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RESEARCH ARTICLE

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Haematological consequences of acute uncomplicated falciparum malaria: a WorldWide Antimalarial Resistance Network pooled analysis of individual patient data

The WorldWide Antimalarial Resistance Network Falciparum Haematology Study Group*

Abstract

Background: *Plasmodium falciparum* malaria is associated with anaemia-related morbidity, attributable to host, parasite and drug factors. We quantified the haematological response following treatment of uncomplicated *P. falciparum* malaria to identify the factors associated with malarial anaemia.

Methods: Individual patient data from eligible antimalarial efficacy studies of uncomplicated *P. falciparum* malaria, available through the WorldWide Antimalarial Resistance Network data repository prior to August 2015, were pooled using standardised methodology. The haematological response over time was quantified using a multivariable linear mixed effects model with nonlinear terms for time, and the model was then used to estimate the mean haemoglobin at day of nadir and day 7. Multivariable logistic regression quantified risk factors for moderately severe anaemia (haemoglobin < 7 g/dL) at day 0, day 3 and day 7 as well as a fractional fall $\geq 25\%$ at day 3 and day 7.

Results: A total of 70,226 patients, recruited into 200 studies between 1991 and 2013, were included in the analysis: 50,859 (72.4%) enrolled in Africa, 18,451 (26.3%) in Asia and 916 (1.3%) in South America. The median haemoglobin concentration at presentation was 9.9 g/dL (range 5.0–19.7 g/dL) in Africa, 11.6 g/dL (range 5.0–20.0 g/dL) in Asia and 12.3 g/dL (range 6.9–17.9 g/dL) in South America. Moderately severe anaemia (Hb < 7g/dl) was present in 8.4% (4284/50,859) of patients from Africa, 3.3% (606/18,451) from Asia and 0.1% (1/916) from South America. The nadir haemoglobin occurred on day 2 post treatment with a mean fall from baseline of 0.57 g/dL in Africa and 1.13 g/dL in Asia. Independent risk factors for moderately severe anaemia on day 7, in both Africa and Asia, included moderately severe anaemia at baseline (adjusted odds ratio (AOR) = 16.10 and AOR = 23.00, respectively), young age (age < 1 compared to ≥ 12 years AOR = 12.81 and AOR = 6.79, respectively), high parasitaemia (AOR = 1.78 and AOR = 1.58, respectively) and delayed parasite clearance (AOR = 2.44 and AOR = 2.59, respectively). In Asia, patients treated with an artemisinin-based regimen were at significantly greater risk of moderately severe anaemia on day 7 compared to those treated with a non-artemisinin-based regimen (AOR = 2.06 [95%CI 1.39–3.05], $p < 0.001$).

Conclusions: In patients with uncomplicated *P. falciparum* malaria, the nadir haemoglobin occurs 2 days after starting treatment. Although artemisinin-based treatments increase the rate of parasite clearance, in Asia they are associated with a greater risk of anaemia during recovery.

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Keywords: *Plasmodium falciparum*, Artemisinin-based therapy, Non-artemisinin-based therapy, Antimalarials, Haemoglobin, Severe anaemia, Pooled analysis of individual patient data

Background

Malaria remains a major cause of anaemia in malaria endemic countries, with a complex pathogenesis attributable to red cell destruction and haematopoietic suppression [1] that can be compounded by malnutrition, helminth carriage and inherited blood disorders [2]. Artemisinin-based combination therapy (ACT) is the first-line antimalarial treatment for uncomplicated malaria in almost all endemic countries [3], achieving high cure rates, rapid parasite clearance and reduced ongoing transmission of the parasite [4, 5]. However, artemisinin derivatives can suppress reticulocytosis and contribute to haemolysis; their use has been associated with delayed-onset anaemia [6, 7]. The haematological recovery and adverse consequences of the artemisinin derivatives, following the treatment of falciparum malaria, may vary between different ACTs [8].

To assess the comparative benefits of different antimalarial treatment regimens, it is critical to quantify the haematological impact attributable to *P. falciparum* infection and the clinical and demographic factors that underlie this. The aim of this study was to determine the pattern of haematological recovery following uncomplicated falciparum malaria and define the risk factors for moderately severe haematological outcomes at baseline and during early follow-up.

Methods

The WWARN repository and study selection

Haemoglobin concentrations are often not reported in antimalarial trial publications, even if these data are collected. Since a review of published literature would not provide sufficiently comprehensive information, the focus of this individual patient data meta-analysis was on studies identified in the WWARN repository. The WWARN repository contains data from 451 antimalarial efficacy studies in which patients were enrolled from locations in 69 countries, with a diverse range of *P. falciparum* transmission intensities. Data in the repository have been standardised and collated using methodology described previously in the WWARN Clinical Module Data Management and Statistical Analysis Plan [9].

The WWARN repository was searched in August 2015 for all antimalarial efficacy studies of uncomplicated *P. falciparum* malaria in non-pregnant patients that followed subjects prospectively for a minimum of 28 days and reported haemoglobin concentration (or haematocrit) at least at baseline (day 0). Investigators of

the identified studies were invited to participate in this study group and information was made available on the WWARN website [10]. Uncomplicated *P. falciparum* malaria was defined as microscopy-proven falciparum malaria without features of severe malaria [11]. Patients were excluded if they had severe malaria.

Outcomes of interest

The primary outcome of the analysis was the risk of moderately severe anaemia (Hb < 7 g/dL) on day 7 after initiation of treatment. Secondary outcomes included the mean fall in haemoglobin at day of nadir and day 7, the timing of nadir haemoglobin, risk of moderately severe anaemia at days 0 and 3, and the risk of a large reduction in haemoglobin from baseline, defined as a fractional fall in Hb of $\geq 25\%$ on day 3 or 7.

Statistical methods

All statistical analyses were done using R (Version 3.2.5, The R Foundation for Statistical Computing) or Stata MP 15, based on an a priori statistical plan shared with data contributors [10].

Haematocrit measurements were converted to haemoglobin concentrations using the following formula: Haemoglobin = (Haematocrit - 5.62)/2.60 [12]. The timing of sampling was defined as day 0 if occurring on the day of enrolment / first day of treatment, with sequential numbering thereafter. Data were stratified by region (Africa, Asia and South America). Univariable and multivariable mixed effects logistic regression models were used to model risk of (i) moderately severe anaemia on day 0, 3 or 7 and (ii) large reduction in haemoglobin on day 3 or 7. Study site (sites within countries) was included as a random intercept in these models.

Changes in mean haemoglobin over time were examined, after stratifying by region, using linear mixed effects models. Fractional polynomial terms for time were fitted as random effects for patients to capture the nonlinear associations and random intercepts for patients and study site. All available haemoglobin measurements were included in these analyses. Additional analyses of mean haemoglobin over time within each region were undertaken, stratified by age group (< 5 years and ≥ 5 years).

