WWARN)

www.wwarn.org

# Contents

Contents 3

1. Introduction and Rationale 5

1.2. Aim of the study 5

1.3. Eligibility criteria for inclusion in the pooled analysis 5

1.3.1 Essential inclusion criteria 5

1.3.2 Desirable criteria 6

1.3.3 Exclusion criteria 6

1.4. Data Pooling 6

2. Outline of Statistical Analysis 7

2.1 Specific objectives of the study 7

2.2 Study endpoints 7

2.2 Definitions of Endpoints 7

2.4 Exposures of interest 8

2.4.1 Primaquine Regimens 8

2.4.2 Number of P. vivax recurrences 9

2.4.3 Timing of P. vivax recurrences 9

2.4.3 Antimalarial elimination half life 9

2.5 Study and patient characteristics 10

2.5 Summary of statistical analyses 11

2.5.1 Description and baseline characteristics of study sample: 11

2.5.2 Baseline characteristics of patients: 11

2.5.3 Causal inference framework and directed acyclic graph describing causal pathways in haemoglobin response: 12

2.5.4 Risk of anaemia at day 90, 180 and 360: 12

2.5.5 Effect of primaquine use and dose on haemoglobin profile over time 13

2.5.6 Effect of primaquine use and dose on incidence rate of anaemia over 12 months 13

2.5.7 Effect of primaquine use and dose on cumulative risk of anaemia over 12 months 14

2.5.8 Effect of number and timing of recurrences on haemoglobin 14

2.5.9 Effect of schizontocidal antimalarial half-life on haemoglobin 14

2.5.10 Effect of number and timing of recurrences, and antimalarial half-life on risk of anaemia from Hb measurements at day 60, 90, 180 and 360 15

4. PRISMA Statement 15

5. Tools 15

6. Study Group Governance, Management, Coordination and Publication Policy 15

7. References 16

# 1. Introduction and Rationale

Recurrent *P. vivax* causes a cumulative risk of severe anaemia and attributable morbidity and mortality. The haematological profile following vivax malaria is complex and related to the risk of recurrent parasitaemia, the timing and frequency of these recurrences and the co-administration of primaquine. Following an acute episode of malaria, the mean haemoglobin (Hb) falls to a nadir on day 2-3 before recovering to baseline values at about day 28 to 42. Patients with recurrent parasitaemia have a lower Hb compared to those patients who remain aparasitaemic. Although recurrent malaria can be prevented by co-administration of primaquine with blood schizontocidal treatment, these patients can have a greater initial fall in Hb compared to those treated with schizontocidal treatment (chloroquine or ACT) alone.

A recent pooled analysis of the haematological response in patients with vivax malaria, focused on clinical trials in which patients were followed until the first recurrent episode of malaria. Most of these studies had a duration of follow-up of 42 days or less. Whilst these data provide valuable insights into the acute risks of anaemia and the initial impact of primaquine they do not provide information on the longer term risks and benefits of primaquine including the effect of timing of recurrences and multiple recurrences.

This study aims to investigate the complex interaction between primaquine, vivax recurrences and a patient’s haematological profile over a prolonged follow up period following treatment of the initial *P. vivax* infection.

## 1.2. Aim of the study

The aim of this study is to assess the effect of treatment with primaquine radical cure and *P. vivax* recurrences on the haematological recovery of patients treated for uncomplicated *P. vivax* malaria.

## 1.3. Eligibility criteria for inclusion in the pooled analysis

## ****Essential inclusion criteria****

* Prospective clinical efficacy studies of uncomplicated vivax malaria
* A minimum follow up of 90 days
* Follow up of patients to study completion irrespective of malaria recurrence(s)
* Treatment with chloroquine or one of four common artemisinin-based combination therapies (artemether-lumefantrine, artesunate-mefloquine, artesunate-amodiaquine, dihydroartemisinin-piperaquine) with or without primaquine (given over multiple days and commencing within seven days of blood schizontocidal treatment)
* Information on use, timing and dose of primaquine
* Study meta-data as described in the [Clinical Data Management and Statistical Analysis Plan](http://www.wwarn.org/sites/default/files/ClinicalDMSAP.pdf) (1)
* Baseline data on patient age and gender
* Asexual parasite density at day 0
* Parasite presence during follow up
* Haemoglobin (hb) or haematocrit (hct) measured on day 0 and at least one further point throughout follow up

