Standard report for Vivax Malaria

WWARN Vivax Primaquine Study Group

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05 May, 2025

Introduction

This report has been produced for countries: India, Nepal, Bangladesh

The studies included within this report are shown in Table 0.

Table 0: Studies included in this report

Author-year	Country	Recruitment Period	Age range (years)	Follow up (days)	Included treatment arms*	PQ supervison	Patients available
Llanos-Cuentas-2014	India	2011 - 2013	16 - 60	180	Cq_Pq_3.5_14d_D1, Cq	<50% supervised	16
Rijal-2019	Nepal	2015 - 2016	5 - 75	365	Cq, Cq_Pq_3.5_14d_D0	<50% supervised	206
Saravu-2016	India	2012 - 2015	17 - 75	28	Cq_Pq_3.5_14d_D0	Unsupervised	155
Ley-2016	Bangladesh	2014 - 2015	1 - 66	30	Cq_Pq_3.5_14d_D2	Unsupervised	55

∗ *ACT – artemisinin-based combination treatment; As – artesunate; AL – artemether-lumefantrine; Aq – amodiaquine; Cq – chloroquine; DP – dihydroartemisinin-piperaquine; GI – gastrointestinal; Mf – mefloquine; PQ/Pq – primaquine; SP – sulfadoxine-pyrimethamine;*

Treatment code describes (schizontocidal drug)(hypnozoitocidal drug)(total primaquine dose)(duration of primaquine treatment eg 14d = 14 days)(primaquine start day)

1: EFFICACY

1.1: Description

The efficacy study was undertaken to better understand the impact of primaquine dose on the prevention of P. vivax recurrences. Inclusion in the efficacy meta-analysis was restricted to studies with 42 days or more follow up and patients with data on day 0 parasitaemia.

In this report the efficacy study includes 222 patients across 5 study sites, from 2 studies.

1.2: Characteristics of Study Population

Table 1_eff: Characteristics of the study population for the efficacy study analysis, categorised by total primaquine category

	Primaquine (PQ) Treatment				
	No primaquine (N=111)	Very low dose total primaquine (<2 mg/kg)(N=0)	Low dose total primaquine (2 - <5 mg/kg)(N=106)	High dose total primaquine (>= 5 mg/kg)(N=5)	Total **(N=222)**
Age (years)		**NA**			
Mean (SD)	29 (13)	NA	30 (14)	12 (5.8)	29 (14)
Age Category		**NA**			
<5	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)
5-<15	8 (7%)	NA	2 (2%)	3 (60%)	13 (6%)
>=15	103 (93%)	NA	104 (98%)	2 (40%)	209 (94%)
Gender		**NA**			
Male	26 (23%)	NA	20 (19%)	2 (40%)	48 (22%)
Female	85 (77%)	NA	86 (81%)	3 (60%)	174 (78%)
Weight (kg)		**NA**			
Mean (SD)	54 (12)	NA	57 (8.3)	27 (14)	55 (12)
Malnutrition		**NA**			
No	1 (1%)	NA	0 (0%)	0 (0%)	1 (0%)
Yes	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)
Missing	110 (99.1%)	NA	106 (100%)	5 (100%)	221 (99.5%)
Fever day 0		**NA**			
No	7 (6%)	NA	5 (5%)	0 (0%)	12 (5%)
Yes	104 (94%)	NA	101 (95%)	5 (100%)	210 (95%)
P. vivax baseline parasitaemia		**NA**			
Median (IQR)	7500 [3800, 15320]	NA	8040 [4308, 13090]	12800 [9850, 20500]	8080 [4100, 14000]
Haemoglobin day 0 (g/dL)		**NA**			
Mean (SD)	12 (1.7)	NA	12 (1.8)	11 (1.2)	12 (1.7)
PQ daily dose (mg/kg)		**NA**			
Mean (SD)		NA	3.7 (0.50)	6.4 (1.4)	3.8 (0.79)
Missing		NA	0 (0%)	0 (0%)	0(0%)
7 days		NA	0 (0%)	0 (0%)	0 (0%)
14 days		NA	106 (100%)	5 (100%)	111 (100%)
Missing		NA	0 (0%)	0 (0%)	0(0%)
Method to calculate PQ dose		**NA**			
Per actual dose		NA	0 (0%)	0 (0%)	0 (0%)
Per dosing protocol		NA	106 (100%)	5 (100%)	111 (100%)
Start day of PQ treatment		**NA**			
Day 0		NA	100 (94%)	5 (100%)	105 (95%)
Day 1		NA	6 (6%)	0 (0%)	6 (5%)
Day 2		NA	0 (0%)	0 (0%)	0 (0%)
Day 3		NA	0 (0%)	0 (0%)	0 (0%)
Day 4		NA	0 (0%)	0 (0%)	0 (0%)