For all regression models, independent risk factors were identified following the strategy recommended by Collet [13]. Covariates examined included the

following: age in years (categorised as < 1 year, 1 to 4 years, 5 to 11 years and ≥ 12 years), sex, fever (temperature > 37.5 °C) on enrolment, baseline parasitaemia (after log transformation), mixed *Plasmodium* species infection, underweight (defined as weight-for-age Z-score < -2 for children younger than 5 years) [14], high parasitaemia (defined as > 100,000 parasites/ μ L [15]), presence of gametocytaemia on enrolment, transmission intensity, treatment (artemisinin-based therapy versus non-artemisinin-based therapy) and parasite clearance (early clearance on day 1 or day 2 versus delayed parasite clearance on day 3 or later). Red cell indices were not available. Malaria transmission intensity was defined based on estimates of *P. falciparum* prevalence rate (PfPR) according to enrolment year and location [16], assuming low transmission for study sites with a PfPR < 0.15, moderate transmission if PfPR 0.15 to < 0.40 and high transmission if PfPR ≥ 0.40 . Fractional polynomials were used to define the nonlinear relationships between outcome and continuous covariates.

Ethics

All data included in this analysis were obtained in accordance with ethical approvals from the countries of origin. The data are fully anonymised and cannot be

traced back to individuals. This analysis did not require separate ethical approval according to the guidelines of the Oxford Central University Research Ethics Committee.

Results

A total of 200 *P. falciparum* clinical trials undertaken between 1991 and 2013 met the inclusion criteria and were available for analysis (Fig. 1, Additional file 1: Tables S1-S2, and Additional file 2: Figure S1) [1, 17–177]. Individual records were available from 70,226 patients, of whom 50,859 (72.4%) were enrolled in Africa, 18,451 (26.3%) in Asia and 916 (1.3%) in South America (Table 1). In Asia and South America, 61.8% (11,963/19,367) of the patients were male and 35.0% (6775/19,357) were younger than 12 years old. In African studies, there was an equal sex distribution (51.1% males, 25,566/49,998) and 88.3% (44,890/50,859) were younger than 12 years old. Overall, 76.5% (53,730) of patients received artemisinin-based treatment varying from 72.5% in Africa, to 87.2% in Asia and 89.6% in South America (Table 1 and Additional file 3: Table S3). In the 53,730 patients receiving an artemisinin-based treatment, artemether-lumefantrine (AL) was administered in 34.2% (18,359) of cases, artesunate-amodiaquine

