APPENDIX

Factors Affecting the Electrocardiographic QT Interval in Malaria: A Systematic Review and Meta-analysis of Individual Patient Data

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REFERENCES
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Search Strategy

An electronic literature search was conducted of the MEDLINE, EMBASE, and Global Health databases.

We searched for studies of the quinoline and structurally-related antimalarials amodiaquine, chloroquine, halofantrine, lumefantrine, mefloquine, piperaquine, primaquine, pyronaridine, and quinine for malaria-related indications in human participants with and without clinical *Plasmodium falciparum* and/or *P. vivax* malaria in which electrocardiograms (ECGs) were recorded at documented timepoints before and after drug administration.

We searched for malaria type, antimalarial drug names, and levels of repolarisation-related cardiovascular toxicity as title, abstract, and subject heading keywords, using synonyms and variant spellings as additional search terms.

We excluded animal studies, but did not apply language or publication date limits. Review articles, pooled analyses, case reports, commentary/correspondence articles, and conference abstracts were also excluded. All references were imported into EndNote bibliographic software, de-deduplicated, and screened against eligibility criteria using the Covidence software platform.

E.g. Medline search on 21 August 2017

# Searches

▲
1  Malaria/
2  Malaria, Cerebral/
3  Malaria, Falciparum/
4  Malaria, Vivax/
5  plasmodium falciparum/
6  plasmodium vivax/
7  malaria.ti,ab.
8  falciparum.ti,ab.
9  vivax.ti,ab.
10  plasmodium.ti,ab.
11  1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12  piperaquine.ti,ab.
13  chloroquine.ti,ab.
14  quinine.ti,ab.
15  amodiaquine.ti,ab.
16  lumefantrine.ti,ab.
17  benflumetol.ti,ab.
18  coartem.ti,ab.
19  halofantrine.ti,ab.
20  mefloquine.ti,ab.
21  primaquine.ti,ab.
22  (pyronaridine or pyramax).ti,ab.
23  Amodiaquine/ad, ae, ct, pk, pd, po, to, tu, me, ur, bl, aa
24  Mefloquine/ad, ae, ct, pk, pd, po, to, tu, me, ur, bl, aa
25  Chloroquine/ad, ae, ct, pk, pd, po, to, tu, me, ur, bl, aa
Study-Level Data Extraction

The following information was extracted from study publications, reports, and protocols, and where necessary, requested from study investigators:

1) Study characteristics: year of publication, recruitment period, location, antimalarial treatment indication, participant inclusion and exclusion criteria, number of study participants who had ECG monitoring

2) ECG measurement methodology: centralised or study site-based, manual or automated, cardiologist or other physician reader, intermittent or continuous, any other relevant details

3) Cardiovascular adverse events: sudden cardiac death, life-threatening ventricular tachyarrhythmias (ventricular fibrillation, ventricular tachycardia, torsade de pointes), any other clinically significant arrhythmias or cardiovascular adverse events
Individual Patient-Level Data Standardisation

This was implemented via a bespoke Application Programming Interface in Python version 3.6.3.

**ECG Intervals**

Where the same ECG recording was measured by more than one set of readers, the measurements from the more specialist set of ECG readers were selected.

Measurements from triplicate ECG recordings were averaged.

Only measurements from intermittent ECG readings were used.

**RR Interval**

Heart rates in beats per minute were converted into RR intervals in milliseconds:

- \( \text{RR interval} = \frac{60000}{\text{heart rate}} \)

RR intervals were then transformed with power functions:

- \( \sqrt{\text{RR}} = \sqrt{\frac{1}{\text{RR}}} \) (Bazett’s correction-like)
- \( \text{cbrtRR} = \sqrt[3]{\frac{1}{\text{RR}}} \) (Fridericia’s correction-like)

**QT/QTc interval**

Where only corrected QT intervals were available, uncorrected QT intervals were calculated as follows:

- \( QT = QTcB \times \sqrt{\frac{1}{\text{RR}}} \)
  as \( QTcB = \frac{QT}{\sqrt{\frac{1}{\text{RR}}}} \) (Bazett’s correction formula)

- \( QT = QTcF \times \sqrt[3]{\frac{1}{\text{RR}}} \)
  as \( QTcF = \frac{QT}{\sqrt[3]{\frac{1}{\text{RR}}}} \) (Fridericia’s correction formula)

where RR intervals are in units of seconds

**Demographics**

**Age**

Age was extracted as standardised to years, and otherwise calculated based on the number of years between the subject’s date of birth and the date of the start of the study.

**Weight**

Weight was extracted as standardised to kilogrammes.

**Vital Signs**

**Temperature**

Oral and tympanic body temperatures were extracted as documented in the original data, and converted to degrees Celsius as required. Axillary body temperatures were extracted, converted to degrees Celsius as required, then standardised by the addition of 0.5°C to original readings.

Body temperature was standardised to degrees Celsius using the following formula:

- \( \text{Temperature (°C)} = \frac{[\text{Temperature (°F)} - 32]}{1.8} \)

Temperature recordings documented to be >30 minutes apart from ECG recordings were not considered to be from the same timepoint and therefore not extracted into the pooled dataset.
Laboratory Parameters

Parasitaemia

The highest parasite density available for each timepoint was extracted.

Malaria parasite count measurements were standardised as parasite density per microlitre of blood according to the following formulae before being logarithmically transformed:

- Parasitaemia = (parasite count per 500 WBC / 500) * WBC count [if WBC count available]
- Parasitaemia = (parasite count per 500 WBC / 500) * 8000 [if WBC count missing]

where WBC counts are in units of mm$^3$ of blood

- Parasitaemia = parasite count per 1000 RBC * 125.6 * haematocrit [if haematocrit available]
- Parasitaemia = parasite count per 1000 RBC * 125.6 * 33 [if haematocrit missing]

where haematocrit is in units of %

Haemoglobin

For studies in which only haematocrit was measured, haemoglobin was calculated as follows:

- Haemoglobin (g/dl) = [haematocrit (%) – 5.62] / 2.6 as
  Haematocrit (%) = 5.62 + 2.60 x haemoglobin (g/dl)$^3$

Individual Patient-Level Data Integrity Checks

Individual patient data were checked for completeness, as well as for invalid, out-of-range, or inconsistent entries. Values incompatible with what would be observed in malaria clinical trials were considered missing. Queries were raised with study investigators and resolved where possible.
Data Analysis

Exploratory Analyses

Pairwise relationships among collected variables were visualised using scatterplot matrices. We also summarised correlations among individual-level variables with principal component analysis biplots to identify potential redundancy (Figure S1).

Variable Selection

Variable selection was based on directed acyclic graphs of proposed causal relationships among collected variables informed by literature review and expert consultation used to determine minimal sufficient adjustment sets for regression modelling (Figure S2).

Model Formulation

\begin{align*}
m1: & \quad QT \sim \sqrt{RR} + s(\text{age:sex}) + \text{sex} + (1|\text{study}) \\
m2: & \quad QT \sim \sqrt{RR} + s(\text{age:sex}) + \text{sex} + \text{temperature} + (1|\text{study}) \\
m3: & \quad QT \sim \sqrt{RR} + s(\text{age:sex}) + \text{sex} + \text{temperature} + \text{indication} + (1|\text{study}) \\
m4: & \quad QT \sim \sqrt{RR} + s(\text{age:sex}) + \text{sex} + \text{temperature} + \text{indication} + \sqrt{RR}:\text{indication} + (1|\text{study})
\end{align*}

where \( s() \) denotes a smooth term and : denotes an interaction between variables

Model Priors

We used weakly informative normal prior distributions summarised below:

| Description | Parameter Class | Prior Distribution |
|-------------|----------------|--------------------|
| Coefficients of population-level effects/predictor variables | Coefficient | Normal (0, 50) |
| Standard deviations of group-level/varying effects and splines | Standard deviation | Normal (0, 100) |
| Standard deviation of residuals | Sigma | Normal (0, 30) |

Model Diagnostics & Posterior Predictive Checks

Posterior distributions were estimated using Markov chain Monte Carlo (MCMC) with the Hamiltonian algorithm. Convergence of the Hamiltonian algorithm was done by running four independent chains.