(continued)

	No primaquine (N=111)	Very low dose total primaquine (<2 mg/kg)(N=0)	Low dose total primaquine (2 - <5 mg/kg)(N=106)	High dose total primaquine (>= 5 mg/kg)(N=5)	Total **(N=222)**
Day 5		NA	0 (0%)	0 (0%)	0 (0%)
Day 6		NA	0 (0%)	0 (0%)	0 (0%)
Level of PQ supervision		**NA**			
Unsupervised		NA	0 (0%)	0 (0%)	0 (0%)
Partially supervised		NA	106 (100%)	5 (100%)	111 (100%)
Fully supervised		NA	0 (0%)	0 (0%)	0 (0%)
Missing		NA	0 (0%)	0 (0%)	0(0%)
Was PQ taken with food?		**NA**			
No		NA	0 (0%)	0 (0%)	0 (0%)
Yes		NA	6 (6%)	0 (0%)	6 (5%)
Recommended		NA	100 (94%)	5 (100%)	105 (95%)
Other treatment given		**NA**			
AL	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)
AsAq	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)
AsMf	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)
Cq	111 (100%)	NA	106 (100%)	5 (100%)	222 (100%)
DP	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)
Transmission intensity of the site		**NA**			
Low	101 (91%)	NA	100 (94%)	5 (100%)	206 (93%)
Moderate	10 (9%)	NA	6 (6%)	0 (0%)	16 (7%)
High	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)
Not available	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)
Geographical region		**NA**			
Africa	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)
Americas	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)
Asia-Pacific	111 (100%)	NA	106 (100%)	5 (100%)	222 (100%)
Relapse Peridocity		**NA**			
Low periodicity	10 (9%)	NA	6 (6%)	0 (0%)	16 (7%)
High periodicity	101 (91%)	NA	100 (94%)	5 (100%)	206 (93%)
G6PD categories (Qualitative test)		**NA**			
<30%	2 (2%)	NA	0 (0%)	0 (0%)	2 (1%)
>=30%	109 (98%)	NA	106 (100%)	5 (100%)	220 (99%)
G6PD categories (Quantitative test)		**NA**			
<30%	2 (2%)	NA	0 (0%)	0 (0%)	2 (1%)
30-<70%	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)
>=70%	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)
Missing	109 (98.2%)	NA	106 (100%)	5 (100%)	220 (99.1%)

1.3: Risk of recurrence

Kaplan-Meier survival analysis was used to calculate risk of recurrence between day 7 and 365. Patients were left censored at day 7 and right censored at the first of: the day last reviewed, the last day prior to a 60-day blood smear gap or the last day of study follow up. Outcomes were stratified by primaquine treatment arm: no primaquine, low total dose primaquine (2 to <5 mg/kg) and high total dose primaquine ($\geq$ 5 mg/kg). Very low total dose primaquine (<2 mg/kg) was not presented due to low numbers of patients treated with this dose.