## ****Desirable criteria****

* Information on dose of schizontocidal treatment
* Weight
* Individual tablet or mg dosing
* Data on dose adherence
* Documentation on the supervision of drug administration
* Malnutrition as gauged by weight and age +/- height or MUAC
* Qualitative or quantitative assessment of G6PD status
* CYP2D6 status
* History of malaria within the past 28 days
* History of fever
* Data on vomiting post administration
* Symptoms at recurrence
* Genotyping to potentially distinguish recrudescence and reinfection

## ****Exclusion criteria****

* Pregnancy or lactation
* Retrospective studies
* Studies of severe malaria
* Studies without active follow up
* Adjunctive antimalarial treatments

## 1.4. Data Pooling

A systematic review of all prospective clinical efficacy trials involving *Plasmodium vivax* mono-infection will be performed. Trials published or undertaken since the year 2000 inclusive that fulfil the study criteria will be targeted through direct email to the corresponding author and/or principal investigator. Data from unpublished and ongoing clinical studies will also be included if available. Once data are uploaded into the WWARN repository, they will be curated and standardised using the WWARN Data Management and Statistical Analysis Plans (1) for clinical data and pooled into a single database of quality-assured individual patient data.

# 2. Outline of Statistical Analysis

## **Specific objectives of the study**

1. Investigate the effect of primaquine use and dose on i) haematological decline and recovery and ii) the risk of moderate and moderately severe anaemia.
2. Quantify the association between the number and timing of recurrences and i) haematological decline and recovery and ii) the risk of moderate and moderately severe anaemia.
3. Determine the effect of slowly and rapidly eliminated blood schizontocidal treatments on i) haematological decline and recovery and ii) the risk of moderate and moderately severe anaemia.

## **2.2 Study endpoints**

**Primary**:

* Incidence rate of moderate and moderately severe anaemia observed at monthly intervals up to 12 months

**Secondary**:

* Cumulative risk of moderately severe anaemia over 12 months in patients presenting with a Hb ≥7 g/dL
* Risk of moderate and moderately severe anaemia at day 60, 90, 180 and 360
* Mean change in haemoglobin between day 0 and day 60
* Mean change in haemoglobin between day 0 and day 90
* Mean change in haemoglobin between day 0 and day 180
* Mean change in haemoglobin between day 0 and day 360

## Definitions of Endpoints

The incidence rate of moderate and moderately severe anaemia will be determined from monthly (30 days) observations up to 12 months. If more than one observation is available within the observation period then the minimum haemoglobin will be used. The following assumptions will be made for the cumulative risk analysis where there are missing haemoglobin data for a single month X:

|  |  |
| --- | --- |
| Haemoglobin | Assumption for month X |
| Month X-1 | Month X | Month X+1 |
| Not anaemic | Missing | Not anaemic | Not anaemic |
| Anaemic | Missing | Anaemic | Anaemic |
| Not anaemic | Missing | Anaemic | Not anaemic |
| Anaemic | Missing | Not anaemic | Anaemic |
| Either | Missing | Missing |  Missing |
| Missing | Missing | Either | Missing |

Anaemia will be defined as:

* + Moderate (Hb ≥7 g/dL and <10g/dl),
	+ Moderately severe (<7g/dl)

The mean change in haemoglobin between day X and day 0 will be calculated from the haemoglobin that is closest to the day of the planned endpoint, or the first of two days that are equidistant allowing for 14 days variation either side of day 90, 180 and 360 or 10 days variation either side of day 60.

## **2.4 Exposures of interest**

## **2.4.1 Primaquine Regimens**

Total primaquine dose will be assessed as a continuous variable and as a categorical variable (low vs high dose).

**Total PQ** dose categories will be defined as:

* *Very low* *dose* if <2.5 mg/kg
* *Low dose* if 2.5 to <5 mg/kg
* *High dose* in ≥5 mg/kg (6).

**Daily PQ** dose will be defined as:

* *Low dose* if <0.5 mg/kg/day
* *High dose* if ≥0.5 mg/kg/day.

The primaquine dose received will be calculated from the number of daily tablets administered to each patient. If the daily tablet counts are not available, doses will be back-calculated using the dosing scheme available from study protocols. For each component, a total dose per weight will be calculated for each patient.

Primaquine regimens will be further classified according to:

* **Duration of treatment** in days
* **Supervision**
* *Supervised* if all doses were directly observed
* *Partially supervised* if ≥50% of doses were observed
* *Unsupervised* if <50% of doses were observed.