For each parameter:

- Trace plots were inspected for stationarity and mixing of chains
- Effective sample size (ESS) computed to be more than 10% of total sample size
- Gelman-Rubin (\( R \)) convergence statistic checked to be 1 at convergence

In addition, the following Hamiltonian Monte Carlo diagnostics were checked in ShinyStan\textsuperscript{5} version 2.5.0:

- Tree depth information
- Energy Bayesian Fraction of Missing Information
- Divergence information

Visual posterior predictive checks were also performed.
**Model Checking and Comparison**

Comparing two models on PSIS-LOO, if the absolute estimated difference in log predictive density (elpd_diff) is larger than twice the estimated standard error, this suggests one model is expected to have better predictive performance over the other. A negative elpd_diff favours the first model, while a positive elpd_diff favours the second.

**Sensitivity Analyses**

For all participants – alternative transformation for modelling the RR interval

- Alternative RR interval transformation into cube root instead of square root term:
  \[ QT \sim \sqrt[3]{RR} + s(\text{age:sex}) + \text{sex} + \text{temperature} + \text{indication} + \sqrt[3]{RR} : \text{indication} + (1 | \text{study}) \]

For all participants – addition of potential confounder variables

- Addition of binary variable for whether individual was enrolled in a study with one or more TdP risk factors as exclusion criteria:
  \[ QT \sim \sqrt{RR} + s(\text{age:sex}) + \text{sex} + \text{temperature} + \text{indication} + \sqrt{RR} : \text{indication} + \text{TdPriskexclusion} + (1 | \text{study}) \]

- Addition of haemoglobin as a continuous variable:
  \[ QT \sim \sqrt{RR} + s(\text{age:sex}) + \text{sex} + \text{temperature} + \text{indication} + \sqrt{RR} : \text{indication} + \text{haemoglobin} + (1 | \text{study}) \]

In the subgroup of malaria patients only – addition of parasitaemia as a potential confounder

- Addition of log parasitaemia as a continuous variable only:
  \[ QT \sim \sqrt{RR} + s(\text{age:sex}) + \text{sex} + \text{temperature} + \text{indication} + \sqrt{RR} : \text{indication} + \log \text{parasitaemia} + (1 | \text{study}) \]

- Further addition of interaction term for log parasitaemia and treatment indication:
  \[ QT \sim \sqrt{RR} + s(\text{age:sex}) + \text{sex} + \text{temperature} + \text{indication} + \sqrt{RR} : \text{indication} + \log \text{parasitaemia} + \log \text{parasitaemia}:\text{indication} + (1 | \text{study}) \]

For all participants – alternative model formulation for non-linear QT-RR relationship

- Log-log linear model with base 10 logarithmic transformation of QT and RR:
  \[ \log QT \sim \log RR + s(\text{age:sex}) + \text{sex} + \text{temperature} + \text{indication} + \log RR : \text{indication} + (1 | \text{study}) \]
Figure A: Principal Component Analysis Biplots of Factors Affecting the QT Interval in Malaria

HNV = healthy volunteers, IPTi = intermittent preventive therapy in infancy, IPTp = intermittent preventive therapy in pregnancy, Pv = P. vivax malaria, Pf = uncomplicated P. falciparum malaria, severe = severe P. falciparum malaria

sqrtRR = $\sqrt{RR}$, is_male = sex, tempc = temperature, logpara = log(parasitaemia), hb = haemoglobin
Directed acyclic graph describing proposed causal relationships among factors affecting the QT interval in malaria showing the minimal sufficient covariate adjustment set (facet label & green squares) in addition to the RR interval. The minimal adjustment set disease and demographic variables of malaria type, body temperature, age, and sex, as well as the RR interval were used as predictors and study as a varying intercept for Bayesian hierarchical multivariable regression analyses of the QT interval.
**SUPPLEMENTARY RESULTS**

**Data Availability**

48.4% (77/159) of studies for which individual patient data were sought, and 65.1% (28/43) of included studies, were published or conducted between 2007 and 2017. 65.6% (6852/10452) of included participants were enrolled between 2007 and 2017 inclusive.

| Table A: Availability of Published Datasets by Study Year of Publication |
|---------------------------------------------------------------|
| **Study Year of Publication** | **Included in Meta-analysis** | **Insufficient for Inclusion** | **No Data Shared** | **No Response** | **Investigators Not Contactable** | **Total Studies for which IPD Sought** |
|-------------------------------|-------------------------------|-------------------------------|--------------------|----------------|----------------------------------|---------------------------------------|
| 2012-2017                     | 13                            | 1                             | 16                 | 7              | 1                                | 38                                    |
| 2007-2011                     | 7                             | 2                             | 14                 | 3              | 2                                | 28                                    |
| 2002-2006                     | 1                             | 0                             | 7                  | 3              | 4                                | 15                                    |
| 1997-2001                     | 3                             | 0                             | 10                 | 7              | 1                                | 21                                    |
| 1992-1997                     | 3                             | 0                             | 5                  | 15             | 1                                | 24                                    |
| 1988-1992                     | 1                             | 0                             | 5                  | 3              | 2                                | 11                                    |
| **All Years**                 | 28                            | 3                             | 57                 | 38             | 11                               | 137                                   |

| Table B: Availability of Unpublished Datasets by Study Year of Enrolment |
|------------------------------------------------------------------------|
| **Study Year of Last Enrolment**                                       | **Included in Meta-analysis** | **Insufficient for Inclusion** | **Total Studies for which IPD Sought** |
|------------------------------------------------------------------------|-------------------------------|-------------------------------|---------------------------------------|
| 2012-2017                                                              | 5                             | 1                             | 6                                     |
| 2007-2011                                                              | 3                             | 2                             | 5                                     |
| 2002-2006                                                              | 1                             | 2                             | 3                                     |
| 1997-2001                                                              | 0                             | 0                             | 0                                     |
| 1992-1997                                                              | 6                             | 2                             | 8                                     |
| 1988-1992                                                              | 0                             | 0                             | 0                                     |
| **All Years**                                                          | 15                            | 7                             | 22                                    |
Figure C: Availability of Datasets by Study Location – Asia-Pacific

Legend

- Included
- Excluded
- Shared but not included

Base map from Natural Earth (www.naturalearthdata.com)
Figure D: Availability of Datasets by Study Location – Africa & Europe

Legend

- Included
- Excluded
- Shared but not included

Base map from Natural Earth (www.naturalearthdata.com)
Figure E: Availability of Datasets by Study Location – Americas