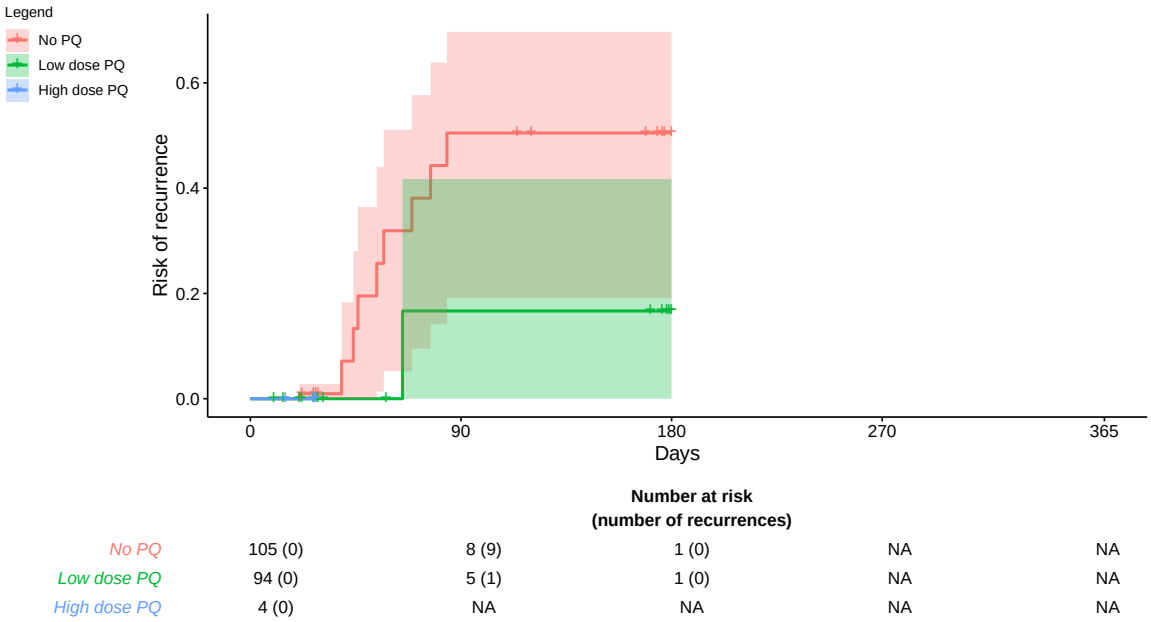

Figure 0_eff: Kaplan-Meier figure of cumulative risk of recurrence between day 7 and day 365 for primaquine treatment category. Please interpret the results of this figure with caution as there may not always be paired treatment comparisons in the original studies contributing to these pooled results.

Cox regression analysis for the time to first vivax recurrence between day 7 and 180 was performed to determine the effect of primaquine dose. Analysis was restricted to patients treated with daily primaquine or no primaquine. Potential confounders including sex, age and baseline parasitaemia were adjusted for with shared frailty for study site.

Similar but separate multivariable Cox regression analyses were undertaken to investigate primaquine duration, also adjusting for total actual mg/kg dose, in i) patients treated with low total dose primaquine and ii) patients treated with high total dose primaquine.

Care should be taken when interpreting these results, as model assumptions have not been fully assessed in this automated report format.

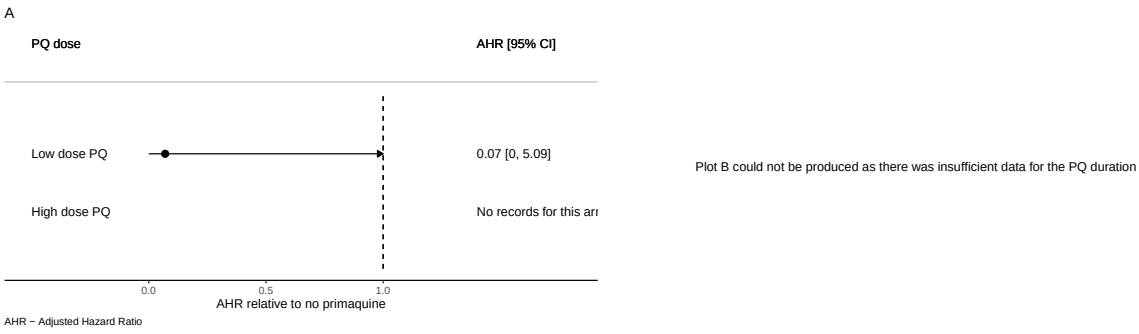

Figure 1_eff: Hazard ratio between day 7 and day 180 for A: total dose of primaquine and B: 14-day vs 7-day primaquine duration, stratified by total dose of primaquine

