APPENDIX

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

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SUPPLEMENTARY METHODS

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

26 Quinine/ad, ae, ct, pk, pd, po, to, tu, me, ur, bl, aa
27 Primaquine/ad, ae, ct, pk, pd, po, to, tu, me, ur, bl, aa
28 Drug Administration Schedule/
29 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 Electrocardiography/
31 Electrocardiography, Ambulatory/
32 Cardiotoxicity/
33 Arrhythmias, Cardiac/ci, co, di, pp
34 Heart Conduction System/ab, de, pp
35 Long QT Syndrome/ci
36 Torsades de Pointes/ci
37 Cardiovascular Diseases/ci, co
38 Heart/de
39 Heart rate/de, ph, pd
40 Blood Pressure/co, de, pd, ph, th
41 (QT or QTc).ti,ab.
42 (electrocardiogra$ or ECG).ti,ab.
43 cardiotoxicity.ti,ab.
44 toxic$.ti,ab.
45 safety.ti,ab.
46 (adverse adj effect$).ti,ab.
47 (blood adj pressure).ti,ab.
48 pharmacokinetic$.ti,ab.
49 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50 11 and 29 and 49

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[1] 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:

- RR interval = 60000/heart rate

RR intervals were then transformed with power functions:

- sqrtRR = $\sqrt{RR}$ (Bazett's correction-like)
- cbrtRR = $\sqrt[3]{RR}$ (Fridericia's correction-like)

QT/QTc interval

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

- $QT = QTcB * \sqrt{RR}$ as $QTcB = \frac{QT}{\sqrt{RR}}$ (Bazett's correction formula)
- $QT = QTcF * \sqrt[3]{RR}$ as $QTcF = \frac{QT}{\sqrt[3]{RR}}$ (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[2], 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:

- Temperature (°C) = [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[4] used to determine minimal sufficient adjustment sets for regression modelling (Figure S2).

Model Formulation

m1: QT ~ $\sqrt{RR}$ + s(age:sex) + sex + (1 | study)

m2: QT ~ $\sqrt{RR}$ + s(age:sex) + sex + temperature + (1 | study)

m3: QT ~ $\sqrt{RR}$ + s(age:sex) + sex + temperature + indication + (1 | study)

m4: QT ~ $\sqrt{RR}$ + s(age:sex) + sex + temperature + indication + $\sqrt{RR}$:indication + (1 | study)

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 ($\hat{R}$) convergence statistic checked to be 1 at convergence

In addition, the following Hamiltonian Monte Carlo diagnostics were checked in ShinyStan[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 ~ $\sqrt[3]{RR}$ + s(age:sex) + sex + temperature + indication + $\sqrt[3]{RR}$:indication + (1|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 ~ $\sqrt{RR}$ + s(age:sex) + sex + temperature + indication + $\sqrt{RR}$:indication + TdPriskexclusion + (1|study)
- Addition of haemoglobin as a continuous variable:
  QT ~ $\sqrt{RR}$ + s(age:sex) + sex + temperature + indication + $\sqrt{RR}$:indication + haemoglobin + (1|study)

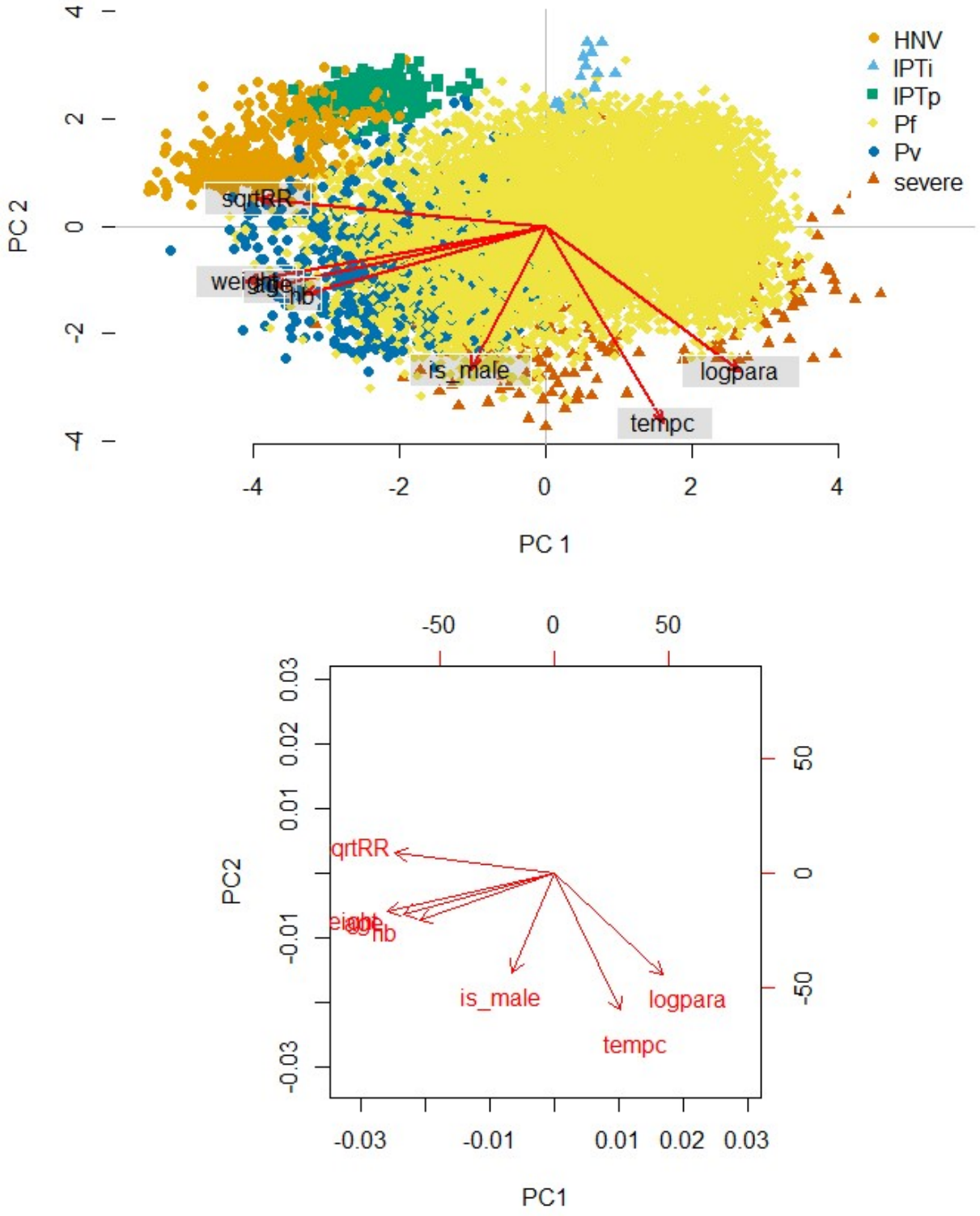
In the subgroup of malaria patients only – addition of parasitaemia as a potential confounder

