Standard report for Vivax Malaria

WWARN Vivax Primaquine Study Group

For further information go to https://www.iddo.org/wwarn/vivax-reports

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Introduction

This report has been produced for the region/s of: Asia-Pacific

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
Chu-2018	Thailand	2010 - 2011	1.5 - 63	365	Cq_Pq_7.0_14d_D0, Cq	Fully supervised	420
Longley-2016	Thailand	2014	7 - 71	270	Cq_Pq_3.5_14d_D1	Fully supervised	43
Pasaribu-2013	Indonesia	2010 - 2012	2 - 70	365	AsAq_Pq_3.5_14d_D0, DP_Pq_3.5_14d_D0	Fully supervised	331
Llanos-Cuentas-2019	Vietnam, Thailand	2015 - 2017	15 - 58	180	Cq_Pq_3.5_14d_D1	<50% supervised	23
Taylor-2019	Afghanistan, Indonesia, Vietnam	2014 - 2017	0.8 - 94.3	365	Cq, Cq_Pq_7.0_14d_D0, Cq_Pq_7.0_7d_D0, DP, DP_Pq_7.0_14d_D0, DP_Pq_7.0_7d_D0	Fully supervised	1717
Poespoprodjo-2021	Indonesia	2016 - 2018	1.1 - 63.9	180	DP_Pq_7.0_14d_D2_us, DP_Pq_7.0_14d_D2_s	NA	164
Nelwan-2015	Indonesia	2013	23 - 49	365	DP_Pq_7.0_14d_D0	Fully supervised	56
Lacerda-2019	Philippines, Cambodia, Thailand	2014 - 2017	15 - 55	180	Cq_Pq_3.5_14d_D1, Cq	<50% supervised	52
Llanos-Cuentas-2014	Thailand, India	2011 - 2013	16 - 60	180	Cq, Cq_Pq_3.5_14d_D1	<50% supervised	48
Hasugian-2007	Indonesia	2005	1.2 - 56	84	AsAq_Pq_4.2_14d_D2, DP_Pq_4.2_14d_D2	Unsupervised	115
Barber-2013	Malaysia	2010 - 2015	13 - 62	42	Cq_Pq_D2, AL, Cq_Pq_D1, AL_Pq_D2, AL_Pq_D5, AL_Pq_D1, AL_Pq_D3, Cq, Cq_Pq_D3	Unsupervised	39
Chu-2019	Thailand	2012 - 2014	1.5 - 63	365	DP_Pq_7.0_7d_D0, DP_Pq_7.0_14d_D0, Cq_Pq_7.0_7d_D0, Cq_Pq_7.0_14d_D0	Fully supervised	654
Rijal-2019	Nepal	2015 - 2016	5 - 75	365	Cq, Cq_Pq_3.5_14d_D0	<50% supervised	206
Karunajeewa-unpub	Vanuatu	2013	2 - 35	84	AL_Pq_3.5_14d_D0, AL_Pq_7.0_14d_D0, AL	Fully supervised	26
Awab-2017	Afghanistan	NA	2 - 84	390	Cq, Cq_Pq_3.5_14d_D0	<50% supervised	544

(continued)

Author-year	Country	Recruitment Period	Age range (years)	Follow up (days)	Included treatment arms*	PQ supervison	Patients available
Grigg-2018	Malaysia	2013 - 2015	0.7 - 65	230	Cq_Pq_D1, Cq, Cq_Pq_D3, Cq_Pq_D4, AsMf_Pq_D1, Cq_Pq_D2, AL_Pq_D5, AL, AL_Pq_D1...	Unsupervised	26
Yuan-2015	Myanmar	2012 - 2013	1 - 77	42	Cq_Pq_3.0_8d_D0	<50% supervised	588
Lidia-2015	Indonesia	2013	18 - 88	42	Cq_Pq_3.5_14d_D0, DP_Pq_3.5_14d_D0	Fully supervised	51
Pukrittayakamee-2010	Thailand	1995 - 1998	14 - 61	28	Pq_7.0_7d_D0, Pq_3.5_7d_D0	Fully supervised	85
Thanh-2015	Vietnam	2009 - 2010	3 - 60	28	Cq_Pq_5.0_10d_D0	Fully supervised	260
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 5102 patients across 35 study sites, from 18 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