2: HAEMATOLOGY

2.1: Description

Haematological safety is a key concern for clinicians and policymakers in the implementation of primaquine radical cure, due to the risk of haemolysis in patients with G6PD deficiency. This individual patient data meta-analysis was conducted to assess the evidence for adverse haematological outcomes related to primaquine dose, with consideration of patients G6PD status.

Inclusion in the haematological safety meta-analysis was restricted to studies with 28 days or more follow up, patients with data on day 0 parasitaemia, patients with available data on day 0 haemoglobin levels or haematocrit, patients with an available haemoglobin measurement on at least one more day during the follow-up period and patients with data on daily primaquine dose.

The haematology study included 432 patients across 7 study sites, from 4 studies.

2.2 Characteristics of Study Population

Table 1_saf: Characteristics of the study population for the safety study analysis, categorised by total primaquine category

	Primaquine Treatment				
	No primaquine (N=111)	Low dose daily primaquine (<0.375 mg/kg/day) (N=292)	Intermediate dose daily primaquine (>= 0.375 & <0.75 mg/kg/day) (N=28)	High dose daily primaquine (>= 0.75 mg/kg/day) (N=1)	Total **(N=432)**
Age (years)					
Mean (SD)	29 (13)	32 (14)	16 (17)	2.0 (NA)	30 (14)
Age Category					
<5	0 (0.00%)	0 (0.00%)	1 (3.57%)	1 (100.00%)	2 (0.46%)
5-<15	8 (7.21%)	4 (1.37%)	20 (71.43%)	0 (0.00%)	32 (7.41%)
>=15	103 (92.79%)	288 (98.63%)	7 (25.00%)	0 (0.00%)	398 (92.13%)
Gender					
Male	26 (23.42%)	183 (62.67%)	15 (53.57%)	1 (100.00%)	225 (52.08%)
Female	85 (76.58%)	109 (37.33%)	13 (46.43%)	0 (0.00%)	207 (47.92%)
Weight (kg)					
Mean (SD)	54 (12)	57 (9.2)	24 (11)	10 (NA)	54 (13)
Missing	0 (0%)	20 (6.8%)	0 (0%)	0 (0%)	20 (4.6%)
Malnutrition					
No	1 (0.90%)	0 (0.00%)	3 (10.71%)	1 (100.00%)	5 (1.16%)
Yes	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Missing	110 (99.1%)	292 (100%)	25 (89.3%)	0 (0%)	427 (98.8%)
Fever day 0					
No	7 (6.31%)	17 (5.82%)	9 (32.14%)	0 (0.00%)	33 (7.64%)
Yes	104 (93.69%)	275 (94.18%)	19 (67.86%)	1 (100.00%)	399 (92.36%)
P. vivax baseline parasitaemia					
Median (IQR)	7500 [3800, 15320]	2432 [542, 6435]	172.5 [52, 678]	649.0 [649, 649]	3400 [719, 8723]
Haemoglobin day 0 (g/dL)					
Mean (SD)	12 (1.7)	13 (1.9)	11 (1.7)	9.8 (NA)	12 (1.9)
PQ daily dose (mg/kg)					
Mean (SD)		3.5 (1.1)	6.5 (1.4)	11 (NA)	3.8 (1.4)
Duration of PQ treatment					
Mean (SD)		14 (0)	14 (0)	14 (NA)	14 (0)
Missing		0 (0%)	0 (0%)	0 (0%)	
Method to calculate PQ dose					

(continued)