## **2.4.2 Number of P. vivax recurrences**

*P. vivax recurrence* (or a *P. vivax* parasitaemic episode)will be defined as any recurrenceof *P. vivax* parasitaemia.

***Symptomatic P. vivax recurrence***will be defined as any recurrenceof *P. vivax* parasitaemia in association with an axillary temperature ≥37.5°C, an oral or tympanic temperatue of ≥38.0°C or a self-reported fever within the previous 48 hours.

***Asymptomatic P. vivax recurrence***will be defined as any recurrenceof *P. vivax* parasitaemia in absence of a temperature ≥37.5°C or a self-reported fever within the previous 48 hours.

Parasite recurrences will be counted consecutively from the first parasitaemic episode after the initial presentation (which will be classified as the first recurrence) up to the day of interest for the outcome measurement (e.g. day 90 for the primary outcome).

A recurrence will be classified as separate to the previous recurrence if >7 days have elapsed between the last peripheral parasitaemia detected on blood film and the next peripheral parasitaemia being detected, and a negative film has been reported in the interim.

## **2.4.3 Timing of P. vivax recurrences**

Assessment of the timing of recurrences will be undertaken in monthly intervals. The time between day of outcome measurement (ie day 90, 180 or 360) and the last recurrence before then will be categorised as ≤30 days, >30 days to ≤60 days and >60 days.

Figure 1. Categories of timing of *P. vivax recurrences for day of outcome*

>60 days (day 0-30)

>30 to ≤60 days (day 30-60)

≤30 days (day 60-90)

Day 90:

>60 days (day 0-120)

>30 to ≤60 days (day 120-150)

≤30 days (day 150-180)

Day 180:

>60 days (day 0-300)

>30 to ≤60 days (day 300-330)

≤30 days (day 330-360)

Day 360:

## **2.4.3 Antimalarial elimination half life**

The elimination half-life of the antimalarial regimen will be categorised as:

* Rapid (<1 day),
* Intermediate (1 to 7 days)
* Slow (>7 days)

The elimination half-life of combination therapies will be based upon the longest acting partner drug.

## **2.5 Study and patient characteristics**

The following baseline characteristics will be examined:

**Site**: regional relapse periodicity, transmission intensity, geographical location (region)

**Patient:** age, sex, weight, nutritional status, history of malaria in the last 28 days, history of fever in the last 24 hours, fever (≥37.5°C axillary), G6PD status, CYP2D6 status

**Drug**: schizontocidal treatment and mg/kg dose, primaquine use, timing and mg/kg dose, association with food intake, supervision of drug intake (full or partial), early vomiting of drug (within 1 hour)

**Laboratory:** parasitaemia, haemoglobin concentration

Children will be considered as patients aged <15 years with childhood age stratified into <5 years and 5 to <15 years.

The nutritional status of children aged <5 years of age will be calculated as a weight-for-age z-score, using the igrowup package developed by WHO (5). Those with weight-for-age z-scores < -2 (i.e. below the 3rd centile) will be classified as underweight-for-age (termed underweight). Weight-for-age Z scores will be set to missing if the score is less than -6 or greater than 6.

Schizontocidal treatment will be classified as supervised if all doses were directly observed, partially supervised if at least the morning doses of a twice daily regimen were observed, and not-supervised if fewer doses were observed. The doses of treatment received will be calculated from the number of daily tablets administered to each patient. If the daily tablet counts are not available, doses will then be back-calculated using the dosing scheme available from study protocols. For each component, a total dose per weight will be calculated for each patient.

In studies with haematocrit measured instead of haemoglobin, haematocrit will be converted to haemoglobin using the following relationship (7):

Haematocrit (ht) = 5.62 + 2.60 \* Haemoglobin

For each study, locations of study sites will be recorded. Each location will be categorised into:

1. *Low, moderate and high transmission settings* based on the **observed study site reinfection rate, and the** malaria endemicity estimates obtained for subnational regions and year from the Malaria Atlas Project (8).
2. *Low (long) and high (short) periodicity* *of relapses* according to Battle’s regions (9), with high periodicity considered to include regions where the median periodicity was ≤42 days. Thus regions with the two highest periodicities (region 10 and 12) where the median periodicity is <47 days will be categorised as “high” and others will be categorised as “low”.