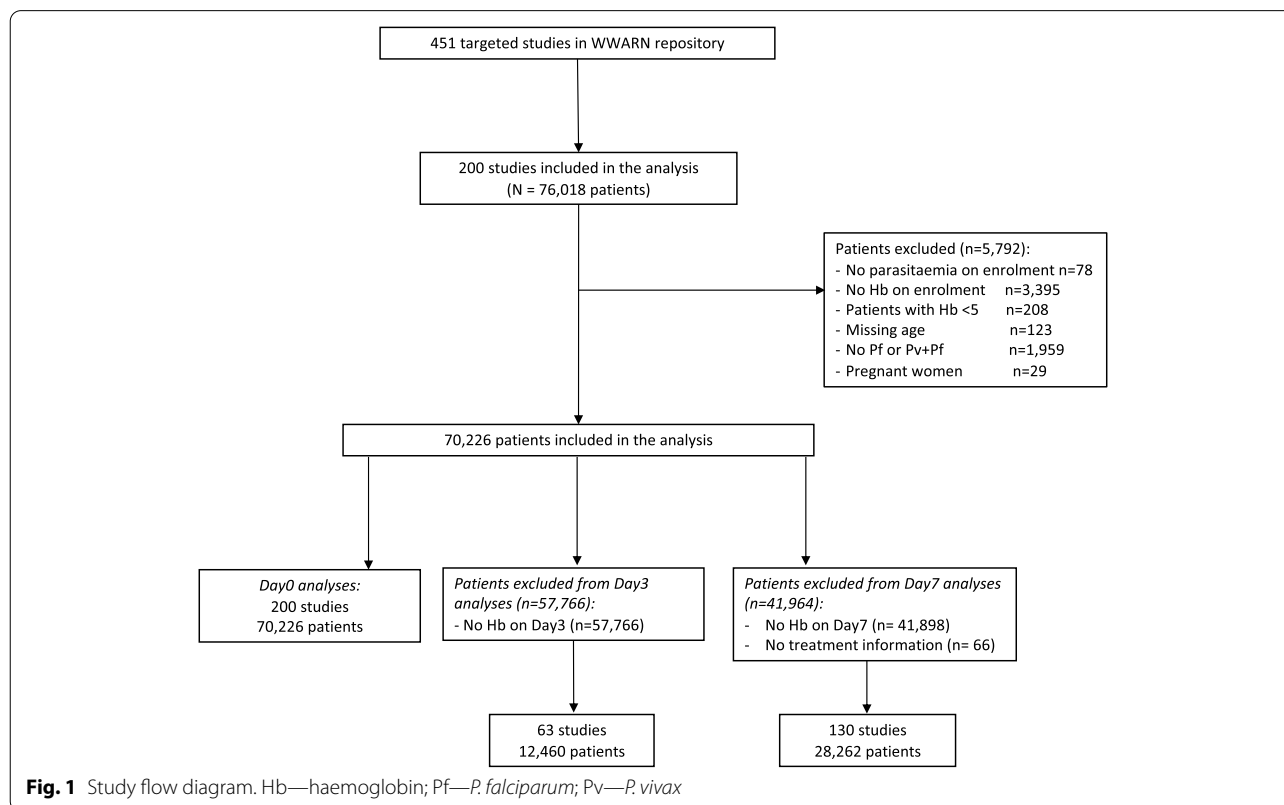


Table 1 Demographic and baseline characteristics

	Africa N (%) or median (range)	Asia N (%) or median (range)	South America N (%) or median (range)
Number of patients evaluated	50,859	18,451	916
Age (years)	3 (0.03–86.7)	16 (0.2–88.0)	23 (3.1–65.0)
<i>Age group</i>			
< 1 year	4562 (9.0)	67 (0.4)	0 (0)
1–4 years	31,225 (61.4)	2071 (11.2)	2 (0.2)
5–11 years	9103 (17.9)	4524 (24.5)	111 (12.1)
≥ 12 years	5969 (11.7)	11,789 (63.9)	803 (87.7)
<i>Sex^a</i>			
Female	24,432 (48.9)	7054 (38.2)	350 (38.2)
Male	25,566 (51.1)	11,397 (61.8)	566 (61.8)
Haemoglobin (g/dL) ^b	9.9 (5.0–19.7)	11 (5.0–20.0)	12.3 (6.9–17.9)
Haematocrit (%) ^c	31.6 (10.0–54.0)	36.3 (14.4–55.0)	37.3 (18–54.1)
Derived haemoglobin (g/dL) ^d	9.9 (5.0–19.7)	11.6 (5.0–20.0)	12.3 (6.9–17.9)
<i>Anaemia</i>			
Moderately severe anaemia (haemoglobin < 7 g/dL)	4284 (8.4)	606 (3.3)	1 (0.1)
Moderate anaemia (haemoglobin 7–< 10 g/dL)	21,676 (42.6)	4260 (23.1)	78 (8.5)
No anaemia (haemoglobin ≥ 10 g/dL)	24,899 (49.0)	13,585 (73.6)	837 (91.4)
Temperature (°C) ^e	38 (34.0–42.0)	37.7 (34.0–42.0)	37.5 (35.1–42.0)
Fever (temperature > 37.5 °C)	32,266 (65.9)	8937 (54.2)	438 (48.0)
Parasitaemia (μL)	21,600 (2.5–486,080)	9375 (7–499,712)	4490 (8–149,925)
High parasitaemia (> 100,000/μl)	5200 (10.2)	1548 (8.4)	3 (0.3)
Presence of gametocytaemia ^f	2339 (8.2)	1530 (11.2)	107 (11.8)
Underweight (WAZ < – 2) ^g	6205 (18.8)	781 (39.0)	2 (100)
<i>Species of infection</i>			
Mixed <i>P. falciparum</i> and <i>P. vivax</i>	0 (0)	1151 (6.2)	0 (0)
<i>P. falciparum</i> mono-infection	50,859 (100)	17,300 (93.8)	916 (100)
<i>Transmission setting</i>			
High	19,766 (38.9)	0 (0)	0 (0)
Moderate	15,357 (30.2)	561 (3.0)	0 (0)
Low	15,736 (30.9)	17,890 (97.0)	916 (100)
<i>Treatment</i>			
Artemisinin-based	36,823 (72.5)	16,086 (87.2)	821 (89.6)
Non-artemisinin-based	13,935 (27.5)	2360 (12.8)	95 (10.4)

Total number of patients enrolled in Africa was 50,859, Asia was 18,451 and South America was 916

^a Data on patient sex were only available for 49,998 patients from Africa

^b Data on baseline haemoglobin were only available for 47,778 patients from Africa and 7139 patients from Asia

^c Data on baseline haematocrit were only available for 13,244 patients from Africa and 13,892 patients from Asia

^d The following conversion from haematocrit was used: haemoglobin = (haematocrit – 5.62)/2.60

^e Data on baseline temperature were only available for 48,982 patients from Africa and 16,483 patients from Asia

^f Data on baseline gametocytes were only available for 28,453 patients from Africa, 13,697 patients from Asia and 904 patients from South America

^g Data on weight-for-age Z-scores (WAZ) were only available for 33,048 patients from Africa, 2001 patients from Asia and 2 patients from South America. WAZ was only evaluated in children < 5 years

(ASAQ) in 19.6% (10,536), artesunate-mefloquine (ASMQ) in 14.5% (7764), dihydroartemisinin-piperaquine (DP) in 15.3% (8197), and other artemisinin-based treatments in 16.5% (8874) (Additional file 3: Table S3).

Haematological status at enrolment

The haematological exclusion criteria differed between studies. The commonest haematological exclusion criterion was a haemoglobin < 5 g/dL (used in 126 studies where 39,940 patients were included), with 2 studies (483

patients) excluding patients with a haemoglobin < 6 g/dL, 9 studies (5964 patients) excluding patients with a haemoglobin < 7 g/dL and 3 studies (566 patients) excluding patients with a haemoglobin < 8 g/dL. In 60 studies, haematological exclusion criteria were not stated; Additional file 1: Table S2. There were 208 patients with a haemoglobin < 5 g/dL at baseline, who were excluded from further analysis, since they met the WHO criteria for severe malaria.

The median haemoglobin at enrolment was 9.9 g/dL (range 5.0–19.7 g/dL) in Africa, 11.6 g/dL (range 5.0–20.0 g/dL) in Asia and 12.3 g/dL (range 6.9–17.9 g/dL) in South America (Table 1). Moderately severe anaemia was defined as haemoglobin concentration < 7 g/dL and was present in 4891 (6.9%) patients at baseline, with a prevalence of 8.4% (4284/50,859) in Africa, 3.3% (606/18,451) in Asia and 0.1% (1/916) in South America. Owing to the limited numbers of patients from South America, all subsequent analyses were restricted to patients from either Africa or Asia and stratified by geographical location.

The mean haemoglobin at enrolment varied with both age and baseline parasitaemia (Additional file 2: Figure S2). The main risk factors for moderately severe anaemia at baseline in both Africa and Asia were young age and presenting without high parasitaemia (> 100,000/ μ L); Additional file 3: Table S4 and S5. In Africa, the risk of moderately severe anaemia was inversely related to

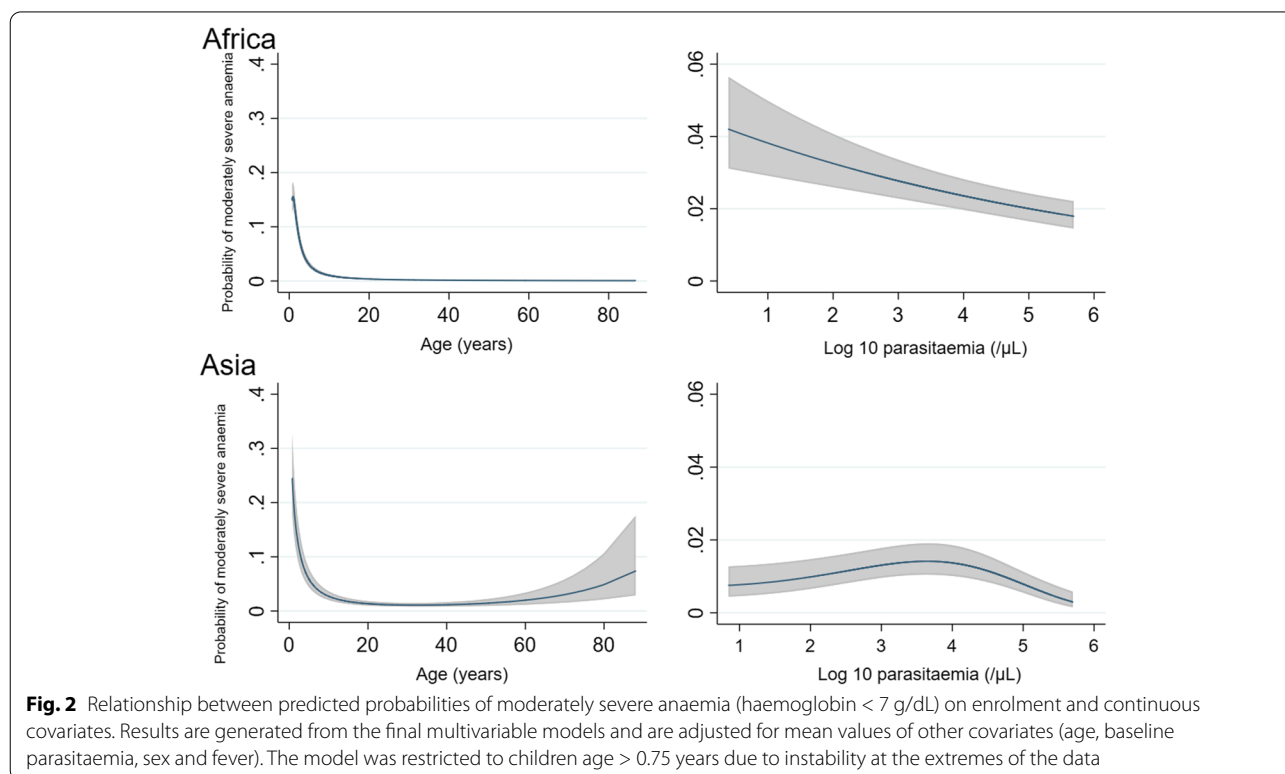
parasitaemia, whereas in Asia the risk rose to a peak at 10,000 parasites/ μ L, and decreased thereafter (Fig. 2).