	No primaquine (N=111)	Low dose daily primaquine (<0.375 mg/kg/day) (N=292)	Intermediate dose daily primaquine (>= 0.375 & <0.75 mg/kg/day) (N=28)	High dose daily primaquine (>= 0.75 mg/kg/day) (N=1)	Total **(N=432)**
Per actual dose		32 (10.96%)	21 (75.00%)	1 (100.00%)	54 (16.82%)
Per dosing protocol		260 (89.04%)	7 (25.00%)	0 (0.00%)	267 (83.18%)
Start day of PQ treatment					
Day 0		254 (86.99%)	6 (21.43%)	0 (0.00%)	260 (81.00%)
Day 1		6 (2.05%)	0 (0.00%)	0 (0.00%)	6 (1.87%)
Day 2		32 (10.96%)	22 (78.57%)	1 (100.00%)	55 (17.13%)
Day 3		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Day 4		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Day 5		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Day 6		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Level of PQ supervision					
Unsupervised		185 (63.36%)	24 (85.71%)	1 (100.00%)	210 (65.42%)
Partially supervised		107 (36.64%)	4 (14.29%)	0 (0.00%)	111 (34.58%)
Fully supervised		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Was PQ taken with food?					
No		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Yes		6 (2.05%)	0 (0.00%)	0 (0.00%)	6 (1.87%)
Recommended		286 (97.95%)	28 (100.00%)	1 (100.00%)	315 (98.13%)
Other treatment given					
AL	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
AsAq	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cq	111 (100.00%)	292 (100.00%)	28 (100.00%)	1 (100.00%)	432 (100.00%)
DP	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Transmission intensity of the site					
Low	101 (90.99%)	133 (45.55%)	26 (92.86%)	1 (100.00%)	261 (60.42%)
Moderate	10 (9.01%)	159 (54.45%)	2 (7.14%)	0 (0.00%)	171 (39.58%)
High	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Geographical region					
Africa	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Americas	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Asia-Pacific	111 (100.00%)	292 (100.00%)	28 (100.00%)	1 (100.00%)	432 (100.00%)
Relapse Peridocity					
Low periodicity	10 (9.01%)	159 (54.45%)	2 (7.14%)	0 (0.00%)	171 (39.58%)
High periodicity	101 (90.99%)	133 (45.55%)	26 (92.86%)	1 (100.00%)	261 (60.42%)
G6PD categories (Qualitative test)					
<30%	2 (1.80%)	9 (3.08%)	0 (0.00%)	0 (0.00%)	11 (2.55%)
>=30%	109 (98.20%)	281 (96.23%)	28 (100.00%)	1 (100.00%)	419 (96.99%)
Unknown	0 (0.00%)	2 (0.68%)	0 (0.00%)	0 (0.00%)	2 (0.46%)
G6PD categories (Quantitative test)					
<30%	2 (1.80%)	9 (3.08%)	0 (0.00%)	0 (0.00%)	11 (2.55%)
30-<70%	0 (0.00%)	1 (0.34%)	0 (0.00%)	0 (0.00%)	1 (0.23%)
>=70%	0 (0.00%)	16 (5.48%)	14 (50.00%)	0 (0.00%)	30 (6.94%)
Unknown	109 (98.20%)	266 (91.10%)	14 (50.00%)	1 (100.00%)	390 (90.28%)

2.3 Summary of the haematology outcomes

Table 2 below provides a summary of the outcome experienced within each primaquine treatment arm for participants with G6PD activity $\geq 30\%$.

Table 2_saf: Summary of safety outcomes, categorised by total primaquine category