Legend
- Included
- Excluded
- Shared but not included

Base map from Natural Earth (www.naturalearthdata.com)
| Study ID   | Country          | Region                        | Recruitment   | Malaria                                                                 | Antimalarial Treatment Indication                                                                 | Participants Enrolled | Participants Available | Participants Included | TdP Risk Factors Excluded | ECG Measurement Location | ECG Measurement Reader      | ECG Measurement Method | Temperature Measurement Method | Published |
|-----------|------------------|-------------------------------|---------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------|------------------------|--------------------------|-----------------------------|--------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------|
| Abernethy 2001<sup>6</sup> | USA Americas     | 1995-1996 No                  |               |                                                                        | Healthy volunteer pharmacokinetics                                                              | 21                     | 15                     | 15                       | Yes                         | Site-based               | Other physician            | Intermittent               | Unknown                    | Yes                      |
| Ahmed 2019<sup>7</sup>   | Indonesia Asia   | 2015-2016 No                  |               |                                                                        | Intermittent preventive therapy - pregnancy                                                     | 33                     | 33                     | 28                       | Yes                         | Centralised              | Cardiologist               | Intermittent               | Auxillary                  | Yes                      |
| Baiden 2015<sup>4</sup>  | Burkina Faso, Ghana, Mozambique, Tanzania Africa | 2013-2014 Yes                |               | Uncomplicated malaria - P. falciparum                                   |                                                                                   | 1002                  | 953                    | 950                       | Yes                         | Centralised              | Cardiologist               | Intermittent               | Auxiliary                  | Yes                      |
| Bassat 2009<sup>9</sup>  | Burkina Faso, Kenya, Mozambique, Uganda, Zambia Africa | 2005-2006 Yes                |               | Uncomplicated malaria - P. falciparum                                   |                                                                                   | 1548                  | 1536                   | 1492                      | No                          | Centralised              | Cardiologist               | Intermittent               | Auxiliary                  | Yes                      |
| Bassi 2004<sup>10</sup>  | Nigeria Africa   | 2001 No                       |               |                                                                        | Healthy volunteer pharmacokinetics                                                              | 8                      | 5                      | 5                        | No                          | Site-based               | Cardiologist               | Intermittent               | Unknown                    | Yes                      |
| Darpo 2015<sup>11</sup>  | Switzerland Europe | 2012-2013 No                  |               |                                                                        | Healthy volunteer pharmacokinetics                                                              | 59                     | 59                     | 59                        | Yes                         | Centralised              | Cardiologist               | Intermittent & Continuous | Tympanic                   | Yes                      |
| Funck-Brentano 2019<sup>12</sup> France Europe | 2010 No            |                               |               |                                                                        | Healthy volunteer pharmacokinetics                                                              | 282                   | 281                    | 281                       | Yes                         | Centralised              | Cardiologist               | Intermittent & Continuous | Oral                        | Yes                      |
| Hanboonkunupakarn 2014<sup>13</sup> Thailand Asia | 2012 No            |                               |               |                                                                        | Healthy volunteer pharmacokinetics                                                              | 16                     | 16                     | 16                        | Yes                         | Site-based               | Machine                   | Intermittent & Continuous | Axillary                    | Yes                      |
| Hanboonkunupakarn 2019<sup>14</sup> Thailand Asia | 2014 No            |                               |               |                                                                        | Healthy volunteer pharmacokinetics                                                              | 14                     | 14                     | 14                        | Yes                         | Site-based               | Machine                   | Intermittent               | Axillary                    | No                       |
| Jittamala 2011           | Thailand Asia     | 2011 No                       |               |                                                                        | Healthy volunteer pharmacokinetics                                                              | 10                     | 10                     | 10                        | Yes                         | Site-based               | Machine                   | Intermittent               | Axillary                    | No                       |
| Kredo 2011<sup>15</sup>  | South Africa Africa | 2008-2009 No                  |               |                                                                        | Healthy volunteer pharmacokinetics                                                              | 36                     | 36                     | 36                        | Yes                         | Site-based               | Cardiologist               | Intermittent               | Unknown                    | Yes                      |
| Kredo 2016<sup>16</sup>  | South Africa Africa | 2009 No                       |               |                                                                        | Healthy volunteer pharmacokinetics                                                              | 16                     | 16                     | 16                        | Yes                         | Site-based               | Cardiologist               | Intermittent               | Unknown                    | Yes                      |
| Krudsood 2010<sup>17</sup> | Thailand Asia     | 2004-2005 Yes                 |               |                                                                        | Uncomplicated malaria - P. falciparum                                                          | 50                     | 50                     | 50                        | No                          | Centralised              | Cardiologist               | Intermittent               | Auxiliary                  | Yes                      |
| Looareesuwan 2005        | Thailand Asia     | 2005 Yes                      |               |                                                                        | Uncomplicated malaria - P. falciparum                                                          | 25                     | 25                     | 25                        | Yes                         | Centralised              | Cardiologist               | Intermittent               | Oral                        | No                       |

**Data Description**

Table C: Characteristics of Included Studies
| Study                      | Location   | Region | Year/Range   | Type of Malaria          | Plasmodiumfalciparum | BaseLine | FollowUp | Site-Based | Documenting ECGs | Physician Type | Intermittent | ECG Location | Literature Search |
|----------------------------|------------|--------|--------------|--------------------------|----------------------|----------|----------|------------|-----------------|----------------|--------------|---------------|-----------------|
| Macintyre 2017             | Benin, Burkina Faso, DR Congo, Gabon, Mozambique, Uganda, Vietnam | Africa & Asia | 2014-2015 | Uncomplicated malaria - P. falciparum | 437 440 435 | Yes       | Centralised | Cardiologist | Intermittent | Auxiliary or Tympnic | After literature search |
| Mytton 2007                | Thailand   | Asia   | 2002-2003   | Uncomplicated malaria - P. falciparum | 56 58 58 | No       | Site-based | Other physician | Intermittent | Tympnic | Yes |
| Navaratnam 2009            | Malaysia   | Asia   | 2005        | Healthy volunteer pharmacokinetics | 23 24 24 | Yes      | Centralised | Cardiologist | Intermittent | Unknown | Yes |
| Ndiaye 2011                | Senegal    | Africa  | 2007-2008   | Uncomplicated malaria - P. falciparum | 171 148 148 | Yes    | Centralised | Cardiologist | Intermittent | Auxiliary | Yes |
| Nosten 1993                | Thailand   | Asia   | 1992        | Uncomplicated malaria - P. falciparum | 51 51 17 | No       | Site-based | Other physician | Intermittent | Auxiliary | Yes |
| Nosten 1993i               | Thailand   | Asia   | 1992        | Uncomplicated malaria - P. falciparum | 10 9 7 | No       | Site-based | Other physician | Intermittent | Auxiliary | Yes |
| Nosten 1993ii              | Thailand   | Asia   | 1992        | Uncomplicated malaria - P. falciparum | 53 64 33 | No       | Site-based | Other physician | Intermittent | Auxiliary | Yes |
| Ogutu 2014                 | Kenya      | Africa  | 2007-2008   | Uncomplicated malaria - P. falciparum | 54 51 51 | Yes    | Centralised | Cardiologist | Intermittent | Auxiliary | Yes |
| Price 1995                 | Thailand   | Asia   | 1993-1994   | Uncomplicated malaria - P. falciparum | 140 140 84 | No      | Site-based | Other physician | Intermittent | Auxiliary | Yes |
| Price 1997                 | Thailand   | Asia   | 1994        | Uncomplicated malaria - P. falciparum | 29 29 29 | No       | Site-based | Other physician | Intermittent | Auxiliary | Without documenting ECGs |
| Price 1997ii               | Thailand   | Asia   | 1994-1995   | Uncomplicated malaria - P. falciparum | 13 13 13 | No       | Site-based | Other physician | Intermittent | Auxiliary | Without documenting ECGs |
| Price 1998a                | Thailand   | Asia   | 1994-1995   | Uncomplicated malaria - P. falciparum | 6 6 5 | No       | Site-based | Other physician | Intermittent | Auxiliary | Without documenting ECGs |
| Price 1998b                | Thailand   | Asia   | 1994-1995   | Uncomplicated malaria - P. falciparum | 41 41 38 | No       | Site-based | Other physician | Intermittent | Auxiliary | Without documenting ECGs |
| PROMOTEi                  | Uganda     | Africa  | 2014-2015   | Intermittent preventive therapy - pregnancy | 42 42 42 | Yes    | Site-based | Other physician | Intermittent | Tympnic | Yes |
| PROMOTEii                 | Uganda     | Africa  | 2014-2015   | Intermittent preventive therapy – pregnancy & infancy | 85 85 73 | Yes    | Site-based | Other physician | Intermittent | Tympnic | After literature search |
| Pukrittayakamee 2014a      | Thailand   | Asia   | 2010        | Healthy volunteer pharmacokinetics | 16 16 16 | Yes    | Site-based | Machine | Intermittent | Auxiliary | Yes |
| Study | Year | Region | Country/Countries | Type | Malaria Type | Case Count | Malaria Count | Site Count | Site-based | Physician Type | Physician | Intermittent | Route | Case Count | Malaria Count | Site Count | Site-based | Physician Type | Physician | Intermittent | Route | Case Count | Malaria Count | Site Count | Site-based | Physician Type | Physician | Intermittent | Route |
|-------|------|--------|-------------------|------|--------------|------------|--------------|-----------|------------|-------------|-----------|-------------|-------|------------|-------------|------------|-----------|-------------|-----------|-------------|-------|------------|-------------|------------|-----------|-------------|-----------|-------------|-------|
| Pukrittayakamee 2014b | 2014 | Asia | Thailand | Healthy volunteer pharmacokinetics | 15 | 15 | Yes | Site-based | Machine | Intermittent | Auxillary | No | Siqueira 2017 | 2011-2013 | Yes | Uncomplicated malaria - P. vivax | 354 | 350 | 350 | No | Site-based | Cardiologist | Intermittent | Auxillary | Yes | Tandon 2007 | 2007 | No | Healthy volunteer pharmacokinetics | 24 | 24 | 24 | Yes | Site-based | Other physician | Intermittent | Oral | No | Toure 2015 | 2010-2012 | Yes | Uncomplicated malaria - P. falciparum | 141 | 141 | 141 | Yes | Site-based | Other physician | Intermittent | Auxillary | Yes | Toure 2016 | 2009-2012 | Yes | Uncomplicated malaria - P. falciparum | 1073 | 1073 | 1031 | Yes | Site-based | Other physician | Intermittent | Auxillary or Oral | Yes | Tran 1996 | 1992-1995 | Yes | Severe malaria | 302 | 287 | 286 | No | Site-based | Other physician | Intermittent | Auxillary | Yes | Valecha 2010 | 2005-2007 | Yes | Uncomplicated malaria - P. falciparum | 1148 | 1149 | 1142 | Yes | Centralised | Cardiologist | Intermittent | Unknown | Yes | Valecha 2012 | 2007-2008 | Yes | Uncomplicated malaria - P. falciparum | 240 | 240 | 240 | Yes | Site-based | Other physician | Intermittent | Auxillary or Oral | Yes | Valecha 2016 | 2011-2012 | Yes | Uncomplicated malaria - P. vivax | 317 | 317 | 316 | Yes | Site-based | Other physician | Intermittent | Auxillary or Oral | Yes | van Vugt 1999 | 1996-1997 | Yes | Uncomplicated malaria - P. falciparum | 100 | 100 | 97 | No | Site-based | Cardiologist | Intermittent | Oral | Yes | van Vugt 2000 | 1997-1998 | Yes | Uncomplicated malaria - P. falciparum | 199 | 199 | 198 | No | Site-based | Cardiologist | Intermittent | Oral | Yes | WANECAM | 2011-2013 | Yes | Uncomplicated malaria - P. falciparum | 2486 | 2486 | 2485 | Yes | Centralised | Cardiologist | Intermittent | Auxillary or Oral | Yes | White 1988 | 1985 | Yes | Severe malaria | 62 | 65 | 57 | No | Site-based | Other physician | Intermittent | Rectal | Yes |
Table D: Additional Characteristics of Included Population