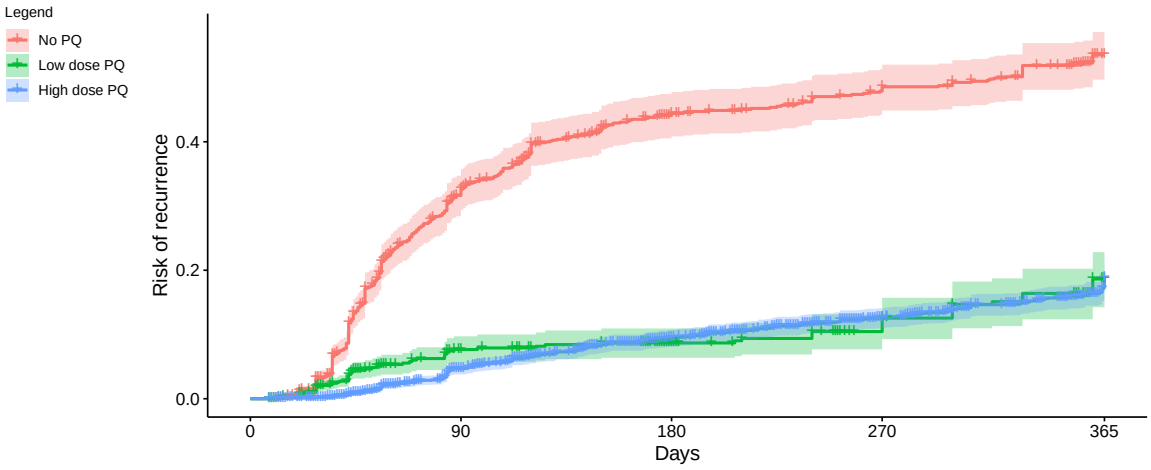
	Primaquine (PQ) Treatment				
	No primaquine (N=1027)	Very low dose total primaquine (<2 mg/kg)(N=22)	Low dose total primaquine (2 - <5 mg/kg)(N=1582)	High dose total primaquine (>= 5 mg/kg)(N=2471)	Total **(N=5102)**
Age (years)					
Mean (SD)	21 (14)	19 (10)	19 (15)	21 (14)	20 (14)
Age Category					
<5	62 (6%)	2 (9%)	148 (9%)	170 (7%)	382 (7%)
5-<15	314 (31%)	5 (23%)	649 (41%)	827 (33%)	1795 (35%)
>=15	651 (63%)	15 (68%)	785 (50%)	1474 (60%)	2925 (57%)
Gender					
Male	642 (63%)	15 (68%)	877 (55%)	1577 (64%)	3111 (61%)
Female	385 (37%)	7 (32%)	705 (45%)	894 (36%)	1991 (39%)
Weight (kg)					
Mean (SD)	45 (19)	50 (22)	46 (20)	42 (18)	44 (19)
Missing	10 (1.0%)	0 (0%)	635 (40.1%)	2 (0.1%)	647 (12.7%)
Malnutrition					
No	51 (5%)	3 (14%)	75 (5%)	156 (6%)	285 (6%)
Yes	23 (2%)	0 (0%)	27 (2%)	45 (2%)	95 (2%)
Missing	953 (92.8%)	19 (86.4%)	1480 (93.6%)	2270 (91.9%)	4722 (92.6%)
Fever day 0					
No	92 (9%)	4 (18%)	116 (7%)	183 (7%)	395 (8%)
Yes	934 (91%)	18 (82%)	1217 (77%)	2232 (90%)	4401 (86%)
Missing	1 (0.1%)	0 (0%)	249 (15.7%)	56 (2.3%)	306 (6.0%)
P. vivax baseline parasitaemia					
Median (IQR)	3520 [1552, 9481]	4554 [1533, 8270]	2280 [760, 5535]	3748 [1019, 10000]	3160 [1011, 8208]
Haemoglobin day 0 (g/dL)					
Mean (SD)	12 (1.8)	12 (2.2)	12 (1.9)	13 (1.8)	12 (1.8)
Missing	8 (0.8%)	0 (0%)	634 (40.1%)	7 (0.3%)	649 (12.7%)
PQ daily dose (mg/kg)					
Mean (SD)		1.0 (0.46)	3.5 (0.60)	7.3 (1.2)	5.8 (2.1)
Duration of PQ treatment					
7 days		6 (27%)	612 (39%)	983 (40%)	1601 (39%)
14 days		12 (55%)	968 (61%)	1459 (59%)	2439 (60%)
Method to calculate PQ dose					
Per actual dose		22 (100%)	89 (6%)	2384 (96%)	2495 (61%)
Per dosing protocol		0 (0%)	1493 (94%)	87 (4%)	1580 (39%)
Start day of PQ treatment					
Day 0		16 (73%)	1334 (84%)	2236 (90%)	3586 (88%)
Day 1		1 (5%)	110 (7%)	10 (0%)	121 (3%)
Day 2		5 (23%)	138 (9%)	220 (9%)	363 (9%)

(continued)

	No primaquine (N=1027)	Very low dose total primaquine (<2 mg/kg)(N=22)	Low dose total primaquine (2 - <5 mg/kg)(N=1582)	High dose total primaquine (>= 5 mg/kg)(N=2471)	Total **(N=5102)**
Day 3		0 (0%)	0 (0%)	2 (0%)	2 (0%)
Day 4		0 (0%)	0 (0%)	3 (0%)	3 (0%)
Day 5		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Day 6		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Level of PQ supervision					
Unsupervised		6 (27%)	128 (8%)	86 (3%)	220 (5%)
Partially supervised		2 (9%)	1040 (66%)	87 (4%)	1129 (28%)
Fully supervised		14 (64%)	414 (26%)	2298 (93%)	2726 (67%)
Was PQ taken with food?					
No		5 (23%)	118 (7%)	206 (8%)	329 (8%)
Yes		13 (59%)	486 (31%)	1931 (78%)	2430 (60%)
Recommended		4 (18%)	978 (62%)	334 (14%)	1316 (32%)
Other treatment given					
AL	31 (3%)	0 (0%)	9 (1%)	22 (1%)	62 (1%)
AsAq	0 (0%)	0 (0%)	197 (12%)	32 (1%)	229 (4%)
AsMf	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (0%)
Cq	796 (78%)	13 (59%)	1130 (71%)	1120 (45%)	3059 (60%)
DP	200 (19%)	8 (36%)	246 (16%)	1297 (52%)	1751 (34%)
Transmission intensity of the site					
Low	224 (22%)	6 (27%)	152 (10%)	347 (14%)	729 (14%)
Moderate	443 (43%)	9 (41%)	970 (61%)	1789 (72%)	3211 (63%)
High	360 (35%)	7 (32%)	460 (29%)	335 (14%)	1162 (23%)
Not available	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Geographical region					
Africa	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Americas	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asia-Pacific	1027 (100%)	22 (100%)	1582 (100%)	2471 (100%)	5102 (100%)
Relapse Peridocity					
Low periodicity	361 (35%)	7 (32%)	303 (19%)	315 (13%)	986 (19%)
High periodicity	666 (65%)	15 (68%)	1279 (81%)	2156 (87%)	4116 (81%)
G6PD categories (Qualitative test)					
<30%	30 (3%)	0 (0%)	12 (1%)	1 (0%)	43 (1%)
>=30%	995 (97%)	21 (95%)	665 (42%)	2391 (97%)	4072 (80%)
Missing	2 (0.2%)	1 (4.5%)	905 (57.2%)	79 (3.2%)	987 (19.3%)
G6PD categories (Quantitative test)					
<30%	30 (3%)	0 (0%)	12 (1%)	1 (0%)	43 (1%)
30-<70%	8 (1%)	0 (0%)	1 (0%)	25 (1%)	34 (1%)
>=70%	166 (16%)	1 (5%)	10 (1%)	614 (25%)	791 (16%)
Missing	823 (80.1%)	21 (95.5%)	1559 (98.5%)	1831 (74.1%)	4234 (83.0%)

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.



Number at risk (number of recurrences)

No PQ	996 (0)	539 (277)	365 (87)	306 (25)	159 (26)
Low dose PQ	1397 (0)	384 (64)	282 (4)	213 (10)	177 (14)
High dose PQ	2442 (0)	1812 (97)	1394 (84)	1165 (45)	215 (54)

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.