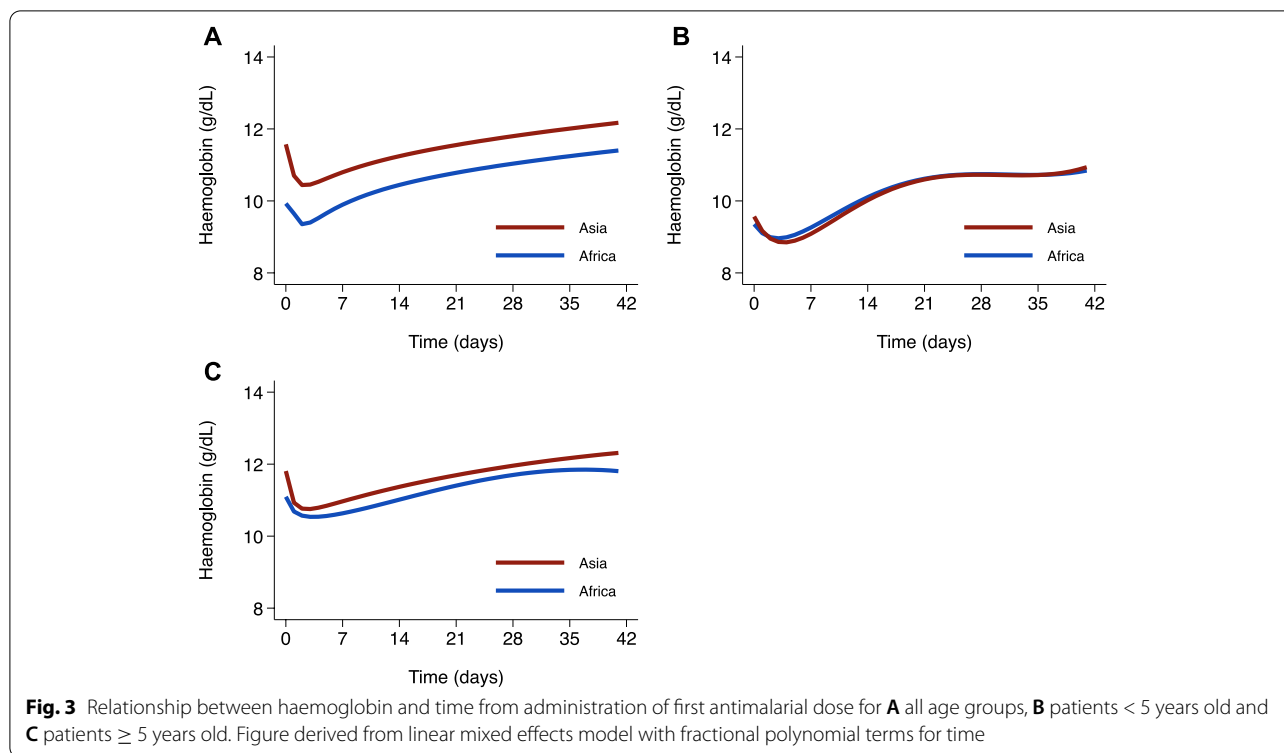
Haemoglobin profile following the start of treatment

A linear mixed effects model of all haemoglobin concentrations over time showed that following the start of treatment haemoglobin concentration fell rapidly to a nadir on day 2 (Fig. 3). The estimated mean fall in haemoglobin in Africa was 0.57 g/dL at day 2 and 0.03 g/dL at day 7, with corresponding estimates in Asia of 1.13 g/dL and 0.78 g/dL. Haemoglobin concentrations returned to baseline by day 8 in Africa and day 22 in Asia, and thereafter continued to increase, reaching a mean concentration at day 42 of 11.40 g/dL (95%CI 11.28–11.52) in Africa (1.47 g/dL above baseline) and 12.17 g/dL (95%CI 11.98–12.36) in Asia (0.60 g/dL above baseline) (Fig. 3).

Haematological recovery was assumed to have occurred by day 42, and therefore, the observation on this day represented the baseline Hb of this patient population without infection. In African patients, 71.3% of the total fall in Hb from predicted baseline occurred before treatment and 28.3% after treatment. The corresponding percentages in Asia were 34.7% and 65.3% respectively.

Differences in the haemoglobin profiles between Africa and Asia were largely attributable to the variation in the age distributions of the study populations. When





the analyses were stratified by age, the haemoglobin profiles were similar for the two continents (Fig. 3).

Moderately severe anaemia after the start of treatment

Overall, 9.1% (1129/12,460) of patients had moderately severe anaemia (Hb < 7 g/dl) on day 3 and 4.4% (1241/28,262) on day 7. The risk of falling below 7 g/dL in people who did not have moderately severe anaemia at baseline was greater in Africa than in Asia on both day 3 (9.6% (987/10,278) versus 6.5% (142/2,182); $p = 0.001$) and day 7 (5.7% (987/17,198) versus 2.3% (254/11,064) respectively; $p < 0.001$).