|                           | Healthy Participants (n = 674) | Malaria Patients (n = 9778) | Overall (n = 10452) |
|---------------------------|--------------------------------|------------------------------|---------------------|
| Weight (kg)               |                                |                              |                     |
| Median (IQR)              | 63.6 (57.0-72.2)               | 33.0 (15.0-52.0)             | 36.9 (15.1-54.0)    |
| Haemoglobin (g/dL)        |                                |                              |                     |
| Mean (SD)                 | 13.5 (1.7)                     | 11.0 (2.3)                   | 11.2 (2.3)          |
| <11                       | 51 (7.6%)                      | 4856 (49.7%)                 | 4907 (46.9%)        |
| <8                        | 0                              | 844 (8.6%)                   | 844 (8.1%)          |
| <5                        | 0                              | 43 (0.4%)                    | 43 (0.4%)           |
| ECG Measurement Methodology|                                |                              |                     |
| Location of ECG interpretation |                         |                              |                     |
| Centralised and study site-based | 392 (58.2%) | 6778 (69.3%) | 7170 (68.6%) |
| Study site-based only     | 282 (41.8%)                    | 3000 (30.7%)                 | 3282 (31.4%)        |
| ECG reader                |                                |                              |                     |
| Cardiologist              | 449 (66.6%)                    | 7423 (75.9%)                 | 7872 (75.3%)        |
| Other physician or trained personnel | 154 (22.8%) | 2355 (24.1%) | 2509 (24.0%) |
| Machine only              | 71 (10.5%)                     | 0                            | 71 (0.7%)           |
| Temperature Measurement Method |                              |                              |                     |
| Axillary                  | 99 (14.7%)                     | 7771 (79.5%)                 | 7870 (75.3%)        |
| Oral                      | 305 (45.3%)                    | 613 (6.3%)                   | 918 (8.8%)          |
| Tympanic                  | 174 (25.8%)                    | 195 (2.0%)                   | 369 (3.5%)          |
| Rectal                    | 0                              | 57 (0.6%)                    | 57 (0.5%)           |
| Unknown                   | 96 (14.2%)                     | 1142 (11.7%)                 | 1238 (11.8%)        |
| Year of Enrolment         |                                |                              |                     |
| 2012-2017                 | 247 (36.6%)                    | 5316 (54.4%)                 | 5563 (53.2%)        |
| 2007-2011                 | 383 (56.8%)                    | 906 (9.3%)                   | 1289 (12.3%)        |
| 1997-2006                 | 29 (4.3%)                      | 2916 (29.8%)                 | 2945 (28.2%)        |
| 1985-1996                 | 15 (2.2%)                      | 621 (6.4%)                   | 636 (6.1%)          |
| Not reported              | 0                              | 19 (0.2%)                    | 19 (0.2%)           |
Table E: Comparison of Characteristics of Included and Excluded Studies

| Characteristics                                           | Included Studies (n = 43) | Excluded Studies (n = 116) |
|-----------------------------------------------------------|---------------------------|----------------------------|
| **Antimalarial Treatment Indication, studies (%)**        |                           |                            |
| Severe/complicated malaria                                | 2 (4.7%)                  | 17 (14.7%)                 |
| Uncomplicated malaria                                     | 25 (58.1%)                | 61 (52.6%)                 |
| *P. falciparum* mono- or mixed infection                  | 23 (53.5%)                | 52 (44.8%)                 |
| *P. vivax* mono-infection                                 | 2 (4.7%)                  | 3 (2.6%)                   |
| *P. falciparum* or *P. vivax* mono- or mixed infection    | 0                         | 6 (5.2%)                   |
| Intermittent preventive therapy (IPT)                     | 4 (9.3%)                  | 8 (6.9%)                   |
| IPT in pregnancy (IPTp)                                   | 3 (7.0%)                  | 3 (2.6%)                   |
| IPT in infancy (IPTi)                                     | 1 (2.3%)                  | 1 (0.9%)                   |
| Seasonal malaria chemoprevention (SMC)                    | 0                         | 1 (0.9%)                   |
| Occupational prophylaxis                                  | 0                         | 3 (2.6%)                   |
| Healthy volunteer pharmacokinetics                        | 13 (30.2%)                | 30 (25.9%)                 |
| Healthy volunteers only                                   | 13 (30.2%)                | 27 (23.3%)                 |
| Healthy volunteers and uncomplicated malaria (*P. falciparum or *P. vivax infection) | 0 | 3 (2.6%) |
| **Geographical Region, studies (%)**                      |                           |                            |
| Asia-Pacific                                             | 25 (58.1%)                | 57 (49.1%)                 |
| Africa                                                    | 11 (25.6%)                | 28 (24.1%)                 |
| Americas                                                  | 2 (4.7%)                  | 6 (5.2%)                   |
| Europe                                                    | 2 (4.7%)                  | 17 (14.7%)                 |
| Asia-Pacific & Africa                                     | 3 (7.0%)                  | 4 (3.4%)                   |
| Others (Asia-Pacific & Americas, Africa & Europe, Americas & Europe) | 0 | 3 (2.6%) |
| Not reported                                              | 0                         | 1 (0.9%)                   |
| **Year Enrolment Completed, studies (%)**                 |                           |                            |
| 2007-2017                                                 | 24 (55.8%)                | 25 (21.6%)                 |
| Pre-2007                                                  | 19 (44.2%)                | 80 (69.0%)                 |
| Not reported                                              | 0                         | 11 (9.5%)                  |
| **Torsade de Pointes Risk Factors Excluded, studies (%)** |                           |                            |
|                                                           | 26 (60.5%)                | 46 (39.7%)                 |
| **Mean Age in Years, median (IQR)**                       | 26.2 (17.4-32.4)          | 26.6 (16.2-31.5)*          |
| **Percentage of Females, median (IQR)**                   | 41.0 (24.4-53.2)          | 28.7 (0-48.7)*             |
| **Risk of Bias Assessment, studies (%)**                  |                           |                            |
| Low                                                       | 39 (90.7%)                | 75 (64.7%)                 |
| Unclear                                                   | 4 (9.3%)                  | 39 (33.6%)                 |
| High                                                      | 0                         | 2 (1.7%)                   |