- Addition of log parasitaemia as a continuous variable only:
  QT ~ $\sqrt{RR}$ + s(age:sex) + sex + temperature + indication + $\sqrt{RR}$:indication + log parasitaemia + (1|study)
- Further addition of interaction term for log parasitaemia and treatment indication:
  QT ~ $\sqrt{RR}$ + s(age:sex) + sex + temperature + indication + $\sqrt{RR}$:indication + log parasitaemia + log parasitaemia:indication + (1|study)

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

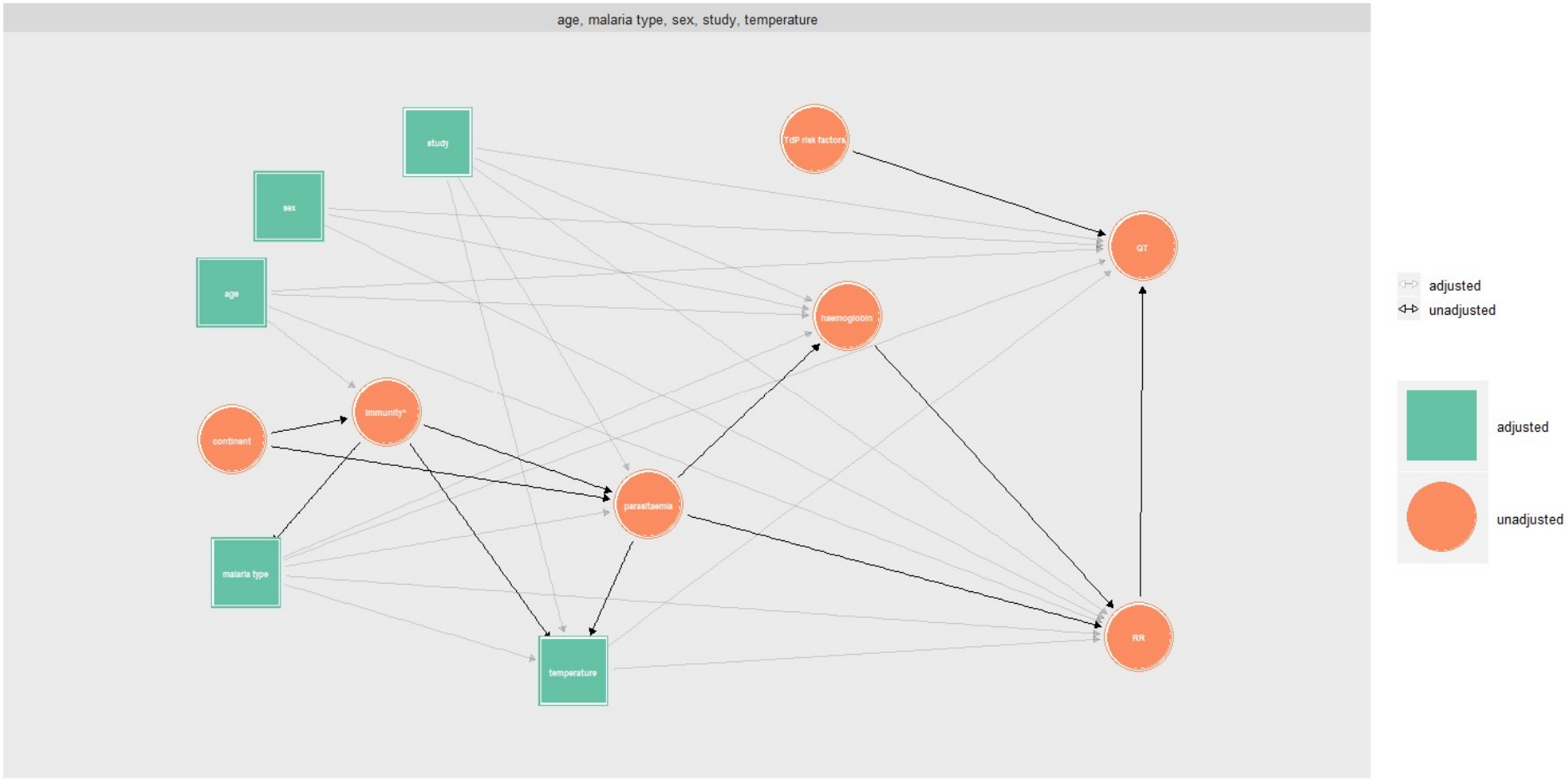
- Log-log linear model with base 10 logarithmic transformation of QT and RR:
  logQT ~ logRR + s(age:sex) + sex + temperature + indication + logRR:indication + (1|study)