The following independent predictors of moderately severe anaemia at day 7 in both Africa and Asia were identified: moderately severe anaemia at baseline (AOR = 16.10 (95%CI 12.59–20.60), $p < 0.001$ for Africa and 23.00 (14.27–37.06), $p < 0.001$ for Asia), younger age (for age < 1 year compared to patients ≥ 12 years AOR = 12.81 (95%CI 6.79–24.17), $p < 0.001$ and AOR = 6.79 (95%CI 2.36–19.58), $p < 0.001$ and for age 1 to 4 years compared to patients ≥ 12 years AOR = 6.09 (95%CI 3.33–11.13), $p < 0.001$ and AOR = 2.87 (95%CI 1.84–4.47), $p < 0.001$) and parasitaemia > 100,000/ μL (AOR = 1.78 (95%CI 1.42–2.24), $p < 0.001$ and 1.58 (1.10–2.27), $p = 0.013$) (Table 2 and Additional file 3: Table S6, Fig. 4). In Africa, fever (AOR = 1.66 (95%CI 1.33–2.09); $p < 0.001$) was an independent predictor of moderately severe anaemia

whilst female sex (AOR = 0.80 (95%CI 0.69–0.93); $p = 0.004$) was protective. In Asia, female sex was an independent predictor (AOR = 1.51 (95%CI 1.15–1.99), $p = 0.003$) and mixed infection was protective (AOR = 0.44 (95%CI 0.24–0.80), $p = 0.007$). The effect of sex was explored by evaluating the models separately in children compared with adolescents and adults. In adolescents and adults (age ≥ 12 years), female sex was associated with moderately severe anaemia, and this reached statistical significance in Asia (AOR = 2.55 (95%CI 1.65–3.94), $p < 0.001$), but not Africa (AOR = 1.98 (95%CI 0.71–5.49), $p = 0.191$). In contrast, in children (age < 12 years) female sex was associated with a lower risk of moderately severe anaemia, reaching statistical significance in Africa (AOR = 0.78 (95%CI 0.67–0.91), $p = 0.001$), but not Asia (AOR = 0.98 (95%CI 0.73–1.32), $p = 0.903$).

Compared with those treated with non-artemisinin-based treatments, patients in Asia treated with artemisinin-based therapy were at significantly greater risk of moderately severe anaemia on day 7 (AOR = 2.06 (95%CI 1.39–3.05); $p < 0.001$), but this was not the case in African patients (AOR = 1.01 (95%CI 0.56–1.82); $p = 0.987$). In Asia, the difference in risk between artemisinin- and non-artemisinin-based treatments remained when only the 8570 patients enrolled before 2007 (when artemisinin resistance was first described in the Greater Mekong Sub-region) were included in the model (AOR = 1.98 (95%CI

Table 2 Risk factors for moderately severe anaemia (Hb < 7 g/dL) at day 7: Multivariable logistic regression

Parameter	Africa			Asia		
	% (Number with moderately severe anaemia/N)	AOR (95% CI)	P value	% (Number with moderately severe anaemia/N)	AOR (95% CI)	P value
<i>Age group</i>						
< 1 year	16.9% (177/1045)	12.81 (6.79–24.17)	< 0.001	9.7% (3/31)	6.79 (2.36–19.58)	< 0.001
1–4 years	6.5% (651/10,086)	6.09 (3.33–11.13)	< 0.001	7.3% (63/861)	2.87 (1.84–4.47)	< 0.001
5–11 years	3.6% (101/2826)	4.41 (2.30–8.48)	< 0.001	3.5% (83/2341)	2.35 (1.56–3.52)	< 0.001
≥ 12 years	0.7% (18/2706)	Reference		1.3% (91/6898)	Reference	
<i>Sex</i>						
Female	5.2% (415/8058)	0.80 (0.69–0.93)	0.004	3.2% (124/3884)	1.51 (1.15–1.99)	0.003
Male	6.2% (532/8605)	Reference		1.9% (116/6247)	Reference	
<i>Fever</i>						
Yes	7.0% (700/10,062)	1.66 (1.33–2.09)	< 0.001	2.7% (148/5578)	1.26 (0.92–1.71)	0.152
No	3.7% (247/6601)	Reference		2.0% (92/4553)	Reference	
<i>Moderately severe anaemia at day 0</i>						
Yes	42.4% (383/904)	16.10 (12.59–20.60)	< 0.001	32.6% (78/239)	23.00 (14.27–37.06)	< 0.001
No	3.6% (564/15,759)	Reference		1.6% (162/9892)		
<i>High parasitaemia^a</i>						
Yes	9.4% (152/1621)	1.78 (1.42–2.24)	< 0.001	3.9% (35/900)	1.58 (1.10–2.27)	0.013
No	5.3% (795/15,042)	Reference		2.2% (205/9231)	Reference	
<i>Mixed infection</i>						
Yes	0% (0/0)			1.5% (11/717)	0.44 (0.24–0.80)	0.007
No	5.7% (947/16,663)			2.4% (229/9414)	Reference	
<i>Treatment</i>						
Artemisinin-based	5.5% (841/15,209)	1.01 (0.56–1.82)	0.987	2.5% (225/8958)	2.06 (1.39–3.05)	< 0.001
Non-artemisinin-based	7.3% (106/1454)	Reference		1.3% (15/1173)	Reference	

N total number of evaluable patients, AOR adjusted odds ratio

^a Parasitaemia > 100,000/μL. Univariable risk factors are presented in Additional file 3: Table S6

1.39–2.82); $p < 0.001$). Overall, the risk factors for moderately severe anaemia on day 3 were similar to those at day 7, with patients treated with artemisinin-based therapy at significantly greater risk of moderately severe anaemia on day 3 in Asia (AOR = 3.27 (95%CI 2.42–4.42); $p < 0.001$), but not in Africa (AOR = 0.69 (95%CI 0.32–1.49); $p = 0.343$) (Additional file 3: Table S7–S8 and Additional file 2: Figure S3).

The fractional fall in haemoglobin on day 7 was correlated positively with the baseline haemoglobin ($r = 0.47$; $p < 0.001$ adjusted for clustering of study site). A high baseline haemoglobin was associated with a greater risk of a large fractional fall ($\geq 25\%$) on day 7 in Africa (AOR for every 1 g/dL increase in baseline haemoglobin = 1.52 (95%CI 1.40–1.65); $p < 0.001$) and in Asia (AOR for every 1 g/dL increase in baseline haemoglobin = 1.43 (95%CI 1.35–1.52); $p < 0.001$) (Additional file 2: Figure S4). Other risk factors for a large fractional fall in haemoglobin on day 7 were similar to the risk factors for moderately severe anaemia on this day (Additional file 3: Table S9).

Parasite clearance and moderately severe anaemia

Of the 13,939 African patients who had haemoglobin concentrations measured on day 7, 11.1% (1547) were parasitaemic on day 2 and 2.6% (358) were parasitaemic on day 3. The corresponding proportions in Asia were 14.9% (1339/8960) and 4.2% (375/8960). After controlling for confounding factors, the risk of moderately severe anaemia at day 7 was greater in patients with delayed parasite clearance in both Africa (AOR = 2.44 (95%CI 1.59–3.75); $p < 0.001$) and Asia (AOR = 2.59 (95%CI 1.20–5.58); $p = 0.015$) (Table 3). There was no interaction between artemisinin use and delayed parasite clearance.