**CYP2D6 status will be classified by expected phenotype using the activity score system (10, 11) to estimate phenotype from genotype. The activity score assigns** values of 0 to 2 to the CYP2D6 alleles identified in the patient as follows: zero, no-function alleles (\*4, \*4xN, \*5); 0.5, decreased-function (\*9, \*10, \*17, \*29, \*41); 1, normal-function (\*1, \*2, \*39) and 2, increased function (\*1xN, \*2xN). The AS of diplotypes results from the sum of the assigned value to each allele. Patients with AS = 0, AS = 0.5, and AS > 2 are designated as genetic poor, intermediate, and ultrarapid metabolisers, respectively. Patients with AS = 1, 1.5 and 2 AS = 1.5, and AS = 2 are designated as genetic normal metabolisers.

**G6PD deficiency will be classified into severely deficient (<30% activity or a positive qualitative test (eg FST)), intermediate deficiency (**≥**30% to <70% activity or an equivocal qualitative test) or normal (**≥**70% activity).**

## **2.5 Summary of statistical analyses**

## **2.5.1 Description and baseline characteristics of study sample:**

1. A summary (study profile) of the relevant trials uploaded to the WWARN repository will be presented to highlight potential selection bias.
2. A summary of the relevant studies will be presented, including (but not restricted to) distribution of age and baseline Hb, treatment given at baseline and during follow up, treatment of recurrent asymptomatic parasitaemic episodes, food intake with primaquine, follow up duration, description of location by country, transmission intensity, regional relapse periodicity and study sampling procedures. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any differences in the baseline distributions between studies will be noted.
3. A comparison table of the summary statistics of studies that were targeted but not included will be presented to allow evaluation of inclusion bias related to study selection.

## **Baseline characteristics of patients:**

A summary of relevant baseline patient characteristics will be presented including age, sex, weight, malnutrition, treatment given, treatment supervision, blood schizontocidal mg/kg dose, mg/kg dose and timing of primaquine (ie first day of treatment), G6PD status, CYP2D6 status, haemoglobin concentration, asexual parasitaemia, presence of fever (axillary temperature ≥37.5°C or fever recorded).

The distribution of continuous variables will be described using the mean and standard deviation if the data are normally distributed, geometric mean and 95% reference range if the data are normally distributed following a log transformation, or the median and interquartile range if the data are non-normally distributed. Categorical data will be described with frequency and percent. Summary statistics will also be classified by age category (<5, 5-<15, ≥15 years).

## **Causal inference framework and directed acyclic graph describing causal pathways in haemoglobin response:**

Confounders will be selected using a causal diagram framework. Feasibility of causal effect estimation will also be assessed using a directed acyclic graph.

*Figure 2. Causal diagram for exposures of interest: a) PQ use, b) number of recurrences, c) timing of recurrences, d) antimalarial half-life. Confounders are shown in red; ancestors of exposures in green and ancestors of outcomes in blue.*



D

C

B

A

## **Risk of anaemia at day 90, 180 and 360:**

The proportion of patients with mild or moderate anaemia at day 90, 180 and 360 will be determined and described stratified by the use and dose of primaquine, number of recurrences, timing of recurrences, and antimalarial elimination half-life. Number and timing of recurrences will be analysed separately for any *P. vivax* recurrence and symptomatic *P. vivax* recurrences.

## **Effect of primaquine use and dose on haemoglobin profile over time**

Linear mixed effects modeling will be used to assess the impact of primaquine on haemoglobin over time, with estimation of the effect of primaquine on haemoglobin at the outcome day (day 90, 180 and 360) derived from the model. The mean Hb-time response following treatment will be estimated using a linear mixed effects model with non-linear terms, derived by fractional polynomial regression; with fixed effects for the confounders identified in Figure 2A (G6PD status and baseline haemoglobin) and then for additional mediator-outcome variables that are not induced by treatment (age, sex, baseline parasitaemia, relapse periodicity, schizontocidal elimination half-life); with random effects fitted to the terms for time according to an individual within each site. The inclusion of transmission intensity and/or relapse periodicity will be explored based on their correlation. The interaction between PQ use and time will be included, in order to capture the different time course of Hb responses following different regimens. In the subgroup of patients treated with PQ, the effect of total PQ dose on Hb response will be estimated using a similar linear mixed effects model.

Sensitivity analyses will be undertaken excluding i) studies that gave different treatment at presentation and during subsequent parasitaemic episodes and ii) studies that treated patients with asymptomatic recurrences.