	Primaquine Treatment				Total
	No primaquine	**Low dose daily primaquine (<0.375 mg/kg/day)**	**Intermediate dose daily primaquine (0.375 & <0.75 mg/kg/day)**	**High dose daily primaquine (0.75 mg/kg/day)**	
Drop in haemoglobin of >25% AND Hb below 7 g/dL					
No	109 (100.0 %)	137 (48.8 %)	26 (92.9 %)	1 (100.0 %)	273 (65.2 %)
Yes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	0 (0%)	144 (51.2%)	2 (7.1%)	0 (0%)	146 (34.8%)
Drop in haemoglobin of >5 g/dL from baseline between days 1-14					
No	109 (100.0 %)	137 (48.8 %)	26 (92.9 %)	1 (100.0 %)	273 (65.2 %)
Yes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	0 (0%)	144 (51.2%)	2 (7.1%)	0 (0%)	146 (34.8%)
Drop in haemoglobin to <5 g/dL between days 1 and 14					
No	109 (100.0 %)	137 (48.8 %)	26 (92.9 %)	1 (100.0 %)	273 (65.2 %)
Yes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	0 (0%)	144 (51.2%)	2 (7.1%)	0 (0%)	146 (34.8%)
Anaemia developed at days 2 or 3					
Nil (Hb: >=11 g/dL)	73 (67.0 %)	100 (35.6 %)	6 (21.4 %)	0 (0.0 %)	179 (42.7 %)
Mild (Hb: >=8 g/dL & <11 g/dL)	3 (2.8 %)	7 (2.5 %)	5 (17.9 %)	0 (0.0 %)	15 (3.6 %)
Moderate (Hb: >=5 g/dL & <8 g/dL)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Severe (Hb <5 g/dL)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	33 (30.3%)	174 (61.9%)	17 (60.7%)	1 (100%)	225 (53.7%)
Anaemia developed at days 5-7					
Nil (Hb: >=11 g/dL)	68 (62.4 %)	86 (30.6 %)	7 (25.0 %)	0 (0.0 %)	161 (38.4 %)
Mild (Hb: >=8 g/dL & <11 g/dL)	2 (1.8 %)	5 (1.8 %)	4 (14.3 %)	0 (0.0 %)	11 (2.6 %)
Moderate (Hb: >=5 g/dL & <8 g/dL)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Severe (Hb <5 g/dL)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	39 (35.8%)	190 (67.6%)	17 (60.7%)	1 (100%)	247 (58.9%)
Change in haemoglobin on days 2-3 from day 0					
Mean (SD)	0.00416 (0.565)	-0.383 (0.768)	-0.661 (1.34)	-0.900 (NA)	-0.255 (0.797)
Missing	0 (0%)	145 (51.6%)	3 (10.7%)	0 (0%)	148 (35.3%)
Change in haemoglobin on days 5-7 from day 0					
Mean (SD)	0.110 (0.484)	-0.235 (0.657)	-0.485 (1.33)	-0.300 (NA)	-0.117 (0.720)
Missing	7 (6.4%)	164 (58.4%)	3 (10.7%)	0 (0%)	174 (41.5%)
Relative percentage (%) change in haemoglobin on days 2-3 from day 0					
Mean (SD)	-0.165 (4.41)	2.86 (5.43)	6.07 (13.0)	9.18 (NA)	1.96 (6.45)
Missing	0 (0%)	145 (51.6%)	3 (10.7%)	0 (0%)	148 (35.3%)
Relative percentage (%) change in haemoglobin on days 5-7 from day 0					
Mean (SD)	-1.06 (3.95)	1.84 (5.09)	4.17 (12.9)	3.06 (NA)	0.874 (6.18)
Missing	7 (6.4%)	164 (58.4%)	3 (10.7%)	0 (0%)	174 (41.5%)

2.4: Change in Haemoglobin (Hb) levels between primaquine treatment groups

The following figure provides the estimated change in haemoglobin from day 0 for different primaquine doses at at day 2/3 and days 5/7, adjusted for baseline haemoglobin, age, sex and day 0 parasitaemia and allowing for clustering by study site, in participants with $\geq$ 30% G6PD activity.

Care should be taken when interpreting these results, as model assumptions have not been fully assessed in this automated report format.