Assessment of potential bias

Methodological factors potentially contributing to bias are presented in Additional file 1: Table S2. Although many studies were unblinded, haemoglobin measurement is automated, thus minimising the risk of observer bias. Publication bias was unlikely, since haemoglobin

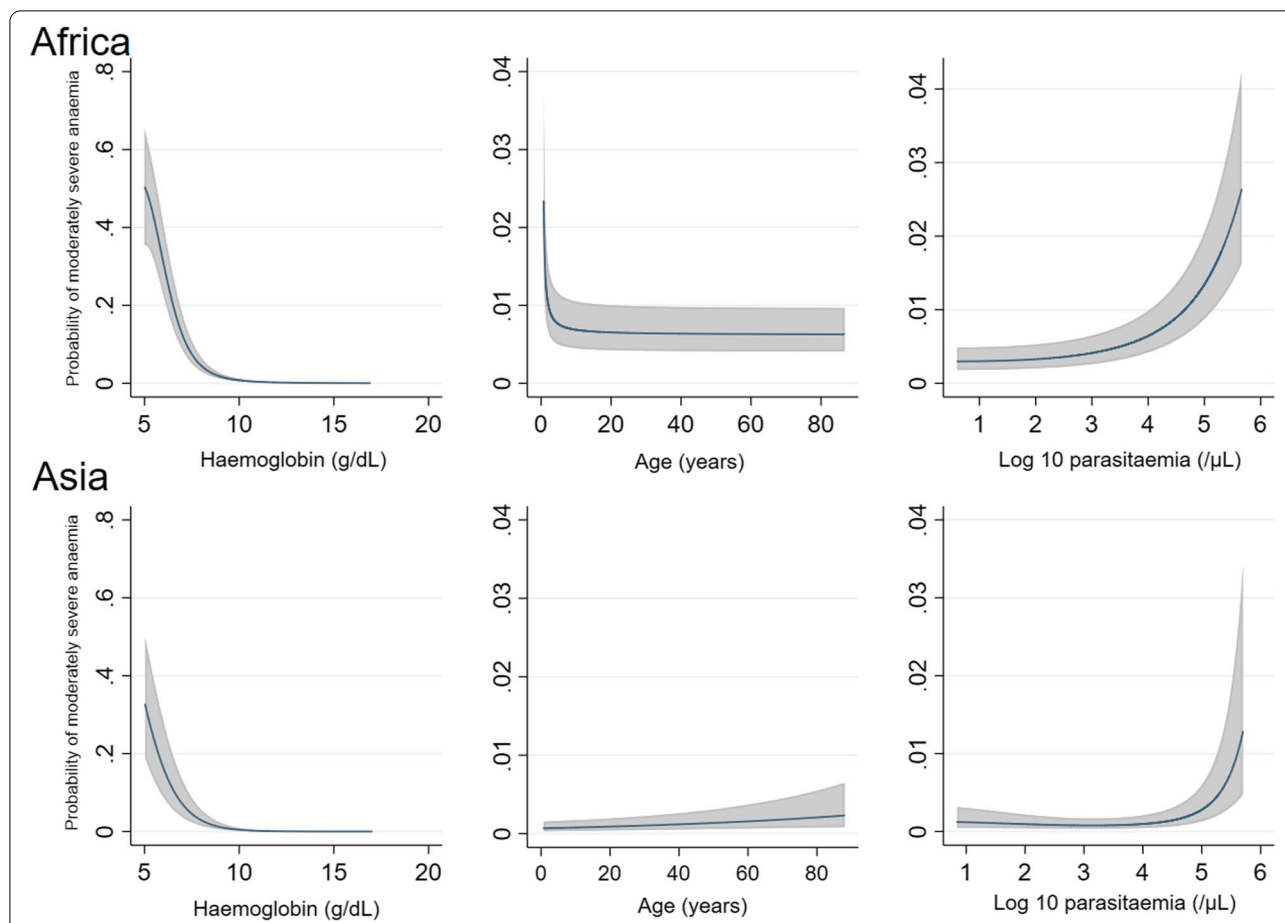


Fig. 4 Relationship between predicted probabilities of moderately severe anaemia (haemoglobin < 7 g/dL) on day 7 and continuous covariates. Results come from the final multivariable models and are adjusted for mean values of other covariates (haemoglobin, age, parasitaemia, sex, fever, treatment (artemisinin-based vs non-artemisinin-based) and mixed infection (Asia only)). The model was restricted to children with age > 0.75 years and haemoglobin ≤ 17 g/dL due to instability at the extremes of the data

Table 3 Effect of parasite clearance time on moderately severe anaemia after treatment

	Africa			Asia		
	% (Number with moderately severe anaemia/N ^a)	AOR (95% CI)	P value	% (Number with moderately severe anaemia/N ^a)	AOR (95% CI)	P value
Moderately severe anaemia on day 3						
Clearance between day 0 and day 1	6.5% (221/3410)	Reference		4.4% (39/889)	Reference	
Clearance between day 1 and day 2	11.0% (473/4299)	1.52 (1.20–1.92)	0.001	6.5% (41/628)	1.16 (0.57–2.36)	0.685
Clearance between day 2 and day 3	15.0% (94/626)	2.26 (1.55–3.29)	< 0.001	6.3% (16/254)	2.04 (0.76–5.47)	0.156
Clearance after day 3	11.5% (9/78)	2.04 (0.82–5.09)	0.126	2.5% (5/197)	0.67 (0.06–7.08)	0.742
Moderately severe anaemia on day 7						
Clearance between day 0 and day 1	4.8% (243/5106)	Reference		1.6% (52/3177)	Reference	
Clearance between day 1 and day 2	6.1% (417/6834)	1.02 (0.76–1.35)	0.916	2.7% (100/3759)	1.32 (0.87–2.01)	0.187
Clearance between day 2 and day 3	8.4% (99/1182)	1.28 (0.88–1.85)	0.199	2.8% (26/938)	1.57 (0.92–2.68)	0.102
Clearance after day 3	12.4% (44/354)	2.44 (1.59–3.75)	< 0.001	2.9% (10/346)	2.59 (1.20–5.58)	0.015

Effects are adjusted for all independent predictors identified in the final multivariable models for Africa and Asia in Table 2 (Main text) and Additional file 3: Table S8

AOR adjusted odds ratio

^a N number of patients for each variable/levels of factors

measurements were not a primary outcome in any of the publications and haemoglobin concentrations are unlikely to have influenced the decision to publish. Exclusion due to variable haemoglobin criteria will have caused a small reduction in the apparent proportion of patients with moderately severe anaemia at baseline and may also have artificially reduced the proportion of patients becoming severely anaemic during follow-up. In a sensitivity analysis, exclusion of patients from the 14 studies that had baseline haemoglobin cut-offs greater than 5 g/dL had minimal impact on the results (Additional file 3: Tables S10 and S11).