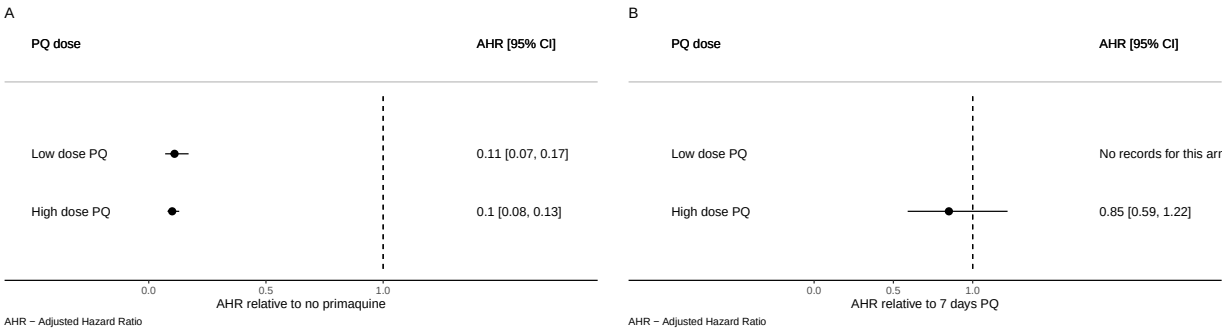


Figure 1_eff: Hazard ratio between day 7 and day 180 for A: total dose of primaquine and B: 14-day vs 7-day primaquine duration, stratified by total dose of primaquine

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 4329 patients across 34 study sites, from 17 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=1016)	Low dose daily primaquine (<0.375 mg/kg/day) (N=761)	Intermediate dose daily primaquine (>= 0.375 & <0.75 mg/kg/day) (N=1422)	High dose daily primaquine (>= 0.75 mg/kg/day) (N=1059)	Total **(N=4329)**
Age (years)					
Mean (SD)	21 (14)	25 (15)	22 (14)	20 (13)	22 (14)
Age Category					
<5	61 (6.00%)	59 (7.75%)	91 (6.40%)	65 (6.14%)	288 (6.65%)
5-<15	308 (30.31%)	131 (17.21%)	436 (30.66%)	373 (35.22%)	1265 (29.22%)
>=15	647 (63.68%)	571 (75.03%)	895 (62.94%)	621 (58.64%)	2776 (64.13%)
Gender					
Male	636 (62.60%)	485 (63.73%)	949 (66.74%)	676 (63.83%)	2786 (64.36%)
Female	380 (37.40%)	276 (36.27%)	473 (33.26%)	383 (36.17%)	1543 (35.64%)
Weight (kg)					
Mean (SD)	45 (19)	51 (19)	43 (18)	42 (17)	45 (18)
Missing	9 (0.9%)	24 (3.2%)	43 (3.0%)	42 (4.0%)	118 (2.7%)
Malnutrition					
No	50 (4.92%)	56 (7.36%)	89 (6.26%)	60 (5.67%)	263 (6.08%)
Yes	23 (2.26%)	15 (1.97%)	25 (1.76%)	16 (1.51%)	84 (1.94%)
Missing	943 (92.8%)	690 (90.7%)	1308 (92.0%)	983 (92.8%)	3982 (92.0%)
Fever day 0					
No	92 (9.06%)	52 (6.83%)	108 (7.59%)	94 (8.88%)	346 (7.99%)
Yes	923 (90.85%)	709 (93.17%)	1258 (88.47%)	965 (91.12%)	3926 (90.69%)
Missing	1 (0.1%)	0 (0%)	56 (3.9%)	0 (0%)	57 (1.3%)
P. vivax baseline parasitaemia					
Median (IQR)	3520 [1578, 9261]	2808 [1136, 6000]	3584 [982, 9945]	3936 [1158, 10322]	3481 [1200, 9152]
Haemoglobin day 0 (g/dL)					
Mean (SD)	12 (1.8)	12 (2.1)	13 (1.8)	13 (1.8)	12 (1.8)
PQ daily dose (mg/kg)					
Mean (SD)		3.6 (0.84)	7.0 (1.4)	7.4 (1.5)	6.3 (2.0)
Missing		0 (0%)	0 (0%)	0 (0%)	71 (2.1%)
Mean (SD)		14 (0)	14 (1.5)	7.2 (1.2)	12 (3.3)
Missing		0 (0%)	0 (0%)	0 (0%)	71 (2.1%)

(continued)

	No primaquine (N=1016)	Low dose daily primaquine (<0.375 mg/kg/day) (N=761)	Intermediate dose daily primaquine (>= 0.375 & <0.75 mg/kg/day) (N=1422)	High dose daily primaquine (>= 0.75 mg/kg/day) (N=1059)	Total **(N=4329)**
Method to calculate PQ dose					
Per dosing protocol		684 (89.88%)	74 (5.20%)	45 (4.25%)	803 (24.24%)
Missing		0 (0%)	0 (0%)	0 (0%)	71 (2.1%)
Start day of PQ treatment					
Day 1		69 (9.07%)	2 (0.14%)	0 (0.00%)	71 (2.14%)
Day 2		155 (20.37%)	138 (9.70%)	50 (4.72%)	343 (10.35%)
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%)
Missing		0 (0%)	0 (0%)	0 (0%)	71 (2.1%)
Level of PQ supervision					
Partially supervised		427 (56.11%)	105 (7.38%)	7 (0.66%)	539 (16.27%)
Fully supervised		36 (4.73%)	1291 (90.79%)	1051 (99.24%)	2378 (71.78%)
Was PQ taken with food?					
No		117 (15.37%)	187 (13.15%)	1 (0.09%)	305 (9.21%)
Recommended		537 (70.57%)	183 (12.87%)	129 (12.18%)	849 (25.63%)
Other treatment given					
AL	31 (3.05%)	10 (1.31%)	7 (0.49%)	0 (0.00%)	48 (1.11%)
AsAq	0 (0.00%)	60 (7.88%)	0 (0.00%)	0 (0.00%)	60 (1.39%)
Cq	789 (77.66%)	619 (81.34%)	695 (48.87%)	472 (44.57%)	2575 (59.48%)
DP	196 (19.29%)	72 (9.46%)	677 (47.61%)	545 (51.46%)	1561 (36.06%)
Missing	0 (0%)	0 (0%)	43 (3.0%)	42 (4.0%)	85 (2.0%)
Transmission intensity of the site					
Low	224 (22.05%)	183 (24.05%)	257 (18.07%)	168 (15.86%)	832 (19.22%)
Moderate	435 (42.81%)	200 (26.28%)	976 (68.64%)	711 (67.14%)	2393 (55.28%)
High	357 (35.14%)	378 (49.67%)	189 (13.29%)	180 (17.00%)	1104 (25.50%)
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	1016 (100.00%)	761 (100.00%)	1422 (100.00%)	1059 (100.00%)	4329 (100.00%)
Relapse Peridocity					
Low periodicity	358 (35.24%)	414 (54.40%)	184 (12.94%)	180 (17.00%)	1136 (26.24%)
High periodicity	658 (64.76%)	347 (45.60%)	1238 (87.06%)	879 (83.00%)	3193 (73.76%)
G6PD categories (Qualitative test)					
<30%	30 (2.95%)	21 (2.76%)	0 (0.00%)	0 (0.00%)	51 (1.18%)
>=30%	983 (96.75%)	724 (95.14%)	1377 (96.84%)	1016 (95.94%)	4171 (96.35%)
Unknown	3 (0.30%)	16 (2.10%)	45 (3.16%)	43 (4.06%)	107 (2.47%)
G6PD categories (Quantitative test)					
<30%	30 (2.95%)	21 (2.76%)	0 (0.00%)	0 (0.00%)	51 (1.18%)
30-<70%	8 (0.79%)	1 (0.13%)	11 (0.77%)	15 (1.42%)	35 (0.81%)
>=70%	166 (16.34%)	22 (2.89%)	322 (22.64%)	311 (29.37%)	821 (18.97%)
Unknown	812 (79.92%)	717 (94.22%)	1089 (76.58%)	733 (69.22%)	3422 (79.05%)