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

Figure B: Directed Acyclic Graph of Factors Affecting the QT Interval in Malaria



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.

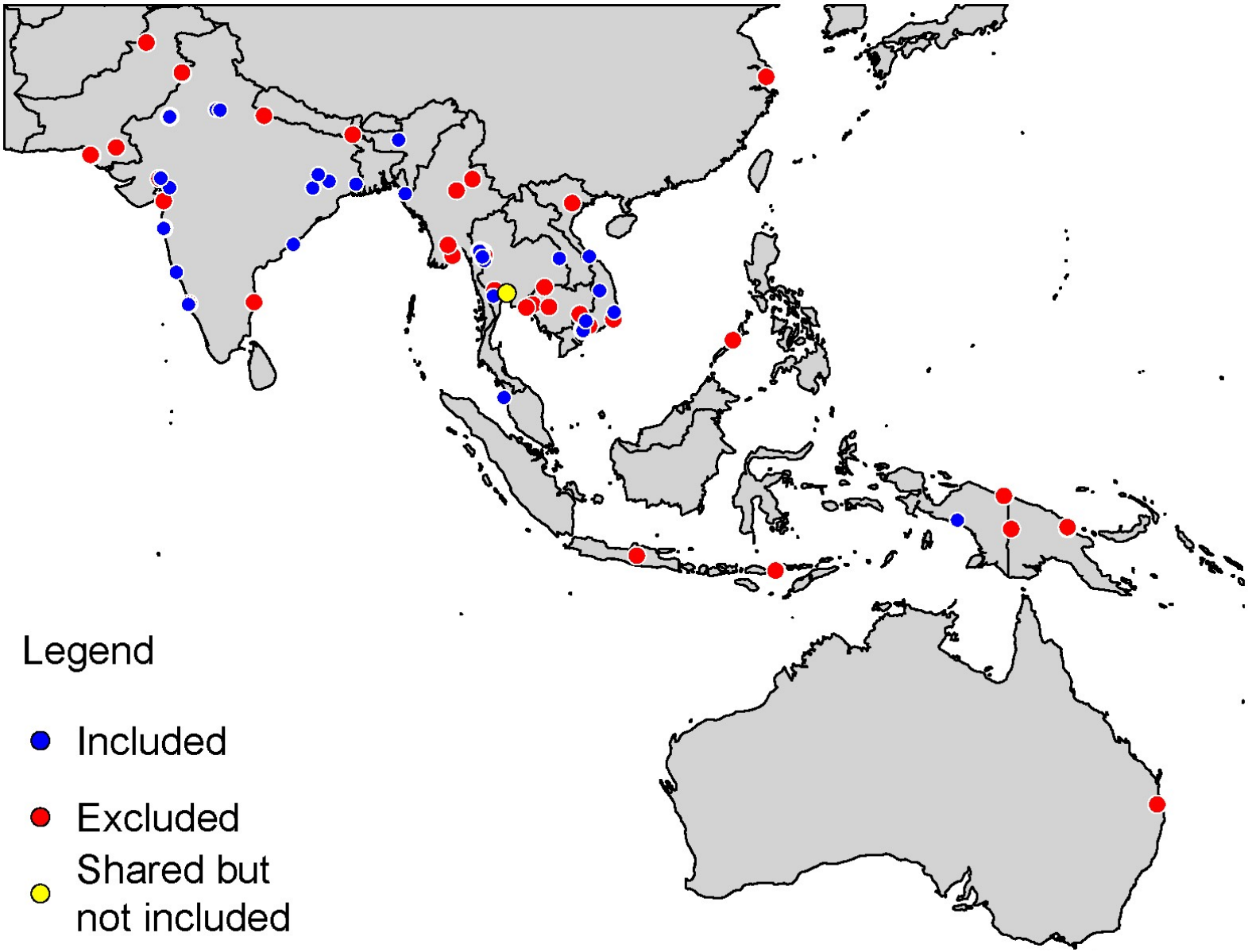
Table A: Availability of Published Datasets by Study Year of Publication

	Studies for which Data Available		*Studies for which Data Not Available*			
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