Discussion

Our study provides a detailed analysis of haemoglobin concentration kinetics in patients with falciparum malaria, enrolled across geographically diverse regions. The available data, exceeding > 70,000 individual data from patients of all ages, provides unprecedented power to define the factors associated with the acute fall in haemoglobin before and after treatment. Malaria is due to an intraerythrocytic infection which results in a reduction of red blood cells, intra- and extravascular haemolysis, bone marrow suppression and sequestration [178]. The administration of antimalarial drugs inhibits these pathological processes by preventing parasite replication and limiting the duration of dyserythropoiesis. Hence, the haematological manifestations of malaria are a function of the duration and degree of parasitaemia prior to treatment and the speed of therapeutic response to antimalarial treatment. Our analysis demonstrated that in Africa, hence in generally relatively high transmission regions, approximately three quarters of the malaria-attributable fall in haemoglobin occurs before presentation and one quarter after treatment, whilst in Asia, in generally relatively low transmission settings, one third occurs before presentation and two-thirds after treatment. The relative drop in haemoglobin was positively correlated with baseline haemoglobin.

Although the greatest fall in haemoglobin occurred before treatment in Africa, our analysis focused primarily on factors associated with the subsequent fall and recovery which may be more amenable to clinical intervention. Consistent with a recent pooled analysis from Africa [179], our study found that in both Africa and Asia, the nadir haemoglobin occurred within 2 days of starting treatment and haemoglobin generally rose thereafter. Whilst a previous analysis identified that nadir haemoglobin occurred on day 7, this was based on weekly assessments, and thus would have missed the true nadir occurring between weekly observations [1]. In vulnerable populations, such as young children and pregnant women, who are at risk of adverse clinical outcomes,

antimalarial clinical trials should implement a routine haemoglobin assessment at day 2 or 3 to ensure early diagnosis of severe anaemia.

The baseline haemoglobin in patients with falciparum malaria varied substantially with age and parasite density at presentation. After controlling for confounding factors, significant site to site variation remained, likely reflecting variations in transmission intensity, host immunity and factors unrelated to malaria. Patients from Asia tended to be older than those enrolled in Africa, but after controlling for age there were minimal differences in haemoglobin between regions, either at baseline or during follow-up. Following treatment, the absolute and proportional reductions in haemoglobin were greater in patients from Asia compared to Africa and were correlated with the higher baseline haemoglobin in Asian patients. Hence, patients presenting with a low haemoglobin concentration were less likely to experience a further fall in their haemoglobin.

The relationship between level of parasitaemia and degree of anaemia is complex [1, 179]. In Africa, anaemia at presentation was greatest in patients with low parasitaemias. There are several possible explanations for this. First, in highly endemic parts of Africa, robust immunity develops early, suppressing parasitaemia and symptoms. A substantial proportion of patients presenting with fever and low-level *Plasmodium* parasitaemia in these regions will have an alternative diagnosis, such as bacterial sepsis, which is also associated with anaemia [180]. Second, immune-mediated suppression of malaria symptoms can result in chronic, untreated parasitaemia that, over time, leads to significant suppression and dysregulation of haematopoiesis. Third, repeated episodes of malaria can result in splenic sequestration, with low-level peripheral parasitaemia, associated splenomegaly and dilutional anaemia [178, 181].

In Asia, the risk of anaemia at presentation increased with rising parasitaemia, peaking at 10,000 parasites/ μ L before decreasing thereafter. As transmission intensity in endemic parts of Asia is generally significantly lower than in Africa, immunity is less robust and a much greater proportion of infections will be symptomatic and of short duration. In this setting, anaemia will be related primarily to acute destruction of both parasitised and unparasitised red cells, the severity of which is correlated with the level of parasitaemia.

Treatment with artemisinin-based therapy in Asia was associated with a twofold higher risk of moderately severe anaemia (but not a large fractional fall in haemoglobin) within 7 days compared with non-artemisinin-based therapy, whereas in Africa, artemisinin-based treatment was not associated with an excess risk of early anaemia. This

relationship was not attributable to the presence of artemisinin resistance. We hypothesise that rapid killing of intraerythrocytic parasites by artemisinins in non-immune Asian adults likely leads to more rapid clearance of whole red blood cells from the circulation than that occurring after slower acting drug treatments. In immune African patients, a greater proportion of infected red cells undergo targeted intraerythrocytic parasite removal (pitting) followed by a return to circulation, thus ameliorating the early development of anaemia [6]. Reticulocytosis probably also occurs more rapidly after treatment in immune compared with non-immune individuals [6]. Further studies are warranted to explore the differences in haematological response to treatment with artemisinin derivatives in populations with different levels of immunity. Our analysis is based upon studies conducted prior to 2014. In the last 5 years, artemisinin-resistant parasites have spread across the Greater Mekong Subregion [182], with recent reports confirming their presence in Sub-Saharan Africa [183, 184]. Slower parasite clearance times and subsequent emergence of resistance to partner drugs will ultimately lead to treatment failure that will impact the generally prompt haemoglobin recovery that we observed in our analysis.

Our study has a number of limitations. The analysis focused on the acute haematological impact of malaria and the early recovery phase and did not address the influence of late treatment failure on subsequent recovery to baseline haemoglobin concentrations. This will be addressed in a subsequent analysis. Our estimates of the pattern of haemoglobin changes during the first few days after diagnosis may have been influenced by selection bias, as only a small subset of patients had multiple haemoglobin measurements during the first 7 days of follow-up. Although we did not employ a traditional systematic review to identify eligible studies, our analysis is the largest meta-analysis to date of patients treated for malaria in both Africa and Asia. This unprecedented data collection ensures robust parameter estimates and minimises the risk of inclusion bias. Furthermore, a systematic review would not preclude bias, since some studies recorded haemoglobin/haematocrit measurements but did not present these data in published manuscripts. Whilst the results of the current study are likely to be generalisable to Africa and Asia, the small number of patients from the Americas prevents the generalisability of our findings to this region. An additional potential cause of bias is the exclusion of patients from the original studies, prior to pooling, according to variable definitions of severe anaemia. Almost two-thirds of studies excluded patients with a haemoglobin < 5 g/dL, with a few studies excluding patients based on higher cut-offs and the remaining 30% having an unknown cut-off. Additional limitations of our study include the use of various methodologies to measure haematocrit or haemoglobin, a lack

of a robust conversion factor to adjust haematocrit to haemoglobin in different studies' populations and no reliable data on the following confounding factors that can influence haemoglobin and its recovery: the duration of prior parasitaemia (which has been shown to correlate with anaemia at presentation [178]), host genetic factors associated with anaemia (e.g. sickle cell anaemia, thalassaemia), administration of haematinics (or treatment for anaemia) and hydration status.