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	780 (79.2 %)	529 (73.0 %)	1222 (86.0 %)	1038 (98.1 %)	3569 (85.2 %)
Yes	1 (0.1 %)	0 (0.0 %)	4 (0.3 %)	6 (0.6 %)	11 (0.3 %)
Missing	204 (20.7%)	196 (27.0%)	195 (13.7%)	14 (1.3%)	609 (14.5%)
Drop in haemoglobin of >5 g/dL from baseline between days 1-14					
No	780 (79.2 %)	529 (73.0 %)	1220 (85.9 %)	1039 (98.2 %)	3568 (85.2 %)
Yes	1 (0.1 %)	0 (0.0 %)	6 (0.4 %)	5 (0.5 %)	12 (0.3 %)
Missing	204 (20.7%)	196 (27.0%)	195 (13.7%)	14 (1.3%)	609 (14.5%)
Drop in haemoglobin to <5 g/dL between days 1 and 14					
No	781 (79.3 %)	529 (73.0 %)	1225 (86.2 %)	1042 (98.5 %)	3577 (85.4 %)
Yes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	2 (0.2 %)	2 (0.0 %)
Missing	204 (20.7%)	196 (27.0%)	196 (13.8%)	14 (1.3%)	610 (14.6%)
Anaemia developed at days 2 or 3					
Nil (Hb: >=11 g/dL)	525 (53.3 %)	349 (48.1 %)	816 (57.4 %)	677 (64.0 %)	2367 (56.5 %)
Mild (Hb: >=8 g/dL & <11 g/dL)	45 (4.6 %)	22 (3.0 %)	155 (10.9 %)	134 (12.7 %)	356 (8.5 %)
Moderate (Hb: >=5 g/dL & <8 g/dL)	1 (0.1 %)	1 (0.1 %)	0 (0.0 %)	4 (0.4 %)	6 (0.1 %)
Severe (Hb <5 g/dL)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	414 (42.0%)	353 (48.7%)	450 (31.7%)	243 (23.0%)	1460 (34.9%)
Anaemia developed at days 5-7					
Nil (Hb: >=11 g/dL)	529 (53.7 %)	346 (47.7 %)	753 (53.0 %)	639 (60.4 %)	2267 (54.1 %)
Mild (Hb: >=8 g/dL & <11 g/dL)	35 (3.6 %)	15 (2.1 %)	140 (9.9 %)	155 (14.7 %)	345 (8.2 %)
Moderate (Hb: >=5 g/dL & <8 g/dL)	0 (0.0 %)	0 (0.0 %)	3 (0.2 %)	2 (0.2 %)	5 (0.1 %)
Severe (Hb <5 g/dL)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	421 (42.7%)	364 (50.2%)	525 (36.9%)	262 (24.8%)	1572 (37.5%)
Change in haemoglobin on days 2-3 from day 0					
Mean (SD)	-0.333 (0.874)	-0.291 (0.815)	-0.595 (1.12)	-0.571 (1.12)	-0.488 (1.04)
Missing	254 (25.8%)	250 (34.5%)	257 (18.1%)	70 (6.6%)	831 (19.8%)
Change in haemoglobin on days 5-7 from day 0					
Mean (SD)	-0.158 (0.904)	-0.0947 (0.794)	-0.553 (1.23)	-0.557 (1.39)	-0.399 (1.18)
Missing	266 (27.0%)	256 (35.3%)	361 (25.4%)	101 (9.5%)	984 (23.5%)
Relative percentage (%) change in haemoglobin on days 2-3 from day 0					
Mean (SD)	2.43 (6.76)	2.10 (6.45)	4.45 (10.1)	4.27 (8.97)	3.62 (8.70)
Missing	254 (25.8%)	250 (34.5%)	257 (18.1%)	70 (6.6%)	831 (19.8%)
Relative percentage (%) change in haemoglobin on days 5-7 from day 0					
Mean (SD)	0.942 (7.29)	0.531 (6.86)	4.00 (11.1)	4.04 (11.0)	2.82 (9.89)
Missing	266 (27.0%)	256 (35.3%)	361 (25.4%)	101 (9.5%)	984 (23.5%)

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.