## **Effect of primaquine use and dose on incidence rate of anaemia over 12 months**

A Poisson regression model to assess incidence rate of moderate anaemia over 12 months will be undertaken on the subset of studies that followed patients actively and measured haemoglobin at least monthly. The outcome will be assessed for each month of follow up (ie day 31-60, 61-90, etc) with the minimum haemoglobin for each month used in the model. For the first month (day 0-30), only haemoglobin measurements occurring after day 0 will be included; the baseline haemoglobin (at day 0) will be included as a confounder in the model. Primaquine use (exposure of interest) will be controlled for potential confounders identified in Figure 2A (G6PD status and baseline haemoglobin) and also for additional mediator-outcome variables that are not induced by treatment (age, sex, baseline parasitaemia, relapse periodicity, schizontocidal elimination half-life). The inclusion of transmission intensity and/or relapse periodicity will be explored based on their correlation. Patient data will be censored if they were lost to follow up or at the end of the study follow up period if this occurred prior to day 360. Patients with missing data for a month will not be included for that period (ie neither the numerator or denominator data will be included for that period). Results from patients with missing data for >3 months in a row will be excluded after the period that is missing.

Sensitivity analyses will be undertaken i) excluding studies that gave different treatment at presentation and during subsequent parasitaemic episodes, ii) excluding studies that treated patients with asymptomatic recurrences, and iii) including all available data from patients with >3 months missing.

## **Effect of primaquine use and dose on cumulative risk of anaemia over 12 months**

Cox regression analysis for the time to first episode of moderate and moderately severe anaemia during follow-up (90, 180 and 360 days) will be performed separately, with shared frailty for study-site to account for additional variation related to study sites. Inclusion in the analysis will be restricted to the subset of studies that followed patients actively and tested haemoglobin measurements on at least a monthly basis. Primaquine use (exposure of interest) will be controlled for potential confounders identified in Figure 2A (G6PD status and baseline haemoglobin) and also for additional mediator-outcome variables that are not induced by treatment (age, sex, baseline parasitaemia, relapse periodicity, schizontocidal elimination half-life). The inclusion of transmission intensity and/or relapse periodicity will be explored based on their correlation. Variation in the effect of total primaquine dose groups will be explored in a separate Cox regression analysis restricted to patients treated with primaquine. To investigate the impact of small changes in total mg/kg primaquine dose, analyses will be repeated with total mg/kg primaquine dose as a continuous exposure variable. Assumptions about missing data for a single month will be made as described in Section 2.2.

Sensitivity analyses will be undertaken i) excluding studies that gave different treatment at presentation and during subsequent parasitaemic episodes, ii) excluding studies that treated patients with asymptomatic recurrences and iii) making no assumptions about missing data.

## **Effect of number and timing of recurrences on haemoglobin**

The effect of the total number of malaria episodes prior to the outcome day and timing of recurrences (see section 2.4 for categories) prior to the haemoglobin on the outcome day at day 90, 180 and 360 will be assessed using multivariable linear mixed-effects modelling. Separate models will be performed for each day of outcome (90, 180 and 360) and each exposure (number and timing of malaria episodes). Models will be adjusted for the confounders identified in the causal diagrams presented in section 5 (Figures 2A and 2B), which include age, sex, baseline parasitaemia, baseline haemoglobin, schizontocidal elimination half-life, G6PD status, and relapse periodicity/transmission intensity. Study site will be included as a random effect.

The above analyses will be repeated with the exposure adjusted to patients who had symptomatic vivax recurrences.

Sensitivity analyses will be undertaken excluding i) studies that gave different treatment at presentation and during subsequent parasitaemic episodes and ii) studies that treated patients with asymptomatic recurrences.

## **Effect of schizontocidal antimalarial half-life on haemoglobin**

The effect of antimalarial half-lifeon haemoglobin at the outcome day (day 60, 90, 180 and 360) will be assessed using multivariable linear mixed-effects modelling. Patient inclusion will be limited to patients not treated with PQ. Separate models will be performed for each day of outcome (60, 90, 180 and 360). Models will be presented unadjusted and then for additional mediator-outcome variables that are not induced by treatment (Figure 2D: age, sex, baseline parasitaemia, baseline haemoglobin and relapse periodicity/transmission intensity). Study site will be included as a random effect.