Conclusions

In conclusion, the majority of patients with uncomplicated falciparum malaria had a modest fall in haemoglobin following treatment, before subsequent improvement in haemoglobin during recovery. Despite highly effective treatment, some patients remained at significant risk of moderately severe anaemia. Young children had a particularly high risk, likely related to lower immunity and high initial peripheral parasitaemia. The risk of anaemia is exacerbated by prolonged parasitaemia prior to presentation [1] or delayed parasite clearance, both of which are associated with suboptimal treatment regimens particularly in areas where antimalarial drug resistance was emerging [185]. Whilst artemisinin-based treatment generally ensured rapid parasite clearance and high efficacy, in Asia their use was associated with a greater risk of moderately severe anaemia on day 3 and day 7 that could not be accounted for by an underlying rise in artemisinin resistance. Early diagnosis of malaria and treatment with highly effective antimalarials remains critical in minimising anaemia associated with *P. falciparum* infection.

Abbreviations

ACT: Artemisinin-based combination therapy; AL: Artemether-lumefantrine; AOR: Adjusted odds ratio; ASAQ: Artesunate-amodiaquine; ASMQ: Artesunate-mefloquine; CI: Confidence interval; DP: Dihydroartemisinin-piperazine; PfPR: *P. falciparum* parasite rate; WAZ: Weight-for-age Z-score; WHO: World Health Organization.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-022-02265-9>.

Additional file 1: Table S1. Describes studies included in the analysis. **Table S2.** Describes assessment of bias by included study.

Additional file 2: Figure S1. Describes study sites. **Figure S2.** Describes the relationship between haemoglobin on enrolment and continuous covariates. **Figure S3.** Describes the relationship between the predicted probability of moderately severe anaemia on day 3 and continuous covariates. **Figure S4.** Describes the relationship between the predicted probability of a large fractional fall in haemoglobin on day 7 and continuous covariates.

Additional file 3: Table S3. Describes the overview of antimalarial treatments. **Table S4.** Describes the risk factors for moderately severe anaemia at enrolment (univariable logistic regression). **Table S5.** Describes the risk

factors for moderately severe anaemia at enrolment (multivariable logistic regression). **Table S6.** Describes the risk factors for moderately severe anaemia at day 7 (univariable logistic regression). **Table S7.** Describes the risk factors for moderately severe anaemia at day 3 (univariable logistic regression). **Table S8.** Describes the risk factors for moderately severe anaemia at day 3 (multivariable logistic regression). **Table S9.** Describes the risk factors for a large fractional fall in haemoglobin by day 7. **Table S10.** Describes the sensitivity analysis for risk factors for moderately severe anaemia at enrolment (multivariable logistic regression). **Table S11.** Describes the sensitivity analysis for risk factors for moderately severe anaemia at day 7 (multivariable logistic regression).

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RM1, RJC, NMD, JAS, PJG, KS and RNP conceived the idea and wrote the first draft of the manuscript. HA, RB and GSH curated the data. RM1, KS, RJC and JAS undertook the analysis. PJG, KS and RNP acquired the funding. RB, GSH and CLR managed and coordinated the study. BA, JA, IA, GOA, MA, BHA, RA, ENA, AA, EA, EAA, PBSA, NB, HB1, KIB, LB, QB, EB, DJB, DB, AB, CB, TB, PB, HB2, VC, MC, UDA, DD, SD1, TMD, MD, AAD, AMD, GD, CJD, SD2, EE, JFE, CF1, JFF, SF, CF2, MF, OG, BG1, AGR, JG, RG, RFG, FG, BG2, AG, CH, EMH, JH, DSI, EJ, SPK, PK1, EK, MRK, CK, KK1, AK, JRK, PK2, KK2, PGK, DGL, ML, SJL, BL, AWM, AM, MM, WM, RM2, HM, DM, FM, BRM, OMM, AN, JLN, PNN, BEN, FN1, AMN, HN, FN2, BRO, OO, LO, JBO, SOA, AP, LKP, PP, MP, ZP, MR, LR, CR, PJR, SS, ASE, LVS, CS, SBS, FS, FAS, SGS, PS, NSW, IS, TDS, DS, AOT, WRT, EAT, JIT, HT, ET, OAT, THT, JU, IV, GV, MVV, SAW, VV, NW, CJW, WY, AY and IZ collected the data. RM1, RJC, NMD, JAS, PJG, KS and RNP interpreted the data and contributed to writing the first draft of the manuscript. BA, JA, IA, GOA, MA, BHA, RA, ENA, AA, EA, EAA, HA, PBSA, NB, HB1, KIB, LB, QB, EB, DJB, DB, AB, CB, TB, PB, HB2, RB, VC, MC, UDA, DD, SD1, TMD, MD, AAD, AMD, GD, CJD, SD2, EE, JFE, CF1, JFF, SF, CF2, MF, OG, BG1, AGR, JG, RG, RFG, FG, BG2, AG, CH, EMH, GSH, JH, DSI, EJ, SPK, PK1, EK, MRK, CK, KK1, AK, JRK, PK2, KK2, PGK, DGL, ML, SJL, BL, AWM, AM, MM, WM, RM2, HM, DM, FM, BRM, OMM, AN, JLN, PNN, BEN, FN1, AMN, HN, FN2, BRO, OO, LO, JBO, SOA, AP, LKP, PP, MP, ZP, MR, CLR, LR, CR, PJR, SS, ASE, LVS, CS, SBS, FS, FAS, SGS, PS, NSW, IS, TDS, DS, AOT, WRT, EAT, JIT, HT, ET, OAT, THT, JU, IV, GV, MVV, SAW, VV, NW, CJW, WY, AY and IZ reviewed the manuscript and provided feedback. All authors read and approved the final version.

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Availability of data and materials

The data that support the findings of this study are available for access via the WorldWide Antimalarial Resistance Network (WWARN.org). Requests for access will be reviewed by a Data Access Committee to ensure that use of data protects the interests of the participants and researchers according to the terms of ethics approval and principles of equitable data sharing. Requests can be submitted by email to malariaDAC@iddo.org via the Data Access Form available at WWARN.org/accessing-data. The WWARN platform is registered with the Registry of Research Data Repositories (re3data.org).

Declarations

Ethics approval and consent to participate

All data included in this analysis were obtained in accordance with ethical approvals from the country of origin. The data are fully anonymised and cannot be traced back to identifiable individuals. This systematic review did not require separate ethical approval according to the guidelines of the Oxford Central University Research Ethics Committee. The inclusion of anonymised data from the US Centers for Disease Control and Prevention underwent human subjects review and received non-research determination.

Consent for publication

Not applicable

Competing interests

All other authors declare that they have no competing interests.

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