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: Americas

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
Chamma-Siqueira-2022	Brazil	NA	17.7	168	Cq_Pq_3.5_7d_D17_obs	Fully supervised	1
Llanos-Cuentas-2019	Brazil, Peru, Colombia	2014 - 2017	17 - 74	180	Cq_Pq_3.5_14d_D1	<50% supervised	62
Lacerda-2019	Brazil, Peru	2013 - 2017	16 - 71	180	Cq, Cq_Pq_3.5_14d_D1	<50% supervised	183
Ladeia-Andrade-2019	Brazil	2014 - 2015	7 - 60	180	Cq_Pq_3.5_7d_D0	Fully supervised	94
Zuluaga-Idarraga-2016	Colombia	2012 - 2013	4 - 71	180	Cq_Pq_3.5_14d_D0	Fully supervised	87
Llanos-Cuentas-2014	Peru, Brazil	2010 - 2013	16 - 72	180	Cq, Cq_Pq_3.5_14d_D1	<50% supervised	55
Daher-2018	Brazil	2012 - 2015	18.4 - 65.8	63	AsMf_Pq_3.5_7-9d_D0, Cq_Pq_3.5_7-9d_D0, AL_Pq_3.5_7-9d_D0	<50% supervised	264
Gonzalez-Ceron-2015	Mexico	2008 - 2010	3 - 78	365	Cq_Pq_3.5_14d_D0	Fully supervised	88
de Sena-2019	Brazil	NA	2 - 14	42	Cq_Pq_3.5_7d_D0	<50% supervised	113
Siqueira-unpublished2024	Brazil	NA	9 - 84	180	Cq_Pq_7.0_14d_D0, DP_Pq_7.0_14d_D0, Cq_Pq_7.0_14d_D42	Unsupervised	224
Pereira-2016	Brazil	2013 - 2014	19 - 68	28	Cq_Pq_4.0_8d_D0, Cq_Pq_4.5_9d_D0, Cq_Pq_3.5_7d_D0	<50% supervised	86

∗ *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 1171 patients across 21 study sites, from 10 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

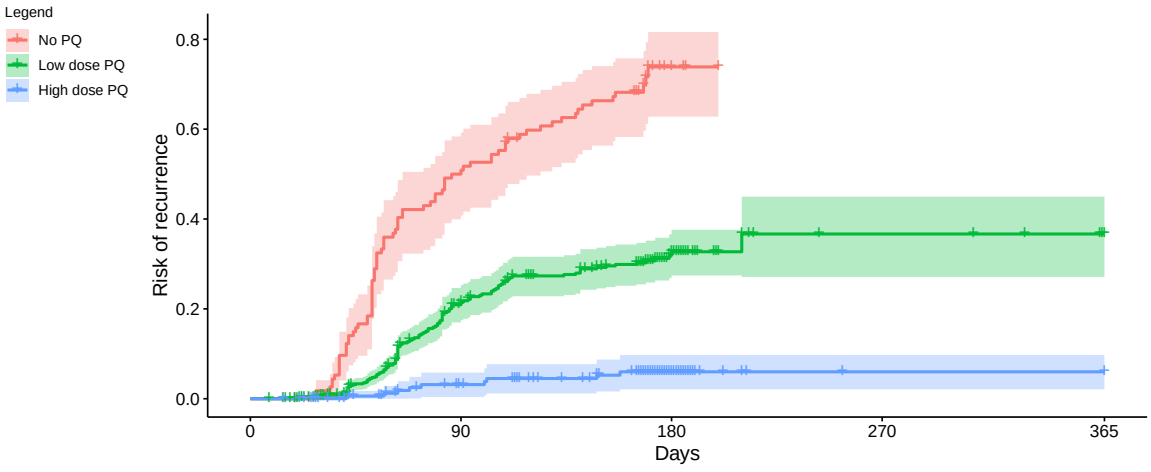
	Primaquine (PQ) Treatment				
	No primaquine (N=119)	Very low dose total primaquine (<2 mg/kg)(N=15)	Low dose total primaquine (2 - <5 mg/kg)(N=849)	High dose total primaquine (>= 5 mg/kg)(N=188)	Total **(N=1171)**
Age (years)					
Mean (SD)	37 (14)	33 (14)	32 (17)	39 (18)	34 (17)
Age Category					
<5	0 (0%)	0 (0%)	31 (4%)	7 (4%)	38 (3%)
5-<15	0 (0%)	2 (13%)	126 (15%)	15 (8%)	143 (12%)
>=15	119 (100%)	13 (87%)	692 (82%)	166 (88%)	990 (85%)
Gender					
Male	82 (69%)	12 (80%)	571 (67%)	115 (61%)	780 (67%)
Female	37 (31%)	3 (20%)	278 (33%)	73 (39%)	391 (33%)
Weight (kg)					
Mean (SD)	66 (12)	80 (23)	62 (20)	64 (17)	63 (19)
Malnutrition					
No	0 (0%)	0 (0%)	32 (4%)	6 (3%)	38 (3%)
Yes	0 (0%)	0 (0%)	0 (0%)	2 (1%)	2 (0%)
Missing	119 (100%)	15 (100%)	817 (96.2%)	180 (95.7%)	1131 (96.6%)
Fever day 0					
No	8 (7%)	3 (20%)	64 (8%)	1 (1%)	76 (6%)
Yes	111 (93%)	12 (80%)	521 (61%)	187 (99%)	831 (71%)
Missing	0 (0%)	0 (0%)	264 (31.1%)	0 (0%)	264 (22.5%)
P. vivax baseline parasitaemia					
Median (IQR)	4750 [1646, 9946]	2698 [792, 3913]	2891 [1140, 5441]	4119 [1865, 6678]	3078 [1202, 5952]
Haemoglobin day 0 (g/dL)					
Mean (SD)	13 (1.4)	14 (1.7)	13 (1.8)	14 (1.8)	13 (1.8)
Missing	0 (0%)	0 (0%)	163 (19.2%)	13 (6.9%)	176 (15.0%)
PQ daily dose (mg/kg)					
Mean (SD)		1.1 (0.48)	3.4 (0.53)	6.3 (1.3)	3.9 (1.4)
Missing		0 (0%)	0 (0%)	0 (0%)	0(0%)
Duration of PQ treatment					
7 days		2 (13%)	464 (55%)	6 (3%)	472 (45%)
14 days		13 (87%)	384 (45%)	182 (97%)	579 (55%)
Missing		0 (0%)	1 (0.1%)	0 (0%)	1 (0.1%)
Method to calculate PQ dose					
Per actual dose		14 (93%)	403 (47%)	186 (99%)	603 (57%)
Per dosing protocol		1 (7%)	446 (53%)	2 (1%)	449 (43%)
Missing		0 (0%)	0 (0%)	0 (0%)	0(0%)
Start day of PQ treatment					
Day 0		14 (93%)	668 (79%)	186 (99%)	868 (83%)