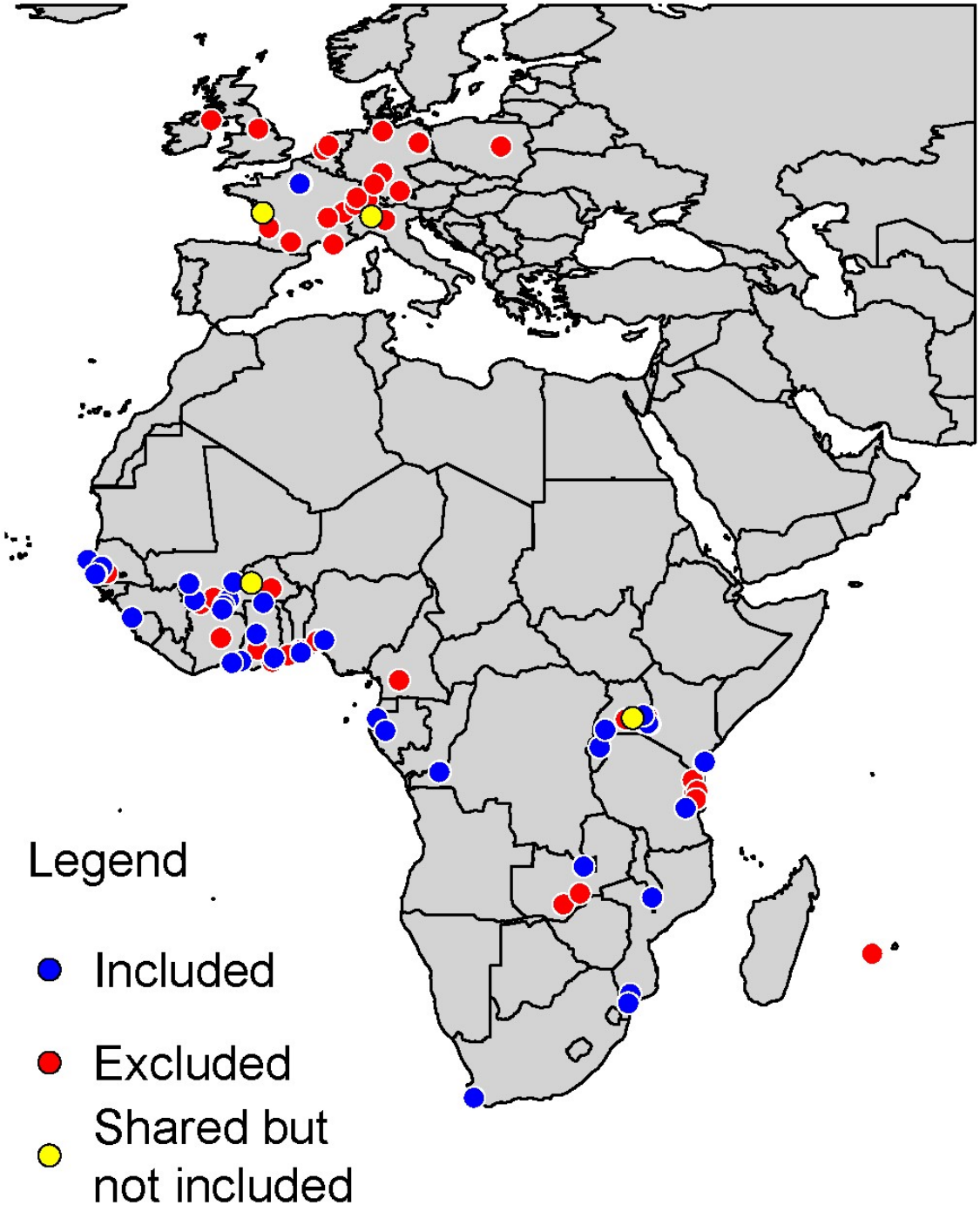
	Studies for which Data Available		
Study Year of Last Enrolment	**Included in Meta-analysis**	**Insufficient for Inclusion**	***Total Studies for which IPD Sought***
2012-2017	5	1	***6***
2007-2011	3	2	***5***
2002-2006	1	2	***3***
1997-2001	0	0	***0***
1992-1997	6	2	***8***
1988-1992	0	0	***0***
All Years	*15*	*7*	***22***