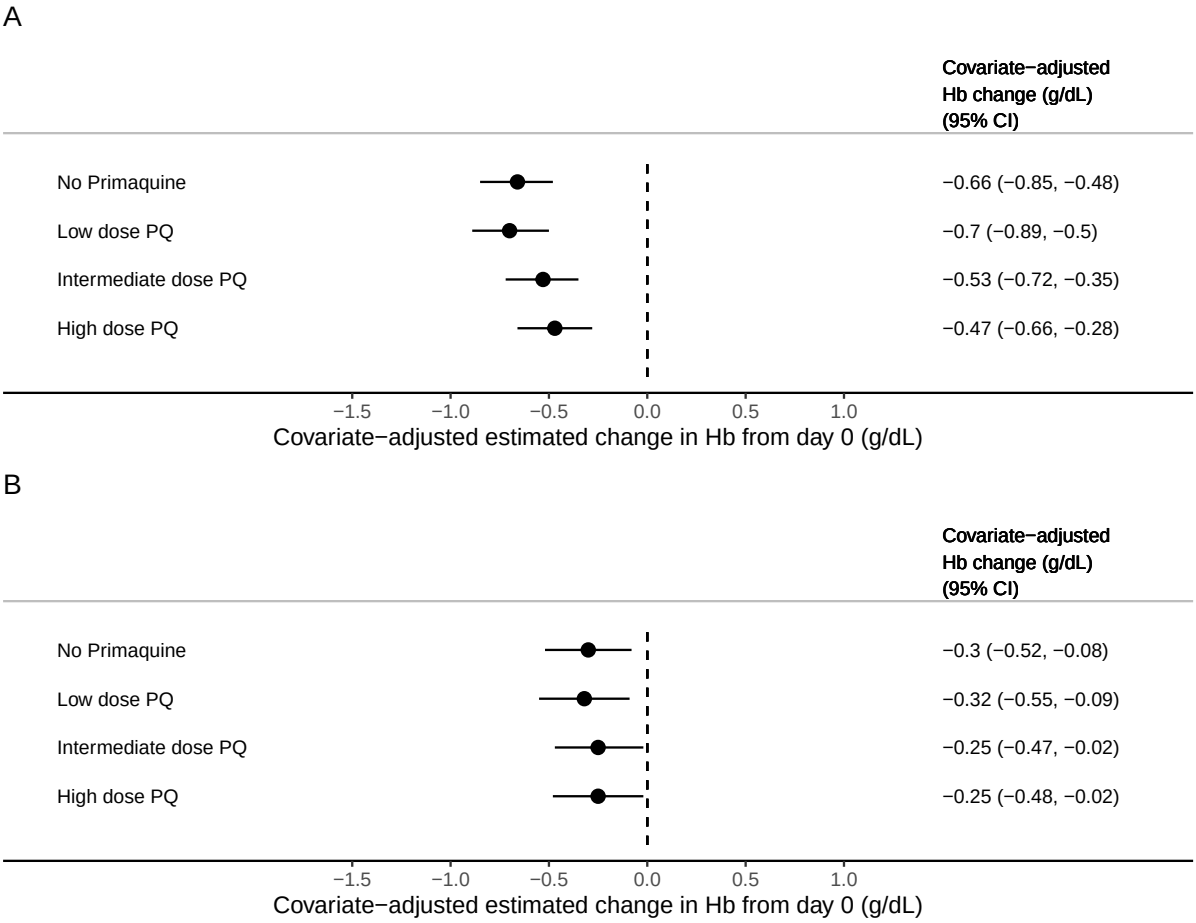


Figure 1_saf: The covariate-adjusted estimated change in Hb between primaquine daily dose groups on (A) days 2-3 and (B) days 5-7, in patients with ≥ 30% G6PD activity.

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 4323 patients across 22 study sites, from 12 studies.

Characteristics of Study Population

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

	Primaquine Treatment				
	No primaquine (N=842)	Low dose daily primaquine (<0.375 mg/kg/day) (N=709)	Intermediate dose daily primaquine (>=0.375 & <0.75 mg/kg/day) (N=1453)	High dose daily primaquine (>= 0.75 mg/kg/day) (N=1319)	Total **(N=4323)**
Age (years)					
Mean (SD)	20 (14)	20 (14)	21 (14)	19 (13)	20 (14)
Age Category					
<5	59 (7%)	79 (11%)	99 (7%)	106 (8%)	343 (8%)
5-<15	297 (35%)	232 (33%)	460 (32%)	492 (37%)	1481 (34%)
>=15	486 (58%)	398 (56%)	894 (62%)	721 (55%)	2499 (58%)
Gender					
Male	561 (67%)	423 (60%)	967 (67%)	834 (63%)	2785 (64%)
Female	281 (33%)	286 (40%)	486 (33%)	485 (37%)	1538 (36%)
Weight (kg)					
Mean (SD)	43 (19)	44 (21)	43 (18)	39 (18)	42 (19)
Missing	6 (0.7%)	4 (0.6%)	43 (3.0%)	42 (3.2%)	95 (2.2%)
Malnutrition					
No	47 (6%)	72 (10%)	93 (6%)	88 (7%)	300 (7%)
Yes	22 (3%)	22 (3%)	29 (2%)	43 (3%)	116 (3%)
Missing	773 (91.8%)	615 (86.7%)	1331 (91.6%)	1188 (90.1%)	3907 (90.4%)
Fever day 0					
No	57 (7%)	24 (3%)	97 (7%)	94 (7%)	272 (6%)
Yes	784 (93%)	685 (97%)	1300 (89%)	1225 (93%)	3994 (92%)
Missing	1 (0.1%)	0 (0%)	56 (3.9%)	0 (0%)	57 (1.3%)
P. vivax baseline parasitaemia					
Median (IQR)	2996 [1400, 7926])	2000 [560, 4480])	3568 [992, 9797])	3837 [1178, 10000])	3200 [1035, 8381])
Haemoglobin day 0 (g/dL)					
Mean (SD)	12 (1.8)	12 (1.9)	13 (1.8)	12 (1.9)	12 (1.9)
Missing	7 (0.8%)	3 (0.4%)	6 (0.4%)	1 (0.1%)	17 (0.4%)
PQ daily dose (mg/kg)					
Mean (SD)		3.8 (0.63)	6.9 (1.4)	6.9 (1.7)	6.3 (1.9)
Duration of PQ treatment					
7 days		0 (0%)	70 (5%)	1288 (98%)	1358 (39%)
14 days		709 (100%)	1383 (95%)	31 (2%)	2123 (61%)

(continued)