*Mean age not available from 8 studies  †Percentage not available from 14 studies
Table F: Risk of Bias Assessment of Included and Excluded Studies

| Study design and objectives | Bias in selection of participants and constitution of study groups | Bias due to withdrawal or loss to follow-up (attrition) | Information bias regarding the drug safety outcome | Other information bias | Conflict of interest | SUMMARY RISK OF BIAS |
|-----------------------------|------------------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------|----------------------|-------------------|----------------------|
| **Randomised Controlled Trials - Included** | | | | | | |
| Abernethy 2001a | | | | | | |
| Bassat 2009b | | | | | | |
| Bassi 2004c | | | | | | |
| Darpo 2015d | | | | | | |
| Funck-Brentano 2019d (subsequently published) | | | | | | |
| Hanboonkunupakarn 2014d | | | | | | |
| Hanboonkunupakarn 2019d (subsequently published) | | | | | | |
| Krudsood 2010d | | | | | | |
| Macintyre 2017d (subsequently published) | | | | | | |
| Mytton 2007d | | | | | | |
| Navaratnam 2009d | | | | | | |
| Ndiaye 2011d | | | | | | |
| Ogutu 2014d | | | | | | |
| Price 1995d | | | | | | |
| Price 1998b | | | | | | |
| PROMOTE | | | | | | |
| Pukrittayakamee 2014a | | | | | | |
| Study Reference                  | Outcome 1 | Outcome 2 | Outcome 3 | Outcome 4 | Outcome 5 | Outcome 6 |
|---------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Pukrittayakamee 2014b (unpublished) | □         | □         | □         | □         | □         | □         |
| Siqueira 2017                  | □         | □         | □         | □         | □         | □         |
| Tandon 2007 (unpublished)      | □         | □         | □         | □         | □         | □         |
| Toure 2015                    | □         | □         | □         | □         | □         | □         |
| Toure 2016                    | □         | □         | □         | □         | □         | □         |
| Tran 1996                     | □         | □         | □         | □         | □         | □         |
| Valecha 2010                  | □         | □         | □         | □         | □         | □         |
| Valecha 2012                  | □         | □         | □         | □         | □         | □         |
| Valecha 2016                  | □         | □         | □         | □         | □         | □         |
| van Vugt 1999                 | □         | □         | □         | □         | □         | □         |
| van Vugt 2000                 | □         | □         | □         | □         | □         | □         |
| WANECAM                       | □         | □         | □         | □         | □         | □         |
| White 1988                    | □         | □         | □         | □         | □         | □         |
| **Randomised Controlled Trials - Excluded** | □         | □         | □         | □         | □         | □         |
| Abdulla 2008                  | □         | □         | □         | □         | □         | □         |
| Abdulla 2010                  | □         | □         | □         | □         | □         | □         |
| Alecrim 2006                  | □         | □         | □         | □         | □         | □         |
| Assimadi 2002                 | □         | □         | □         | □         | □         | □         |
| Benjamin 2015                 | □         | □         | □         | □         | □         | □         |
| Bigira 2014                   | □         | □         | □         | □         | □         | □         |
| Bindschedler 2000             | □         | □         | □         | □         | □         | □         |
| Bindschedler 2002             | □         | □         | □         | □         | □         | □         |
| Bouchaud 2000                 | □         | □         | □         | □         | □         | □         |
| Reference                              | Year          |
|---------------------------------------|---------------|
| Bouyou-Akotet 2010                   |               |
| Bunnag 1989                          |               |
| Cao 1997                              |               |
| D’Alessandro 2006 (unpublished)       |               |
| Haroon 2005                           |               |
| Hien 2011                             |               |
| Jittamala 2015                        |               |
| Kakuda 2013                           |               |
| Karbwang 1991                         |               |
| Karbwang 1992a                        |               |
| Karbwang 1992b                        |               |
| Karbwang 1993b                        |               |
| Karbwang 1995a                        |               |
| Karbwang 1995b                        |               |
| Karbwang 1995c                        |               |
| Karbwang 1997                         |               |
| Kayentao 2012                         |               |
| Kervella 2006 (unpublished)           |               |
| Khan 2011                             |               |
| Kinde-Gazard 2012                     |               |
| Kshirsagar 2000                       |               |
| Laman 2014                            |               |

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| Reference                  | Year | Country | Region | Study Type | Sample Size | Outcomes | Conclusion |
|---------------------------|------|---------|--------|------------|-------------|----------|------------|

**Legend:**
- Green circle: Positive result
- Yellow circle: Negative result
- Red circle: Mixed result
| Study Reference    | Column 1 | Column 2 | Column 3 | Column 4 | Column 5 | Column 6 | Column 7 | Column 8 |
|--------------------|----------|----------|----------|----------|----------|----------|----------|----------|
| Nosten 1990        |          |          |          |          |          |          |          |          |
| Nosten 1994        |          |          |          |          |          |          |          |          |
| Olliaro 2010       |          |          |          |          |          |          |          |          |
| Omoruyi 2007       |          |          |          |          |          |          |          |          |
| Orrell 2008        |          |          |          |          |          |          |          |          |
| Piola 2010         |          |          |          |          |          |          |          |          |
| Poravuth 2011      |          |          |          |          |          |          |          |          |
| Pyar 2007          |          |          |          |          |          |          |          |          |
| Pyar 2009          |          |          |          |          |          |          |          |          |
| Restrepo 1996      |          |          |          |          |          |          |          |          |
| Rueangweerayut 2012|          |          |          |          |          |          |          |          |
| Sabchareon 1988    |          |          |          |          |          |          |          |          |
| SB 1993 (unpublished)|          |          |          |          |          |          |          |          |
| Song 2011          |          |          |          |          |          |          |          |          |
| Sowunmi 1990       |          |          |          |          |          |          |          |          |
| Staedke 2018       |          |          |          |          |          |          |          |          |
| Supan 2017         |          |          |          |          |          |          |          |          |
| Taylor 1998        |          |          |          |          |          |          |          |          |
| Thapa 2007         |          |          |          |          |          |          |          |          |
| Thuma 2000         |          |          |          |          |          |          |          |          |
| Tjitra 2012        |          |          |          |          |          |          |          |          |
| Touze 2002         |          |          |          |          |          |          |          |          |
| Cohorts - Included                                      | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|--------------------------------------------------------|------|------|------|------|------|------|------|------|------|
| Ahmed 2019 (subsequently published)                    |      |      |      |      |      |      |      |      |      |
| Baiden 2015                                            |      |      |      |      |      |      |      |      |      |
| Jittamala 2011 (unpublished)                           |      |      |      |      |      |      |      |      |      |
| Kredo 2011                                             |      |      |      |      |      |      |      |      |      |
| Kredo 2016                                             |      |      |      |      |      |      |      |      |      |
| Looareesuwan 2005 (unpublished)                        |      |      |      |      |      |      |      |      |      |
| Nosten 1993i                                           |      |      |      |      |      |      |      |      |      |
| Nosten 1993ii                                          |      |      |      |      |      |      |      |      |      |
| Nosten 1993iii                                         |      |      |      |      |      |      |      |      |      |
| Price 1997i                                            |      |      |      |      |      |      |      |      |      |
| Price 1997ii                                           |      |      |      |      |      |      |      |      |      |
| Price 1998a                                            |      |      |      |      |      |      |      |      |      |
| PROMOTEii (subsequently published)                     |      |      |      |      |      |      |      |      |      |