Figure C: Availability of Datasets by Study Location – Asia-Pacific



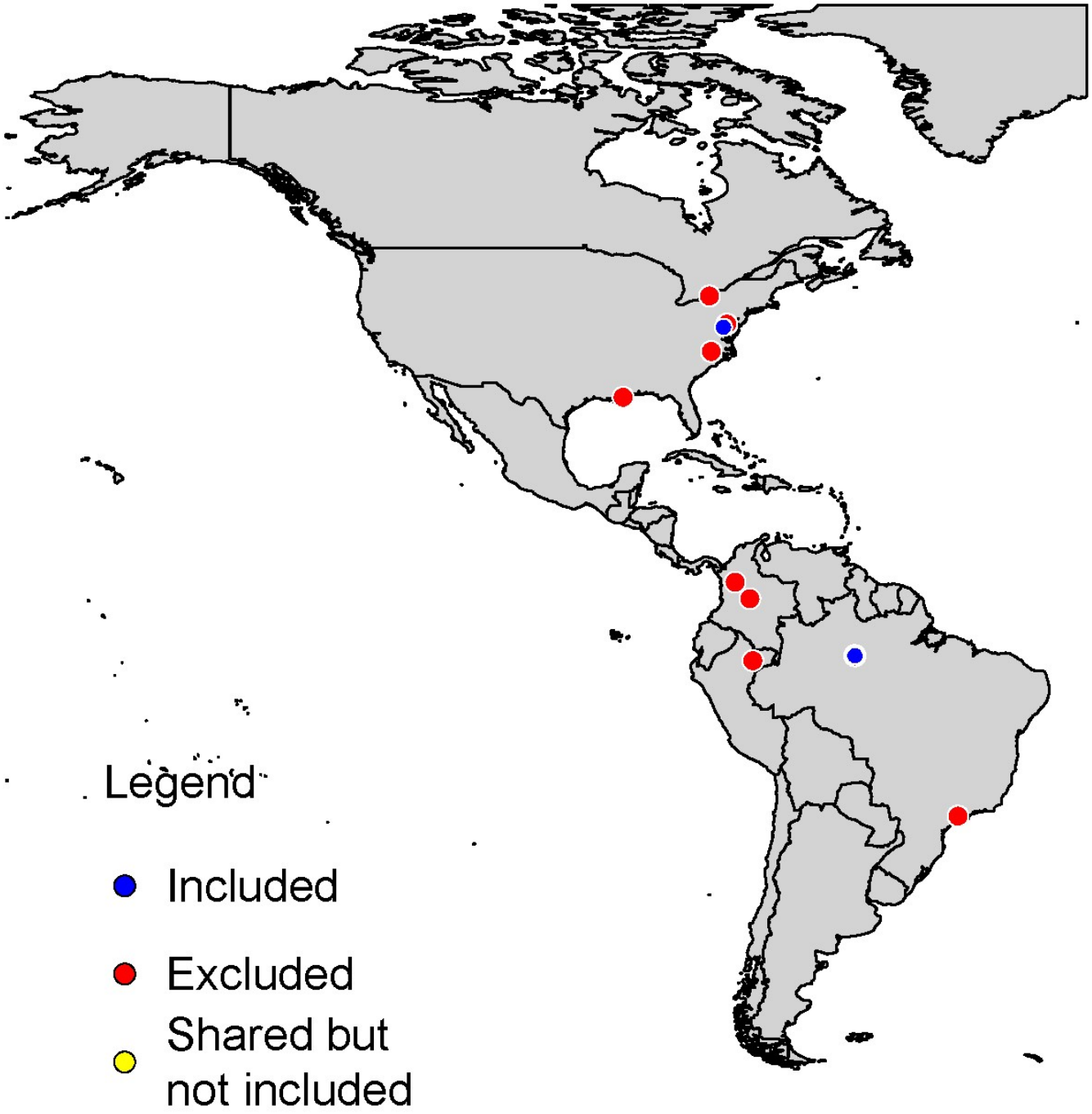
Base map from Natural Earth (www.naturalearthdata.com)

Figure D: Availability of Datasets by Study Location – Africa & Europe



Base map from Natural Earth (www.naturalearthdata.com)

Figure E: Availability of Datasets by Study Location – Americas



Base map from Natural Earth (www.naturalearthdata.com)

Data Description

Table C: Characteristics of Included Studies

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[6]	USA	Americas	1995-1996	No	Healthy volunteer pharmacokinetics	21	15	15	Yes	Site-based	Other physician	Intermittent	Unknown	Yes
Ahmed 2019[7]	Indonesia	Asia	2015-2016	No	Intermittent preventive therapy - pregnancy	33	33	28	Yes	Centralised	Cardiologist	Intermittent	Axillary	After literature search
Baiden 2015[8]	Burkina Faso, Ghana, Mozambique, Tanzania	Africa	2013-2014	Yes	Uncomplicated malaria - P. falciparum	1002	953	950	Yes	Centralised	Cardiologist	Intermittent	Axillary	Yes
Bassat 2009[9]	Burkina Faso, Kenya, Mozambique, Uganda, Zambia	Africa	2005-2006	Yes	Uncomplicated malaria - P. falciparum	1548	1536	1492	No	Centralised	Cardiologist	Intermittent	Axillary	Yes
Bassi 2004[10]	Nigeria	Africa	2001	No	Healthy volunteer pharmacokinetics	8	5	5	No	Site-based	Cardiologist	Intermittent	Unknown	Yes
Darpo 2015[11]	Switzerland	Europe	2012-2013	No	Healthy volunteer pharmacokinetics	59	59	59	Yes	Centralised	Cardiologist	Intermittent & Continuous	Tympanic	Yes
Funck-Brentano 2019[12]	France	Europe	2010	No	Healthy volunteer pharmacokinetics	282	281	281	Yes	Centralised	Cardiologist	Intermittent & Continuous	Oral	After literature search
Hanboonkunupakarn 2014[13]	Thailand	Asia	2012	No	Healthy volunteer pharmacokinetics	16	16	16	Yes	Site-based	Machine	Intermittent	Axillary	Yes
Hanboonkunupakarn 2019[14]	Thailand	Asia	2014	No	Healthy volunteer pharmacokinetics	14	14	14	Yes	Site-based	Machine	Intermittent	Axillary	After literature search
Jittamala 2011	Thailand	Asia	2011	No	Healthy volunteer pharmacokinetics	10	10	10	Yes	Site-based	Machine	Intermittent	Axillary	No
Kredo 2011[15]	South Africa	Africa	2008-2009	No	Healthy volunteer pharmacokinetics	36	36	36	Yes	Site-based	Cardiologist	Intermittent	Unknown	Yes
Kredo 2016[16]	South Africa	Africa	2009	No	Healthy volunteer pharmacokinetics	16	16	16	Yes	Site-based	Cardiologist	Intermittent	Unknown	Yes
Krudsood 2010[17]	Thailand	Asia	2004-2005	Yes	Uncomplicated malaria - P. falciparum	50	50	50	No	Centralised	Cardiologist	Intermittent	Axillary	Yes
Looareesuwan 2005	Thailand	Asia	2005	Yes	Uncomplicated malaria - P. falciparum	25	25	25	Yes	Centralised	Cardiologist	Intermittent	Oral	No