	No primaquine (N=842)	Low dose daily primaquine (<0.375 mg/kg/day) (N=709)	Intermediate dose daily primaquine (>=0.375 & <0.75 mg/kg/day) (N=1453)	High dose daily primaquine (>= 0.75 mg/kg/day) (N=1319)	Total **(N=4323)**
Method to calculate PQ dose					
Per actual dose		45 (6%)	1334 (92%)	1274 (97%)	2653 (76%)
Per dosing protocol		664 (94%)	119 (8%)	45 (3%)	828 (24%)
Start day of PQ treatment					
Day 0		559 (79%)	1337 (92%)	1270 (96%)	3166 (91%)
Day 1		25 (4%)	0 (0%)	0 (0%)	25 (1%)
Day 2		125 (18%)	116 (8%)	49 (4%)	290 (8%)
Day 3		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Day 4		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Day 5		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Day 6		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Level of PQ supervision					
Unsupervised		115 (16%)	2 (0%)	0 (0%)	117 (3%)
Partially supervised		281 (40%)	99 (7%)	7 (1%)	387 (11%)
Fully supervised		313 (44%)	1352 (93%)	1312 (99%)	2977 (86%)
Was PQ taken with food?					
No		119 (17%)	193 (13%)	1 (0%)	313 (9%)
Yes		338 (48%)	1105 (76%)	1189 (90%)	2632 (76%)
Recommended		252 (36%)	155 (11%)	129 (10%)	536 (15%)
Other treatment given					
AL	11 (1%)	10 (1%)	7 (0%)	0 (0%)	28 (1%)
AsAq	0 (0%)	203 (29%)	26 (2%)	0 (0%)	229 (5%)
Cq	635 (75%)	288 (41%)	672 (46%)	732 (55%)	2327 (54%)
DP	196 (23%)	208 (29%)	705 (49%)	545 (41%)	1654 (38%)
Missing	0 (0%)	0 (0%)	43 (3.0%)	42 (3.2%)	85 (2.0%)
Transmission intensity of the site					
Low	64 (8%)	20 (3%)	231 (16%)	427 (32%)	742 (17%)
Moderate	418 (50%)	308 (43%)	1033 (71%)	711 (54%)	2470 (57%)
High	360 (43%)	381 (54%)	189 (13%)	181 (14%)	1111 (26%)
Not available	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Geographical region					
Africa	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Americas	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asia-Pacific	842 (100%)	709 (100%)	1453 (100%)	1319 (100%)	4323 (100%)
Relapse Peridocity					
Low periodicity	351 (42%)	256 (36%)	182 (13%)	181 (14%)	970 (22%)
High periodicity	491 (58%)	453 (64%)	1271 (87%)	1138 (86%)	3353 (78%)
G6PD categories (Qualitative test)					
<30%	24 (3%)	12 (2%)	0 (0%)	0 (0%)	36 (1%)
>=30%	818 (97%)	407 (57%)	1354 (93%)	1018 (77%)	3597 (83%)
Missing	0 (0%)	290 (40.9%)	99 (6.8%)	301 (22.8%)	690 (16.0%)
G6PD categories (Quantitative test)					
<30%	24 (3%)	12 (2%)	0 (0%)	0 (0%)	36 (1%)
30-<70%	8 (1%)	0 (0%)	11 (1%)	15 (1%)	34 (1%)
>=70%	166 (20%)	6 (1%)	308 (21%)	311 (24%)	791 (18%)
Missing	644 (76.5%)	691 (97.5%)	1134 (78.0%)	993 (75.3%)	3462 (80.1%)

3.3 Summary of the gastrointestinal tolerability outcomes

The primary endpoint for this analysis was a composite indicator including the presence of vomiting or anorexia or diarrhoea on days 5-7 after enrolment.

Secondary endpoints for this analysis were:

a) the presence of vomiting, nausea, anorexia, abdominal pain, diarrhoea or dizziness assessed separately on days 5-7[1]

b) the presence of the composite endpoint including vomiting or anorexia or diarrhoea on day 0, days 1-2 and days 5-7, assessed separately

[1]Assessment of nausea, dizziness and abdominal pain was restricted to patients older than 5 years

Table 2 provides a summary of the outcome experienced within each Primaquine treatment arm.

Table 2_tol: Summary of gastrointestinal outcomes, categorised by total primaquine category

	Primaquine Treatment				
	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)**	**Total**
Outcomes include participants of all ages					
	(N=842)	**(N=709)**	**(N=1453)**	**(N=1319)**	**(N=4323)**
Composite on day 0					
No	338 (55.3 %)	248 (57.8 %)	403 (48.6 %)	578 (58.4 %)	1567 (54.8 %)
Yes	273 (44.7 %)	181 (42.2 %)	426 (51.4 %)	412 (41.6 %)	1292 (45.2 %)
Missing	231 (27.4%)	280 (39.5%)	624 (42.9%)	329 (24.9%)	1464 (33.9%)
Composite between days 1-2					
No	458 (75.6 %)	335 (67.5 %)	597 (71.7 %)	746 (76.4 %)	2136 (73.4 %)
Yes	148 (24.4 %)	161 (32.5 %)	236 (28.3 %)	230 (23.6 %)	775 (26.6 %)
Missing	236 (28.0%)	213 (30.0%)	620 (42.7%)	343 (26.0%)	1412 (32.7%)
Composite between days 5-7					
No	589 (98.5 %)	358 (88.2 %)	762 (94.1 %)	875 (91.7 %)	2584 (93.4 %)
Yes	9 (1.5 %)	48 (11.8 %)	48 (5.9 %)	79 (8.3 %)	184 (6.6 %)
Missing	244 (29.0%)	303 (42.7%)	643 (44.3%)	365 (27.7%)	1555 (36.0%)
Vomiting between days 5-7					
No	597 (99.8 %)	382 (96.0 %)	792 (98.3 %)	934 (97.9 %)	2705 (98.1 %)
Yes	1 (0.2 %)	16 (4.0 %)	14 (1.7 %)	20 (2.1 %)	51 (1.9 %)
Missing	244 (29.0%)	311 (43.9%)	647 (44.5%)	365 (27.7%)	1567 (36.2%)
Anorexia between days 5-7					
No	324 (98.2 %)	95 (88.8 %)	704 (96.0 %)	850 (93.5 %)	1973 (94.9 %)
Yes	6 (1.8 %)	12 (11.2 %)	29 (4.0 %)	59 (6.5 %)	106 (5.1 %)
Missing	512 (60.8%)	602 (84.9%)	720 (49.6%)	410 (31.1%)	2244 (51.9%)
Diarrhoea between days 5-7					
No	591 (99.5 %)	374 (94.0 %)	756 (98.6 %)	893 (97.9 %)	2614 (97.9 %)
Yes	3 (0.5 %)	24 (6.0 %)	11 (1.4 %)	19 (2.1 %)	57 (2.1 %)
Outcomes restricted to participants >5 years old					
Missing	**248 (29.5%)** (N=772)	**311 (43.9%)** (N=615)	**686 (47.2%)** (N=1331)	**407 (30.9%)** (N=1188)	**1652 (38.2%)** (N=3906)
Nausea between days 5-7*					
No	540 (97.6 %)	272 (90.7 %)	702 (95.8 %)	783 (92.6 %)	2297 (94.4 %)
Yes	13 (2.4 %)	28 (9.3 %)	31 (4.2 %)	63 (7.4 %)	135 (5.6 %)
Missing	219 (28.4%)	315 (51.2%)	598 (44.9%)	342 (28.8%)	1474 (37.7%)
Abdominal pain between days 5-7*					
No	299 (96.1 %)	99 (79.8 %)	661 (91.6 %)	701 (82.9 %)	1760 (87.9 %)
Yes	12 (3.9 %)	25 (20.2 %)	61 (8.4 %)	145 (17.1 %)	243 (12.1 %)
Missing	461 (59.7%)	491 (79.8%)	609 (45.8%)	342 (28.8%)	1903 (48.7%)
Dizziness between days 5-7*					
No	305 (98.1 %)	111 (91.0 %)	663 (97.6 %)	787 (97.9 %)	1866 (97.4 %)
Yes	6 (1.9 %)	11 (9.0 %)	16 (2.4 %)	17 (2.1 %)	50 (2.6 %)
Missing	461 (59.7%)	493 (80.2%)	652 (49.0%)	384 (32.3%)	1990 (50.9%)