(continued)

	No primaquine (N=119)	Very low dose total primaquine (<2 mg/kg)(N=15)	Low dose total primaquine (2 - <5 mg/kg)(N=849)	High dose total primaquine (>= 5 mg/kg)(N=188)	Total **(N=1171)**
Day 1		1 (7%)	178 (21%)	0 (0%)	179 (17%)
Day 2		0 (0%)	1 (0%)	1 (1%)	2 (0%)
Day 3		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Day 5		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Day 6		0 (0%)	2 (0%)	0 (0%)	2 (0%)
Missing		0 (0%)	0 (0%)	1 (0.5%)	1 (0.1%)
Level of PQ supervision					
Unsupervised		12 (80%)	43 (5%)	169 (90%)	224 (21%)
Partially supervised		3 (20%)	550 (65%)	5 (3%)	558 (53%)
Fully supervised		0 (0%)	256 (30%)	14 (7%)	270 (26%)
Missing		0 (0%)	0 (0%)	0 (0%)	0(0%)
Was PQ taken with food?					
No		0 (0%)	93 (11%)	1 (1%)	94 (9%)
Yes		3 (20%)	286 (34%)	5 (3%)	294 (28%)
Recommended		0 (0%)	426 (50%)	13 (7%)	439 (42%)
Missing		12 (80.0%)	44 (5.2%)	169 (89.9%)	225 (21.4%)
Other treatment given					
AL	0 (0%)	0 (0%)	87 (10%)	0 (0%)	87 (7%)
AsAq	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AsMf	0 (0%)	0 (0%)	89 (10%)	0 (0%)	89 (8%)
Cq	119 (100%)	10 (67%)	652 (77%)	103 (55%)	884 (75%)
DP	0 (0%)	5 (33%)	21 (2%)	85 (45%)	111 (9%)
Transmission intensity of the site					
Low	0 (0%)	0 (0%)	78 (9%)	10 (5%)	88 (8%)
Moderate	0 (0%)	2 (13%)	196 (23%)	8 (4%)	206 (18%)
High	119 (100%)	13 (87%)	575 (68%)	170 (90%)	877 (75%)
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	119 (100%)	15 (100%)	849 (100%)	188 (100%)	1171 (100%)
Asia-Pacific	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Relapse Peridocity					
Low periodicity	119 (100%)	15 (100%)	849 (100%)	188 (100%)	1171 (100%)
High periodicity	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
G6PD categories (Qualitative test)					
<30%	0 (0%)	0 (0%)	2 (0%)	0 (0%)	2 (0%)
>=30%	119 (100%)	1 (7%)	272 (32%)	1 (1%)	393 (34%)
Missing	0 (0%)	14 (93.3%)	575 (67.7%)	187 (99.5%)	776 (66.3%)
G6PD categories (Quantitative test)					
<30%	0 (0%)	0 (0%)	2 (0%)	0 (0%)	2 (0%)
30-<70%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
>=70%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	119 (100%)	15 (100%)	847 (99.8%)	188 (100%)	1169 (99.8%)

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	117 (0)	57 (58)	5 (22)	NA	NA
Low dose PQ	828 (0)	263 (104)	85 (32)	12 (1)	7 (0)
High dose PQ	184 (0)	145 (5)	38 (4)	1 (0)	1 (0)

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.