| Cohorts - Excluded                                     |      |      |      |      |      |      |      |      |      |
|--------------------------------------------------------|------|------|------|------|------|------|------|------|------|
| Adjei 2012                                             |      |      |      |      |      |      |      |      |      |
| Auprayoon 1995                                         |      |      |      |      |      |      |      |      |      |
| Bhatt 2006                                             |      |      |      |      |      |      |      |      |      |
| Reference                      | Column 1 | Column 2 | Column 3 | Column 4 | Column 5 | Column 6 |
|-------------------------------|----------|----------|----------|----------|----------|----------|
| Byakika-Kibwika 2011          |          |          |          |          |          |          |
| Claessen 1998                 |          |          |          |          |          |          |
| Davis 1988                    |          |          |          |          |          |          |
| Davis 1990                    |          |          |          |          |          |          |
| Edwards 1988                  |          |          |          |          |          |          |
| Falade 2005                   |          |          |          |          |          |          |
| Haider 2013                   |          |          |          |          |          |          |
| Hatz 2008                     |          |          |          |          |          |          |
| Hombhanje 1998                |          |          |          |          |          |          |
| Jaspers 1996                  |          |          |          |          |          |          |
| Karbwang 1993                 |          |          |          |          |          |          |
| Karunajeewa 2004              |          |          |          |          |          |          |
| Khan 2006                     |          |          |          |          |          |          |
| Krishna 1993                  |          |          |          |          |          |          |
| Lavallee 2001                 |          |          |          |          |          |          |
| Mansor 1990                   |          |          |          |          |          |          |
| Matson 1996                   |          |          |          |          |          |          |
| Minodier 2005                 |          |          |          |          |          |          |
| Monlun 1995                   |          |          |          |          |          |          |
| Mra 1991                      |          |          |          |          |          |          |
| Na-Bangchang 1994             |          |          |          |          |          |          |
| Nyunt 2012                    |          |          |          |          |          |          |
As this systematic review was conducted to identify studies for an individual patient data meta-analysis, risk of bias assessment of statistical methods of individual studies was considered not relevant.
Table G: Characteristics of Excluded Participants

| Characteristic                          | Healthy Participants (n = 17) | Malaria Patients (n = 243) | Overall (n = 260) |
|----------------------------------------|------------------------------|----------------------------|-------------------|
| **Antimalarial Treatment Indication**  |                              |                            |                   |
| Severe/complicated malaria             | 9 (3.7%)                     | 9 (3.5%)                   |                   |
| Uncomplicated malaria                  | 234 (96.3%)                  | 234 (90%)                  |                   |
| *P. falciparum* mono- or mixed infection | 233 (95.9%)             | 233 (89.6%)                |                   |
| *P. vivax* mono-infection              | 1 (0.4%)                     | 1 (0.38%)                  |                   |
| Intermittent preventive therapy (IPT)  | 17 (100%)                    |                            | 17 (6.5%)         |
| Pregnancy (IPTp)                       | 5 (29.4%)                    |                            | 5 (1.9%)          |
| Infancy (IPTi)                         | 12 (70.6%)                   |                            | 12 (4.6%)         |
| Healthy volunteer pharmacokinetics     | 0                            |                            |                   |
| **Age (years)**                        |                              |                            |                   |
| Median (IQR)                           | 0.61 (0.61-0.62)             | 14.0 (5.0-24.0)            | 13.0 (4.0-24.0)   |
| <15                                    | 12 (70.6%)                   | 128 (52.7%)                | 140 (54.1%)       |
| <1                                     | 12 (70.6%)                   | 4 (1.6%)                   | 16 (6.2%)         |
| 1-<5                                   | 0                            | 51 (21.0%)                 | 51 (19.7%)        |
| 5-<15                                  | 0                            | 73 (30.0%)                 | 73 (28.2%)        |
| ≥15                                    | 4 (23.5%)                    | 115 (47.3%)                | 119 (45.9%)       |
| ≥35                                    | 1 (5.9%)                     | 39 (16.0%)                 | 40 (15.4%)        |
| ≥50                                    | 0                            | 13 (5.3%)                  | 13 (5.0%)         |
| **Weight (kg)**                        |                              |                            |                   |
| Median (IQR)                           | 7.8 (7.6-8.6)                | 37.6 (15.0-49.7)           | 37.0 (13.8-49.1)  |
| **Sex**                                |                              |                            |                   |
| Female                                 | 11 (64.7%)                   | 112 (46.1%)                | 123 (47.3%)       |
| Pregnant                               | 5 (29.4%)                    | 0                          | 5 (1.9%)          |
| Male                                   | 6 (35.3%)                    | 131 (53.9%)                | 137 (52.7%)       |
| **Temperature (°C)**                   |                              |                            |                   |
| Mean (SD)                              | 37.1 (0.4)                   | 38.1 (1.3)                 | 38.0 (1.3)        |
| ≥37.5                                  | 1 (5.9%)                     | 74 (61.7%)                 | 75 (54.7%)        |
| **Parasitaemia (parasites/μL)**        |                              |                            |                   |
| Median (IQR)                           | N/A                          | 8327 (1306-30142)          | 8327 (1306-30142) |
| ≥10,000                                | N/A                          | 105 (47.3%)                | 105 (43.9%)       |
| ≥50,000                                | N/A                          | 38 (17.1%)                 | 38 (15.9%)        |
| ≥100,000                               | N/A                          | 19 (8.6%)                  | 19 (7.9%)         |
| ≥250,000                               | N/A                          | 2 (0.9%)                   | 2 (0.84%)         |
| **Haemoglobin (g/dL)**                 |                              |                            |                   |
| Mean (SD)                              | 10.4 (1.3)                   | 11.7 (2.1)                 | 11.7 (2.1)        |
| <11                                    | 2 (66.7%)                    | 38 (30.4%)                 | 40 (31.3%)        |
| <8                                     | 0                            | 5 (4.0%)                   | 5 (3.9%)          |
| <5                                     | 0                            |                            |                   |
| **Heart Rate (beats per minute)**      |                              |                            |                   |
| Mean (SD)                              | 122 (18)                     | 107 (31)                   | 108 (31)          |
| ≥140                                   | 0                            | 40 (16.5%)                 | 40 (15.4%)        |
| 120-139                                | 12 (70.6%)                   | 29 (11.9%)                 | 41 (15.8%)        |
| 100-119                                 | 2 (11.8%)                    | 61 (25.1%)                 | 63 (24.2%)        |
| 80-99                                   | 3 (17.6%)                    | 62 (25.5%)                 | 65 (25.0%)        |
| 60-79                                   | 0                            | 44 (18.1%)                 | 44 (16.9%)        |
| <60                                    | 0                            | 7 (2.9%)                   | 7 (2.7%)          |
### Torsade de Pointes Risk Factors

| Excluded from the individual study | Not excluded from the individual study |
|------------------------------------|----------------------------------------|
| 17 (100%)                          | 59 (24.3%)                             |
| 0                                  | 184 (75.7%)                            |
| 0                                  | 184 (70.8%)                            |

### Geographical Region

| Region | Excluded from the individual study | Not excluded from the individual study |
|--------|------------------------------------|----------------------------------------|
| Africa | 12 (70.6%)                         | 102 (42.0%)                            |
| Asia   | 5 (29.4%)                          | 141 (58.0%)                            |
|        |                                    | 146 (56.2%)                            |

### Year of Enrolment

| Year of Enrolment | Excluded from the individual study | Not excluded from the individual study |
|-------------------|------------------------------------|----------------------------------------|
| 2012-2017         | 17 (100%)                          | 51 (21.0%)                             |
| 2007-2011         | 0                                  | 2 (0.82%)                              |
| 1997-2006         | 0                                  | 51 (21.0%)                             |
| 1985-1996         | 0                                  | 139 (57.2%)                            |
|                   |                                    | 139 (53.5%)                            |

*1 participant had missing age; †1 participant had missing weight; ‡123 participants had missing temperature; §21 participants had missing parasitaemia; ‡14 participants had missing haemoglobin; ¶118 participants had missing haemoglobin; ††132 participants had missing haemoglobin
**Statistical Analysis**