Figure 1_tol: Distribution of primaquine daily dose by primaquine mg/kg daily dose category. Primaquine daily dose categories: Low: <0.375 mg/kg/day, Int (intermediate): ≥ 0.375 mg/kg/day and <0.750 mg/kg/day, and High: ≥ 0.750 mg/kg/day

3.4: Risk of gastrointestinal intolerance

The risk of gastrointestinal intolerance on days 5-7 was calculated from the number of patients reporting the composite outcome as a proportion of the total number of patients asked about each of the individual components of the composite; i.e. those asked about vomiting or anorexia or diarrhoea on any day between days 5-7. The 95% confidence intervals (CIs) for the risks were calculated as exact binomial CIs. The risks were stratified by primaquine daily dose categories

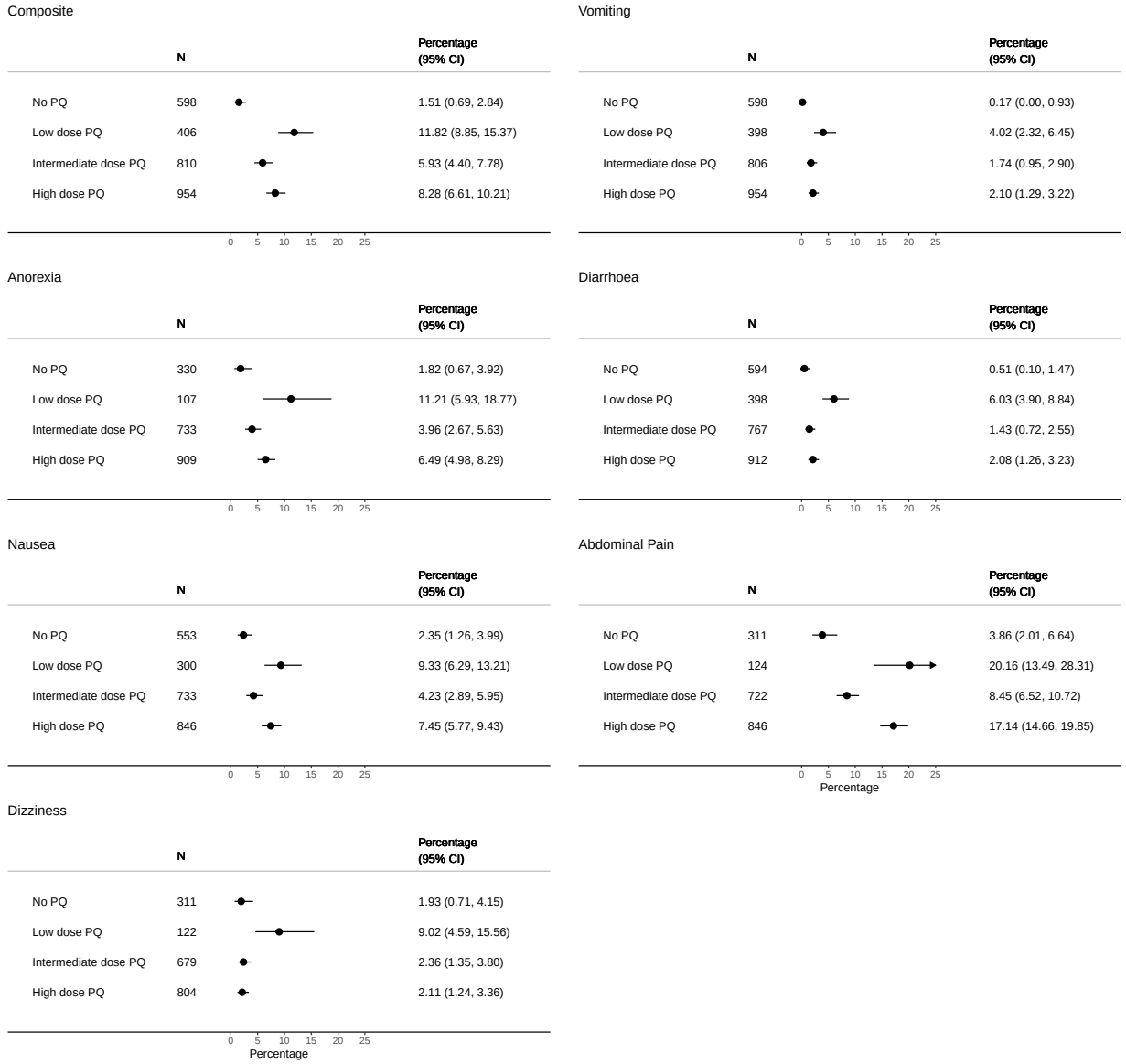


Figure 2_tol: Risk of gastrointestinal intolerance by symptoms. For each outcome the risk was estimated as the number of individuals experiencing the symptom as a proportion of the number of individuals asked about the symptom on any day between days 5-7. The confidence intervals (CIs) are exact binomial CIs.

3.4.1: Adjusted association between primaquine daily dose categories and gastrointestinal intolerance days 5-7

The plots below show the estimated proportion of patients with gastrointestinal symptoms on days 5–7 by primaquine treatment regimen, adjusted for age, sex and baseline parasite density. A logistic model was fit and the adjusted proportions were estimated using mean values for age, sex, and log10 baseline parasite density.
Care should be taken when interpreting these results, as model assumptions have not been fully assessed in this automated report format.