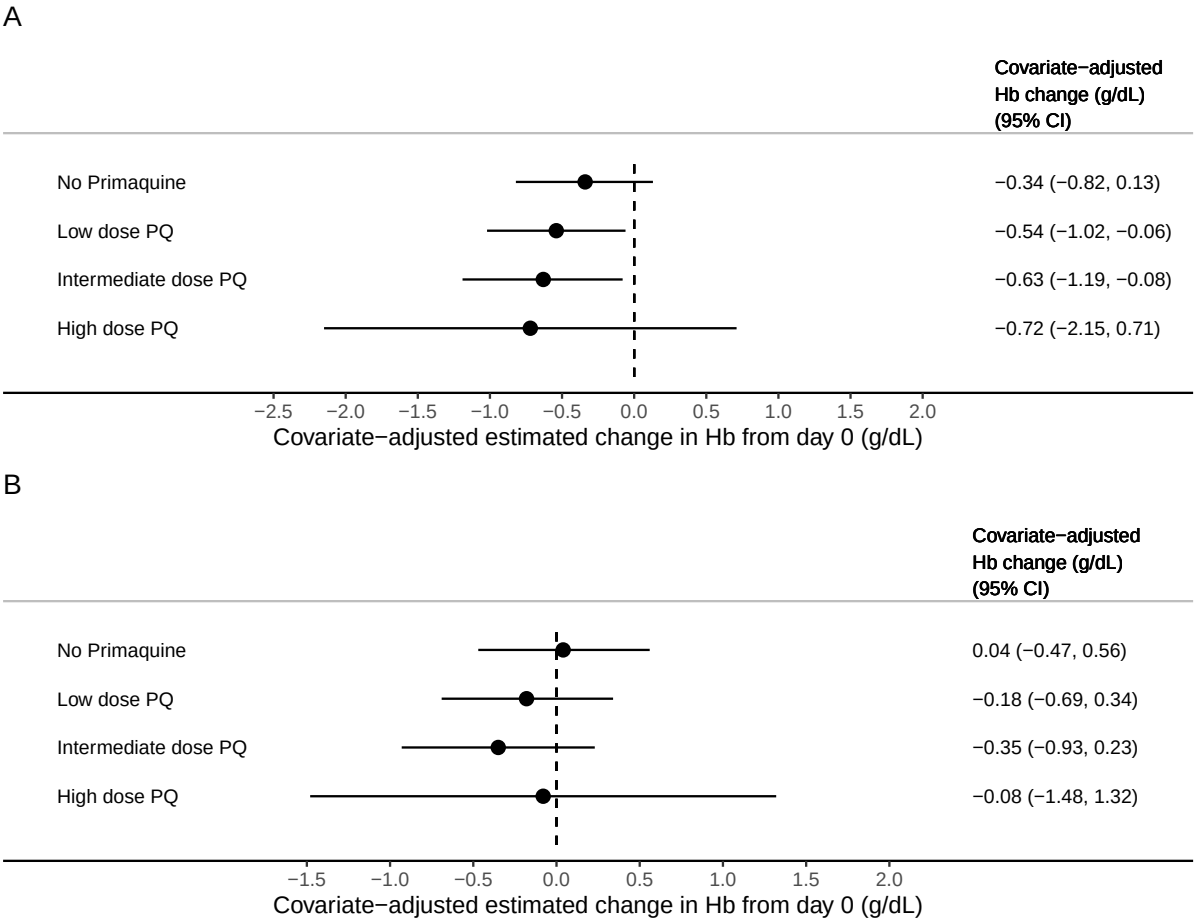

Figure 1_saf: The covariate-adjusted estimated change in Hb between primaquine daily dose groups on (A) days 2-3 and (B) days 5-7, in patients with ≥ 30% G6PD activity.

3: TOLERABILITY

3.1: Description

This individual patient data meta-analysis was conducted in order to understand the effect of primaquine dose on the gastrointestinal side effects.

Inclusion in the gastrointestinal tolerability meta-analysis was restricted to studies with 28 days or more followup, data from pre-specified symptom questionnaires (symptom checklist), patients with data on vivax parasite count at baseline, patients starting primaquine by day 2, patients not receiving intermittent primaquine (defined as primaquine administered weekly or monthly, rather than daily) and patients with data on daily primaquine dose.

The tolerability study included 0 patients across 0 study sites, from 0 studies.

Data on tolerability outcomes are unavailable for this dataset