**Table H: Model Comparison for Main Analysis of All Participants**

For model formulations, please see *Supplementary Methods – Data Analysis* on page 8 of this appendix.

| Models Compared | Difference in Estimated Log Predictive Density (elpd_diff) | Standard Error (SE) | Interpretation |
|-----------------|-----------------------------------------------------------|---------------------|----------------|
| m1 – m2         | 240.34                                                    | 32.28               | Favours m2     |
| m1 – m3         | 240.43                                                    | 32.29               | Favours m3     |
| m1 – m4         | 371.95                                                    | 47.10               | Favours m4     |
| m2 – m3         | 0.09                                                      | 0.89                | Does not favour m2 or m3 |
| m2 – m4         | 131.60                                                    | 33.54               | Favours m4     |
| m3 – m4         | 131.52                                                    | 33.54               | Favours m4     |

Model expected predictive performance was improved by addition of temperature (m2) as well as malaria type both as an independent term and as an interaction term with $\sqrt{RR}$ (m4) but not when malaria type was added as an independent term alone (m3). Overall, m4 was the best model.
### Sensitivity Analyses – Alternative RR Interval Transformation for Main Analysis of All Participants

**Table I: Multivariable Regression Results from Hierarchical Generalised Additive Model**

| Predictor | Number of Participants | Estimate (95% Credible Interval) / Smooth Description | Clinically Significant? |
|-----------|------------------------|------------------------------------------------------|-------------------------|
| $\sqrt{RR}$ interval, per $\sqrt{\text{millisecond}}$ increase (healthy participants) | 10452 | 43.36 (40.82, 45.81) milliseconds | Yes |
| $\sqrt{RR}$ interval, per $\sqrt{\text{millisecond}}$ increase (by malaria type vs healthy participants) | 10452 | Reference | Yes |
| Healthy participants | 674 | Reference | Healthy participants |
| Uncomplicated vivax malaria | 666 | 1.00 (-2.09, 4.10) milliseconds | |
| Uncomplicated falciparum malaria | 8769 | 7.11 (4.57, 9.73) milliseconds | |
| Severe/complicated malaria | 343 | 16.87 (12.62, 21.16) milliseconds | |
| Age | 10452 | Reference | Age |
| Female | 4252 | Lengthens by $\sim$8 milliseconds over childhood, then lengthens more gradually by another $\sim$5 milliseconds in adulthood | |
| Male | 6200 | Lengthens by $\sim$8 milliseconds over childhood, then shortens by $\sim$10 milliseconds around puberty before gradually lengthening by $\sim$10 milliseconds in adulthood | |
| Sex | 10452 | Reference | Sex |
| Female | 4252 | Reference | Female |
| Male | 6200 | -4.23 (-4.99, -3.46) milliseconds | Male |
| Body temperature, per 1°C increase | 10452 | -2.67 (-3.04, -2.30) milliseconds | Body temperature |
| Malaria Type | 10452 | Reference | Malaria Type |
| Healthy participants | 674 | Reference | Healthy participants |
| Uncomplicated vivax malaria | 666 | -3.08 (-35.47, 29.22) milliseconds | Uncomplicated vivax malaria |
| Uncomplicated falciparum malaria | 8769 | -64.42 (-90.31, -39.01) milliseconds | Uncomplicated falciparum malaria |
| Severe/complicated malaria | 343 | -130.84 (-169.47, -91.96) milliseconds | Severe/complicated malaria |

**Table J: Predicted QT Intervals at Baseline and in Recovery from Malaria and Fever**

| Predictors | Healthy | Uncomplicated vivax | Uncomplicated falciparum | Severe malaria |
|------------|---------|----------------------|--------------------------|---------------|
| QT interval at baseline, milliseconds (95% PI) [HR=100bpm] | 327 (283-395) [T=36.5°C] | 328 (281-371) [T=38.5°C] | 318 (275-358) [T=38.5°C] | 333 (288-377) [T=38.5°C] |
| QT interval in recovery, milliseconds (95% PI) [HR=60bpm] | 396 (352-436) [T=36.5°C] | 402 (356-446) [T=36.5°C] | 403 (359-443) [T=36.5°C] | 433 (386-477) [T=36.5°C] |
| QT lengthening from baseline, milliseconds | 69 | 74 | 85 | 100 |
| Additional QT lengthening from baseline compared to healthy subject, milliseconds | 0 | 5 | 16 | 31 |
| Malaria-related QT lengthening from baseline, % | 0 | 7 | 19 | 31 |

**PI** = prediction interval, **HR** = heart rate, **bpm** = beats per minute, **T** = body temperature

Predicted values for a 25-year-old male from multivariable hierarchical generalised additive model adjusting for heart rate/RR interval (as $\sqrt{RR}$), age, sex, malaria type, body temperature, and individual study effects.
### Table K: Multivariable Regression Results from Hierarchical Generalised Additive Model

| Predictor | Number of Participants | Estimate (95% Credible Interval) / Smooth Description | Clinically Significant? |
|-----------|------------------------|------------------------------------------------------|-------------------------|
| $\sqrt{RR}$ interval, per $\sqrt{\text{millisecond}}$ increase (healthy participants) | 10452 | 9.17 (8.60, 9.74) milliseconds | Yes |
| $\sqrt{RR}$ interval, per $\sqrt{\text{millisecond}}$ increase (by malaria type vs healthy participants) | 10452 | | Yes |
| Healthy participants | 674 | Reference | |
| Uncomplicated vivax malaria | 666 | 0.62 (-0.09, 1.34) milliseconds | |
| Uncomplicated falciparum malaria | 8769 | 2.24 (1.66, 2.82) milliseconds | |
| Severe/complicated malaria | 343 | 4.88 (3.89, 5.91) milliseconds | |
| Age | 10452 | | Yes |
| Female | 4252 | Lengthens by ~8 milliseconds over childhood, then lengthens more gradually by another ~5 milliseconds in adulthood | |
| Male | 6200 | Lengthens by ~8 milliseconds over childhood, then shortens by ~10 milliseconds around puberty before gradually lengthening by ~10 milliseconds in adulthood | |
| Sex | 10452 | | Yes |
| Female | 3909 | Reference | |
| Male | 5869 | -4.23 (-5.00, -3.45) milliseconds | |
| Body temperature, per 1°C increase | 10452 | -2.80 (-3.16, -2.43) milliseconds | Yes |
| Malaria Type | 10452 | | Yes |
| Healthy participants | 674 | Reference | |
| Uncomplicated vivax malaria | 666 | -11.15 (-37.34, 15.24) milliseconds | |
| Uncomplicated falciparum malaria | 8769 | -61.25 (-80.23, -42.60) milliseconds | |
| Severe/complicated malaria | 343 | -109.89 (-140.03, -78.95) milliseconds | |
| Torsade de Pointes Risk Factors Excluded from Individual Study | 10452 | | |
| No | 2819 | Reference | |
| Yes | 7633 | -0.78 (-9.69, 7.88) milliseconds | |

### Table L: Model Comparison

For model formulations, please see *Supplementary Methods – Data Analysis* on pages 8 of this appendix.

| Models Compared | Difference in Estimated Log Predictive Density (elpd_diff) | Standard Error (SE) | Interpretation |
|-----------------|----------------------------------------------------------|---------------------|----------------|
| $m_4$ – ($m_4 + \text{TdPriskexclusion}$) | -0.97 | 0.32 | Favours $m_4$ |