Macintyre 2017[18]	Benin, Burkina Faso, DR Congo, Gabon, Mozambique, Uganda, Vietnam	Africa & Asia	2014-2015	Yes	Uncomplicated malaria - P. falciparum	437	440	435	Yes	Centralised	Cardiologist	Intermittent	Axillary or Tympanic	After literature search
Mytton 2007[19]	Thailand	Asia	2002-2003	Yes	Uncomplicated malaria - P. falciparum	56	58	58	No	Site-based	Other physician	Intermittent	Tympanic	Yes
Navaratnam 2009[20]	Malaysia	Asia	2005	No	Healthy volunteer pharmacokinetics	23	24	24	Yes	Centralised	Cardiologist	Intermittent	Unknown	Yes
Ndiaye 2011[21]	Senegal	Africa	2007-2008	Yes	Uncomplicated malaria - P. falciparum	171	148	148	Yes	Centralised	Cardiologist	Intermittent	Axillary	Yes
Nosten 1993i[22]	Thailand	Asia	1992	Yes	Uncomplicated malaria - P. falciparum	51	51	17	No	Site-based	Other physician	Intermittent	Axillary	Yes
Nosten 1993ii[22]	Thailand	Asia	1992	Yes	Uncomplicated malaria - P. falciparum	10	9	7	No	Site-based	Other physician	Intermittent	Axillary	Yes
Nosten 1993iii[22]	Thailand	Asia	1992	Yes	Uncomplicated malaria - P. falciparum	53	64	33	No	Site-based	Other physician	Intermittent	Axillary	Yes
Ogutu 2014[23]	Kenya	Africa	2007-2008	Yes	Uncomplicated malaria - P. falciparum	54	51	51	Yes	Centralised	Cardiologist	Intermittent	Axillary	Yes
Price 1995[24]	Thailand	Asia	1993-1994	Yes	Uncomplicated malaria - P. falciparum	140	140	84	No	Site-based	Other physician	Intermittent	Axillary	Yes
Price 1997i[25]	Thailand	Asia	1994	Yes	Uncomplicated malaria - P. falciparum	29	29	29	No	Site-based	Other physician	Intermittent	Axillary	Without documenting ECGs
Price 1997ii[25]	Thailand	Asia	1994-1995	Yes	Uncomplicated malaria - P. falciparum	13	13	13	No	Site-based	Other physician	Intermittent	Axillary	Without documenting ECGs
Price 1998a[26]	Thailand	Asia	1994-1995	Yes	Uncomplicated malaria - P. falciparum	6	6	5	No	Site-based	Other physician	Intermittent	Axillary	Without documenting ECGs
Price 1998b[27]	Thailand	Asia	1994-1995	Yes	Uncomplicated malaria - P. falciparum	41	41	38	No	Site-based	Other physician	Intermittent	Axillary	Without documenting ECGs
PROMOTEi[28]	Uganda	Africa	2014-2015	No	Intermittent preventive therapy - pregnancy	42	42	42	Yes	Site-based	Other physician	Intermittent	Tympanic	Yes
PROMOTEii[29]	Uganda	Africa	2014-2015	No	Intermittent preventive therapy – pregnancy & infancy	85	85	73	Yes	Site-based	Other physician	Intermittent	Tympanic	After literature search
Pukrittayakamee 2014a[30]	Thailand	Asia	2010	No	Healthy volunteer pharmacokinetics	16	16	16	Yes	Site-based	Machine	Intermittent	Axillary	Yes