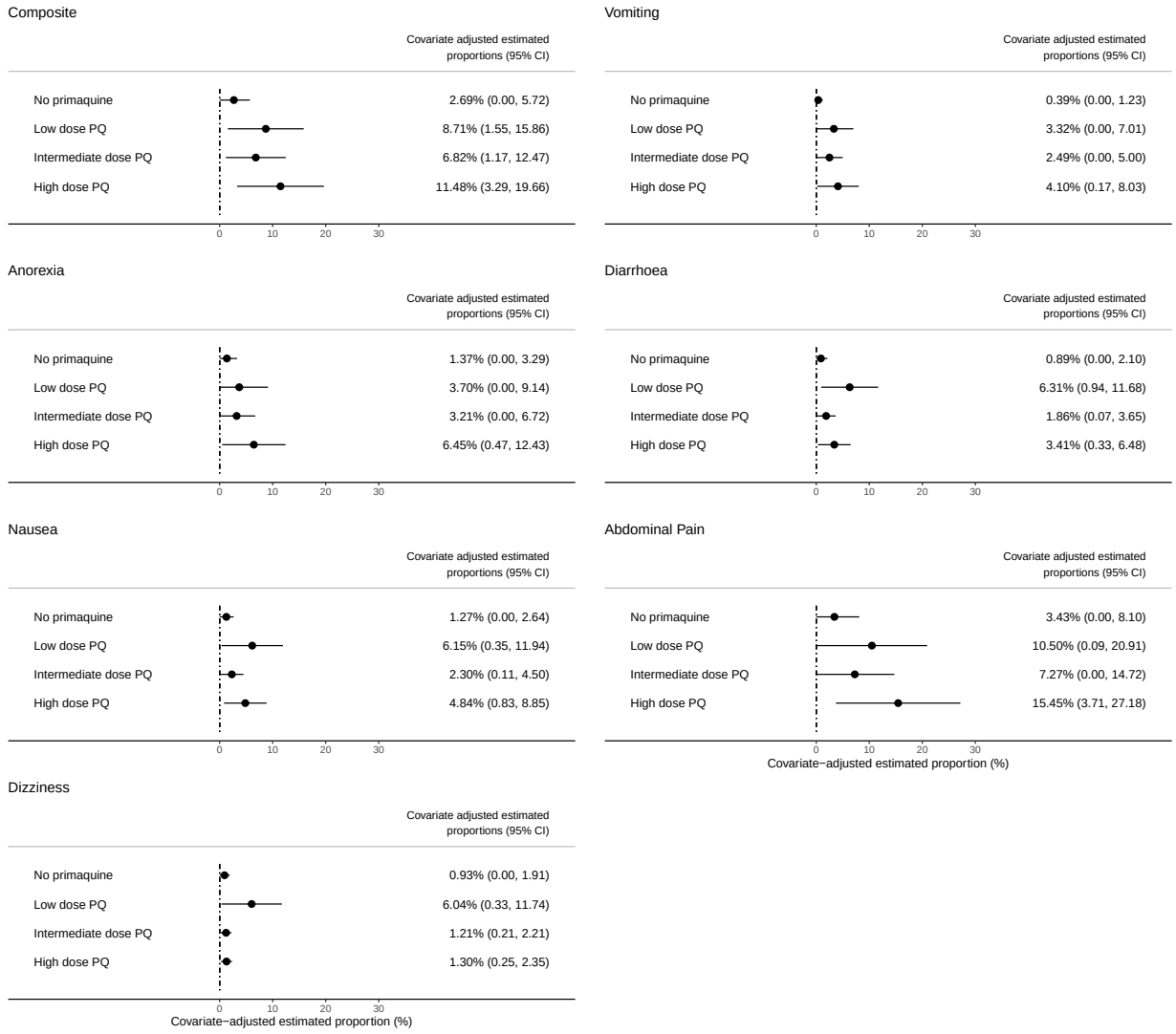


Figure 2_tol: Covariate-adjusted estimated proportion of patients with gastrointestinal symptoms on days 5–7 by primaquine treatment regimen. A logistic mixed effects model was fit, with study site as the random effect, and the adjusted proportions were estimated using mean values for age, sex, and log10 baseline parasite density. Note: The lower confidence intervals have been limited to 0% and the upper limited to 100%.

3.4.2: Risk of Acute Vomiting on days 0-2 and 3-13

The unadjusted risk of vomiting within an hour of primaquine administration (acute vomiting) was calculated on days 0-2 and days 3-13 for each primaquine dose group.

Table 3_tol: Risk of acute vomiting on days 0-2 and 3-13 by primaquine daily dose categories

	Risk of acute vomiting	
Primaquine treatment	Days 0-2	Days 3-13
Low dose daily primaquine (<0.375 mg/kg/day)	8/315 (2.5%)	0/36 (0.0%)
Intermediate dose daily primaquine (>=0.375 & <0.75 mg/kg/day)	19/1351 (1.4%)	5/1246 (0.4%)
High dose daily primaquine (>=0.75 mg/kg/day)	18/1277 (1.4%)	4/1246 (0.3%)

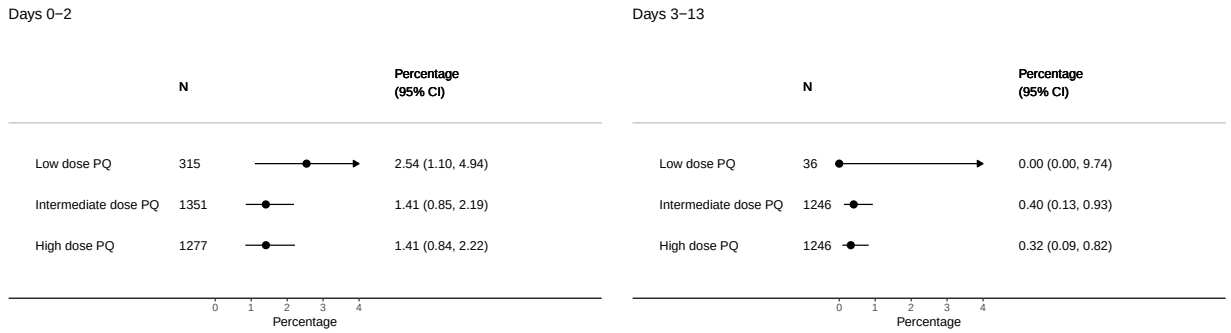


Figure 3_tol: Risk of acute vomiting on days 0-2 and 3-13 by primaquine daily dose categories. The confidence intervals (CIs) are exact binomial CIs.