Model expected predictive performance was not improved by addition of the TdP risk factor exclusion term.
### Table M: Multivariable Regression Results from Hierarchical Generalised Additive Model

| Predictor                                      | Number of Participants | Estimate (95% Credible Interval) / Smooth Description | Clinically Significant? |
|------------------------------------------------|------------------------|------------------------------------------------------|-------------------------|
| √RR interval, per vmillisecond increase (healthy participants) | 10452 | 9.16 (8.59, 9.71) milliseconds | Yes                     |
| √RR interval, per vmillisecond increase (by malaria type vs healthy participants) | 10452 | | Yes                     |
| Healthy participants                          | 674                    | Reference                                           |                         |
| Uncomplicated vivax malaria                   | 666                    | 0.65 (-0.05, 1.38) milliseconds                     |                         |
| Uncomplicated falciparum malaria              | 8769                   | 2.25 (1.68, 2.83) milliseconds                      |                         |
| Severe/complicated malaria                    | 343                    | 4.81 (3.81, 5.84) milliseconds                      |                         |
| Age                                            | 10452                  | Lengthens by ~8 milliseconds over childhood, then lengthens more gradually by another ~5 milliseconds in adulthood | Yes                     |
| Female                                         | 4252                   | Lengthens by ~8 milliseconds over childhood, then lengthens more gradually by another ~5 milliseconds in adulthood |                         |
| Male                                           | 6200                   | Lengthens by ~8 milliseconds over childhood, then shortens by ~10 milliseconds around puberty before gradually lengthening by ~10 milliseconds in adulthood |                         |
| Sex                                            | 10452                  | Reference                                           |                         |
| Female                                         | 3909                   | Reference                                           |                         |
| Male                                           | 5869                   | -3.87 (-4.66, -3.07) milliseconds                   |                         |
| Body temperature, per 1°C increase             | 10452                  | -2.76 (-3.13, -2.38) milliseconds                   | Yes                     |
| Malaria Type                                   | 10452                  | Reference                                           |                         |
| Healthy participants                          | 674                    | Reference                                           |                         |
| Uncomplicated vivax malaria                   | 666                    | -12.67 (-38.78, 12.57) milliseconds                 |                         |
| Uncomplicated falciparum malaria              | 8769                   | -62.63 (-81.47, -44.08) milliseconds                |                         |
| Severe/complicated malaria                    | 343                    | -110.75 (-139.99, -81.57) milliseconds              |                         |
| Haemoglobin, per g/dL increase                | 10452                  | -0.51 (-0.72, -0.30) milliseconds                   | No                      |

### Table N: Model Comparison

For model formulations, please see *Supplementary Methods – Data Analysis* on pages 8 of this appendix.

| Models Compared            | Difference in Estimated Log Predictive Density (elpd_diff) | Standard Error (SE) | Interpretation                  |
|----------------------------|-----------------------------------------------------------|---------------------|---------------------------------|
| m4 – (m4 + haemoglobin)    | 19.89                                                     | 10.65               | Does not favour either model    |

Model expected predictive performance was not improved by addition of the haemoglobin term.
### Table O: Multivariable Regression Results from Hierarchical Generalised Additive Model

| Predictor                                                                 | Number of Participants | Estimate (95% Credible Interval) / Smooth Description                                                                 | Clinically Significant? |
|---------------------------------------------------------------------------|------------------------|--------------------------------------------------------------------------------------------------------------------|-------------------------|
| √RR interval, per vmillisecond increase (uncomplicated falciparum malaria) | 9778                   | 11.48 (11.29, 11.67) milliseconds                                                                                  | Yes                     |
| √RR interval, per vmillisecond increase (by malaria type vs uncomplicated falciparum malaria) | 9778                   | Yes                                                                                                                |                         |
| Uncomplicated vivax malaria                                               | 666                    | -1.68 (-2.15, -1.21) milliseconds                                                                                  |                         |
| Uncomplicated falciparum malaria                                          | 8769                   | Reference                                                                                                          |                         |
| Severe/complicated malaria                                                | 343                    | 2.49 (1.55, 3.40) milliseconds                                                                                     |                         |
| Age                                                                       | 9778                   | Yes                                                                                                                |                         |
| Female                                                                     | 3909                   | Lengthens by ~8 milliseconds in childhood, then lengthens more gradually by another ~5 milliseconds in adulthood     |                         |
| Male                                                                       | 5869                   | Lengthens by ~8 milliseconds over childhood, then shortens by ~10 milliseconds around puberty before gradually lengthening by ~10 milliseconds in adulthood |                         |
| Sex                                                                        | 9778                   | Yes                                                                                                                |                         |
| Female                                                                     | 3909                   | Reference                                                                                                          |                         |
| Male                                                                       | 5869                   | -3.76 (-4.55, -2.95) milliseconds                                                                                  |                         |
| Body temperature, per 1°C increase                                        | 9778                   | -2.85 (-3.22, -2.47) milliseconds                                                                                  | Yes                     |
| Malaria Type                                                               | 9778                   | Yes                                                                                                                |                         |
| Uncomplicated vivax malaria                                               | 666                    | 44.83 (26.33, 63.03) milliseconds                                                                                  |                         |
| Uncomplicated falciparum malaria                                          | 8769                   | Reference                                                                                                          |                         |
| Severe/complicated malaria                                                | 343                    | -37.56 (-66.03, -9.28) milliseconds                                                                                 |                         |
| Parasitaemia, per 10-fold increase (uncomplicated falciparum malaria)     | 9778                   | 0.65 (0.17, 1.14) milliseconds                                                                                     | No                      |
| Parasitaemia, per 10-fold increase (by malaria type vs uncomplicated falciparum malaria) | 9778 | No                                                                                                                 |                         |

### Table P: Model Comparison

For model formulations, please see Supplementary Methods – Data Analysis on pages 8 of this appendix.

| Models Compared                              | Difference in Estimated Log Predictive Density (elpd_diff) | Standard Error (SE) | Interpretation                  |
|----------------------------------------------|-----------------------------------------------------------|---------------------|--------------------------------|
| m4 – (m4 + logpara)                          | 5.58                                                      | 5.35                | Does not favour either model    |
| m4 – (m4 + logpara by indication)            | 3.73                                                      | 8.45                | Does not favour either model    |
| (m4 + logpara) – (m4 + logpara by indication)| -1.85                                                     | 8.03                | Does not favour either model    |

Model expected predictive performance was not improved by addition of parasitaemia terms.
### Table Q: Multivariable Regression Results from Hierarchical Generalised Additive Model

| Predictor                                                                 | Number of Participants | Estimate (95% Credible Interval) / Smooth Description | Clinically Significant? |
|--------------------------------------------------------------------------|------------------------|------------------------------------------------------|-------------------------|
| logRR interval, per log(milliseconds) increase (healthy participants)     | 10452                  | 0.36 (0.34, 0.39) log(milliseconds)                  | Yes                     |
| logRR interval, per log(milliseconds) increase (by malaria type vs healthy participants) | 10452                  |                                                     | Yes                     |
| Healthy participants                                                     | 674                    | Reference                                            |                         |
| Uncomplicated vivax malaria                                              | 666                    | 0.014 (-0.018, 0.047) log(milliseconds)              |                         |
| Uncomplicated falciparum malaria                                         | 8769                   | 0.083 (0.055, 0.11) log(milliseconds)                |                         |
| Severe/complicated malaria                                              | 343                    | 0.20 (0.15, 0.24) log(milliseconds)                  |                         |
| Age                                                                      | 10452                  |                                                     |                         |
| Female                                                                   | 4252                   | Lengthens over childhood, then lengthens more gradually in adulthood |                         |
| Male                                                                     | 6200                   | Lengthens over childhood, then shortens by around puberty before gradually lengthening in adulthood |                         |
| Sex                                                                      | 10452                  |                                                     |                         |
| Female                                                                   | 4252                   | Reference                                            |                         |
| Male                                                                     | 6200                   | -0.0055 (-0.0065, -0.0044) log(milliseconds)         |                         |
| Body temperature, per 1°C increase                                       | 10452                  | -0.0037 (-0.0042, -0.0032) log(milliseconds)         | Yes                     |
| Malaria Type                                                             | 10452                  |                                                     |                         |
| Healthy participants                                                     | 674                    | Reference                                            |                         |
| Uncomplicated vivax malaria                                              | 666                    | -0.034 (-0.13, 0.064) log(milliseconds)              |                         |
| Uncomplicated falciparum malaria                                         | 8769                   | -0.24 (-0.32, -0.15) log(milliseconds)               |                         |
| Severe/complicated malaria                                              | 343                    | -0.54 (-0.66, -0.41) log(milliseconds)               |                         |
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