Pukrittayakamee 2014b	Thailand	Asia	2014	No	Healthy volunteer pharmacokinetics	15	15	15	Yes	Site-based	Machine	Intermittent	Axillary	No
Siqueira 2017[31]	Brazil	Americas	2011-2013	Yes	Uncomplicated malaria - P. vivax	354	350	350	No	Site-based	Cardiologist	Intermittent	Axillary	Yes
Tandon 2007	India	Asia	2007	No	Healthy volunteer pharmacokinetics	24	24	24	Yes	Site-based	Other physician	Intermittent	Oral	No
Toure 2015[32]	India, Ivory Coast, Rwanda	Africa & Asia	2010-2012	Yes	Uncomplicated malaria - P. falciparum	141	141	141	Yes	Site-based	Other physician	Intermittent	Axillary	Yes
Toure 2016[33]	Bangladesh, DR Congo, India, Ivory Coast, Malawi, Mozambique, Senegal, Thailand	Africa & Asia	2009-2012	Yes	Uncomplicated malaria - P. falciparum	1073	1073	1031	Yes	Site-based	Other physician	Intermittent	Axillary or Oral	Yes
Tran 1996[34]	Vietnam	Asia	1992-1995	Yes	Severe malaria	302	287	286	No	Site-based	Other physician	Intermittent	Axillary	Yes
Valecha 2010[35]	India, Lao PDR, Thailand	Asia	2005-2007	Yes	Uncomplicated malaria - P. falciparum	1148	1149	1142	Yes	Centralised	Cardiologist	Intermittent	Unknown	Yes
Valecha 2012[36]	India, Thailand	Asia	2007-2008	Yes	Uncomplicated malaria - P. falciparum	240	240	240	Yes	Site-based	Other physician	Intermittent	Axillary or Oral	Yes
Valecha 2016[37]	India	Asia	2011-2012	Yes	Uncomplicated malaria - P. vivax	317	317	316	Yes	Site-based	Other physician	Intermittent	Axillary or Oral	Yes
van Vugt 1999[38]	Thailand	Asia	1996-1997	Yes	Uncomplicated malaria - P. falciparum	100	100	97	No	Site-based	Cardiologist	Intermittent	Oral	Yes
van Vugt 2000[39]	Thailand	Asia	1997-1998	Yes	Uncomplicated malaria - P. falciparum	199	199	198	No	Site-based	Cardiologist	Intermittent	Oral	Yes
WANECAM[40,41]	Burkina Faso, Guinea, Mali	Africa	2011-2013	Yes	Uncomplicated malaria - P. falciparum	2486	2486	2485	Yes	Centralised	Cardiologist	Intermittent	Axillary or Oral	Yes
White 1988[42]	The Gambia	Africa	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

	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 2001[6]							
Bassat 2009[9]							
Bassi 2004[10]							
Darpo 2015[11]							
Funck-Brentano 2019[12] (subsequently published)							
Hanboonkunupakarn 2014[13]							
Hanboonkunupakarn 2019[14] (subsequently published)							
Krudsood 2010[17]							
Macintyre 2017[18] (subsequently published)							
Mytton 2007[19]							
Navaratnam 2009[20]							
Ndiaye 2011[21]							
Ogutu 2014[23]							
Price 1995[24]							
Price 1998b[27]							
PROMOTEi[28]							
Pukrittayakamee 2014a[30]							

Pukrittayakamee 2014b (unpublished)							
Siqueira 2017[31]							
Tandon 2007 (unpublished)							
Toure 2015[32]							
Toure 2016[33]							
Tran 1996[34]							
Valecha 2010[35]							
Valecha 2012[36]							
Valecha 2016[37]							
van Vugt 1999[38]							
van Vugt 2000[39]							
WANECAM[40,41]							
White 1988[42]							
Randomised Controlled Trials - Excluded							
Abdulla 2008[43]							
Abdulla 2010[44]							
Alecrim 2006[45]							
Assimadi 2002[46]							
Benjamin 2015[47]							
Bigira 2014[48]							
Bindschedler 2000[49]							
Bindschedler 2002[50]							
Bouchaud 2000[51]							

Bouyou-Akotet 2010[52]							
Bunnag 1989[53]							
Cao 1997[54]							
D'Alessandro 2006 (unpublished)							
Haroon 2005[55]							
Hien 2011[56]							
Jittamala 2015[57]							
Kakuda 2013[58]							
Karbwang 1991[59]							
Karbwang 1992a[60]							
Karbwang 1992b[61]							
Karbwang 1993b[62]							
Karbwang 1995a[63]							
Karbwang 1995b[64]							
Karbwang 1995c[65]							
Karbwang 1997[66]							
Kayentao 2012[67]							
Kervella 2006 (unpublished)							
Khan 2011[68]							
Kinde-Gazard 2012[69]							
Kshirsagar 2000[70]							
Laman 2014[71]							

Lefevre 2001[72]							
Lefevre 2002a[73]							
Lefevre 2002b[74]							
Lefevre 2013[75]							
Liu 2014[76]							
Llanos-Cuentas 2014[77]							
Lon 2014[78]							
Manning 2014[79]							
Massougbodji 2002[80]							
McGready 2008[81]							
Miller 2013[82]							
Moore 2014[83]							
Morris 2012[84]							
Murphy 1996[85]							
Mutabingwa 2009[86]							
Mzayek 2007[87]							
Na-Bangchang 2000[88]							
Na-Bangchang 2005[89]							
Nasveld 2010[90]							
Nelwan 2015[91]							
Newton 2001[92]							
Ngouesse 2001[93]							

Nosten 1990[94]							
Nosten 1994[95]							
Olliaro 2010[96]							
Omoruyi 2007[97]							
Orrell 2008[98]							
Piola 2010[99]							
Poravuth 2011[100]							
Pyar 2007[101]							
Pyar 2009[102]							
Restrepo 1996[103]							
Rueangweerayut 2012[104]							
Sabchareon 1988[105]							
SB 1993 (unpublished)							
Song 2011[106]							
Sowunmi 1990[107]							
Staedke 2018[108] (subsequently published)							
Supan 2017[109]							
Taylor 1998[110]							
Thapa 2007[111]							
Thuma 2000[112]							
Tjitra 2012[113]							
Touze 2002[114]							