## **Effect of number and timing of recurrences, and antimalarial half-life on risk of anaemia from Hb measurements at day 60, 90, 180 and 360**

The analyses described in Section 7-10 above will be repeated using the clinical threshold of anaemia as the outcome using a multivariable logistic mixed effects model for the exposures i) number of recurrences (day 90, 180 and 360), ii) timing of recurrences (day 90, 180 and 360), and iii) antimalarial half-life (day 60, 90, 180 and 360) with random effects for both site and the repeated assessments of haemoglobin.

# 4. PRISMA Statement

The analysis will adhere to the PRISMA guidelines for reporting systematic reviews and meta-analyses of individual patient data (12).

# 5. Tools

All statistical analyses will be carried out using Stata (StataCorp, College Station, Texas). However, when equivalent statistical methods are applied in a different statistical software package (e.g. R statistical software), changing the use of statistical software will not require amendment of this SAP.

# 6. Study Group Governance, Management, Coordination and Publication Policy

The Vivax Haematology Study Group: Part 2 comprises participating investigators who contribute relevant data sets to the pooled analysis. Data sets will remain the property of the investigator and will not be shared without their consent. The WWARN statistician(s) will oversee the statistical analyses. Participating investigators will be recognised in publication as contributors under the banner of the **Vivax Haematology** **Study Group: Part 2**. A Writing Committee will coordinate activities including data analysis and drafting of publications and reports for complete group review. The Writing Committee will comprise Rob Commons, Julie Simpson, Nick Douglas, Cindy Chu, Nick White, Ric Price and other interested investigators. They are responsible for undertaking the data analysis and preparation of the manuscript. Authors will be recognised according to the ICMJE guidelines and the [WWARN publication policy](http://www.wwarn.org/working-together/sharing-data/data-usage) (13).

# 7. References

1. WorldWide Antimalarial Resistance Network. Data Management and Statistical Analysis Plan v1.2 Oxford: WorldWide Antimalarial Resistance Network; 2012 [Available from: [www.wwarn.org/sites/default/files/ClinicalDMSAP.pdf](file:///C%3A%5CUsers%5Crobcommons%5CDropbox%5CPhD%5CPQ%20dosing%20for%20children%5CEmails%5Cwww.wwarn.org%5Csites%5Cdefault%5Cfiles%5CClinicalDMSAP.pdf).

2. U.S. Department of Health and Human Services NIoH, National Institute of Allergy and Infectious Diseases, Division of AIDS,. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. 2017.

3. Improv Study Group. Improving the radical cure of vivax malaria (IMPROV): a study protocol for a multicentre randomised, placebo-controlled comparison of short and long course primaquine regimens. BMC Infect Dis. 2015;15:558.

4. Coleman MD, Coleman NA. Drug-induced methaemoglobinaemia. Treatment issues. Drug Saf. 1996;14(6):394-405.

5. World Health Organization. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva; 2006.

6. John GK, Douglas NM, von Seidlein L, Nosten F, Baird JK, White NJ, et al. Primaquine radical cure of Plasmodium vivax: a critical review of the literature. Malar J. 2012;11:280.

7. Lee SJ, Stepniewska K, Anstey N, Ashley E, Barnes K, Binh TQ, et al. The relationship between the haemoglobin concentration and the haematocrit in Plasmodium falciparum malaria. Malar J. 2008;7:149.

8. Battle KE, Lucas TCD, Nguyen M, Howes RE, Nandi AK, Twohig KA, et al. Mapping the global endemicity and clinical burden of Plasmodium vivax, 2000-17: a spatial and temporal modelling study. Lancet. 2019.

9. Battle KE, Karhunen MS, Bhatt S, Gething PW, Howes RE, Golding N, et al. Geographical variation in Plasmodium vivax relapse. Malar J. 2014;13:144.

10. Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Klein T, Leeder JS. Prediction of CYP2D6 phenotype from genotype across world populations. Genet Med. 2017;19(1):69-76.

11. Gaedigk A, Simon SD, Pearce RE, Bradford LD, Kennedy MJ, Leeder JS. The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype. Clin Pharmacol Ther. 2008;83(2):234-42.

12. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA. 2015;313(16):1657-65.

13. WorldWide Antimalarial Resistance Network. WWARN Publication Policy Oxford, UK: WWARN; 2015 [Available from: <http://www.wwarn.org/sites/default/files/attachments/documents/wwarn_publication_policy.pdf>.

14. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika. 1982;69:239-41.