Trung 2009[115]							
Tshefu 2010[116]							
van Agtmael 1999[117]							
van Hensbroek 1996[118]							
Walker 1993[119]							
Cohorts - Included							
Ahmed 2019[7] (subsequently published)							
Baiden 2015[8]							
Jittamala 2011 (unpublished)							
Kredo 2011[15]							
Kredo 2016[16]							
Looareesuwan 2005 (unpublished)							
Nosten 1993i[22]							
Nosten 1993ii[22]							
Nosten 1993iii[22]							
Price 1997i[25]							
Price 1997ii[25]							
Price 1998a[26]							
PROMOTEii[29] (subsequently published)							
Cohorts - Excluded							
Adjei 2012[120]							
Auprayoon 1995[121]							
Bhatt 2006[122]							

Byakika-Kibwika 2011[123]							
Claessen 1998[124]							
Davis 1988[125]							
Davis 1990[126]							
Edwards 1988[127]							
Falade 2005[128]							
Haider 2013[129]							
Hatz 2008[130]							
Hombhanje 1998[131]							
Jaspers 1996[132]							
Karbwang 1993a[133]							
Karunajeewa 2004[134]							
Khan 2006[135]							
Krishna 1993[136]							
Lavallee 2001[137]							
Mansor 1990[138]							
Matson 1996[139]							
Minodier 2005[140]							
Monlun 1995[141]							
Mra 1991[142]							
Na-Bangchang 1994[143]							
Nyunt 2012[144]							

Ogunkunle 2011[145]							
Roggelin 2014[146]							
Rusca 2007 (unpublished)							
SB 1994 (unpublished)							
Sowunmi 1998[147]							
Stein 2015[148]							
Sukontason 1996[149]							
Supanaranond 1997[150]							
Touze 1996[151]							
von Seidlein 1997[152]							
Win 1992[153]							

Legend

	Low		Unclear		High

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

	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		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	0	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	17 (100%)	59 (24.3%)	76 (29.2%)
Not excluded from the individual study	0	184 (75.7%)	184 (70.8%)
Geographical Region			
Africa	12 (70.6%)	102 (42.0%)	114 (43.8%)
Asia	5 (29.4%)	141 (58.0%)	146 (56.2%)
Year of Enrolment			
2012-2017	17 (100%)	51 (21.0%)	68 (26.2%)
2007-2011	0	2 (0.82%)	2 (0.77%)
1997-2006	0	51 (21.0%)	51 (19.6%)
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?
$\sqrt[3]{RR}$ interval, per $\sqrt[3]{}$millisecond increase (healthy participants)	10452	43.36 (40.82, 45.81) milliseconds	Yes
$\sqrt[3]{RR}$ interval, per $\sqrt[3]{}$millisecond increase (by malaria type vs healthy participants)	10452		Yes
Healthy participants	674	Reference	
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		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	4252	Reference	
Male	6200	-4.23 (-4.99, -3.46) milliseconds	
Body temperature, per 1°C increase	10452	-2.67 (-3.04, -2.30) milliseconds	Yes
Malaria Type	10452		Yes
Healthy participants	674	Reference	
Uncomplicated vivax malaria	666	-3.08 (-35.47, 29.22) milliseconds	
Uncomplicated falciparum malaria	8769	-64.42 (-90.31, -39.01) milliseconds	
Severe/complicated malaria	343	-130.84 (-169.47, -91.96) milliseconds	

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

	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 $\sqrt[3]{RR}$), age, sex, malaria type, body temperature, and individual study effects

Sensitivity Analyses – Addition of TdP Risk Factor Exclusion Term for Main Analysis of All Participants

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 √millisecond increase (healthy participants)	10452	9.17 (8.60, 9.74) milliseconds	Yes
$\sqrt{RR}$ interval, per √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
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
m4 – (m4 + TdPriskexclusion)	-0.97	0.32	Favours m4

Model expected predictive performance was not improved by addition of the TdP risk factor exclusion term.

Sensitivity Analyses – Addition of Haemoglobin Term for Main Analysis of All Participants

Table M: Multivariable Regression Results from Hierarchical Generalised Additive Model

Predictor	Number of Participants	Estimate (95% Credible Interval) / Smooth Description	Clinically Significant?
$\sqrt{RR}$ interval, per √millisecond increase (healthy participants)	10452	9.16 (8.59, 9.71) milliseconds	Yes
$\sqrt{RR}$ interval, per √millisecond 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		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	-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		Yes
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.

Sensitivity Analyses – Addition of Parasitaemia Terms for Subgroup Analysis of Malaria Patients Only

Table O: Multivariable Regression Results from Hierarchical Generalised Additive Model

Predictor	Number of Participants	Estimate (95% Credible Interval) / Smooth Description	Clinically Significant?
$\sqrt{RR}$ interval, per √millisecond increase (uncomplicated falciparum malaria)	9778	11.48 (11.29, 11.67) milliseconds	Yes
$\sqrt{RR}$ interval, per √millisecond 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
Uncomplicated vivax malaria	666	2.10 (-0.66, 4.80)	
Uncomplicated falciparum malaria	8769	Reference	
Severe/complicated malaria	343	-1.90 (-3.98, 0.14)	

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.

Sensitivity Analyses – Alternative Model Formulation for Non-Linear QT-RR Relationship for All Participants

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(millisecond) increase (healthy participants)	10452	0.36 (0.34, 0.39) log(milliseconds)	Yes
logRR interval, per log(millisecond) 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		Yes
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		Yes
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		Yes
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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