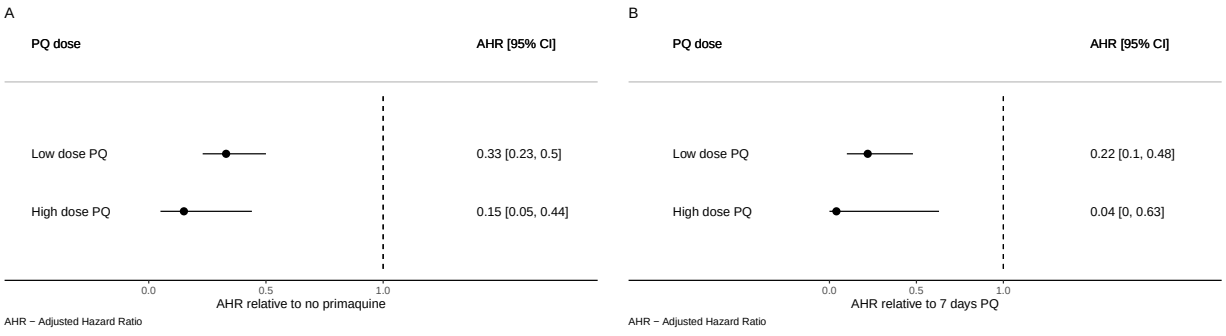


Figure 1_eff: Hazard ratio between day 7 and day 180 for A: total dose of primaquine and B: 14-day vs 7-day primaquine duration, stratified by total dose of primaquine

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 393 patients across 10 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=119)	Low dose daily primaquine (<0.375 mg/kg/day) (N=180)	Intermediate dose daily primaquine (>= 0.375 & <0.75 mg/kg/day) (N=90)	High dose daily primaquine (>= 0.75 mg/kg/day) (N=4)	Total **(N=393)**
Age (years)					
Mean (SD)	37 (14)	39 (14)	26 (14)	12 (2.0)	35 (15)
Age Category					
<5	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
5-<15	0 (0.00%)	0 (0.00%)	21 (23.33%)	3 (75.00%)	24 (6.11%)
>=15	119 (100.00%)	180 (100.00%)	69 (76.67%)	1 (25.00%)	369 (93.89%)
Gender					
Male	82 (68.91%)	117 (65.00%)	59 (65.56%)	2 (50.00%)	260 (66.16%)
Female	37 (31.09%)	63 (35.00%)	31 (34.44%)	2 (50.00%)	133 (33.84%)
Weight (kg)					
Mean (SD)	66 (12)	67 (12)	58 (15)	38 (1.5)	64 (13)
Malnutrition					
No	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Yes	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Missing	119 (100%)	180 (100%)	90 (100%)	4 (100%)	393 (100%)
Fever day 0					
No	8 (6.72%)	14 (7.78%)	3 (3.33%)	0 (0.00%)	25 (6.36%)
Yes	111 (93.28%)	166 (92.22%)	87 (96.67%)	4 (100.00%)	368 (93.64%)
P. vivax baseline parasitaemia					
Median (IQR)	4750 [1646, 9946]	3697 [1506, 9122]	2817 [1437, 3936]	3565 [2560, 6552]	3556 [1514, 8134]
Haemoglobin day 0 (g/dL)					
Mean (SD)	13 (1.4)	13 (1.6)	13 (1.8)	12 (0.33)	13 (1.6)
PQ daily dose (mg/kg)					
Mean (SD)		3.3 (0.56)	3.4 (0.50)	3.4 (1.3)	3.3 (0.56)
Missing		0 (0%)	0 (0%)	0 (0%)	0(0%)
Duration of PQ treatment					
Mean (SD)		14 (0.74)	7.2 (1.0)	7.0 (0)	12 (3.3)
Missing		0 (0%)	0 (0%)	0 (0%)	
Method to calculate PQ dose					

(continued)

	No primaquine (N=119)	Low dose daily primaquine (<0.375 mg/kg/day) (N=180)	Intermediate dose daily primaquine (>= 0.375 & <0.75 mg/kg/day) (N=90)	High dose daily primaquine (>= 0.75 mg/kg/day) (N=4)	Total **(N=393)**
Per actual dose		2 (1.11%)	88 (97.78%)	4 (100.00%)	94 (34.31%)
Per dosing protocol		178 (98.89%)	2 (2.22%)	0 (0.00%)	180 (65.69%)
Missing		0 (0%)	0 (0%)	0 (0%)	0(0%)
Start day of PQ treatment					
Day 0		2 (1.11%)	88 (97.78%)	4 (100.00%)	94 (34.31%)
Day 1		177 (98.33%)	2 (2.22%)	0 (0.00%)	179 (65.33%)
Day 2		1 (0.56%)	0 (0.00%)	0 (0.00%)	1 (0.36%)
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		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Partially supervised		178 (98.89%)	2 (2.22%)	0 (0.00%)	180 (65.69%)
Fully supervised		2 (1.11%)	88 (97.78%)	4 (100.00%)	94 (34.31%)
Was PQ taken with food?					
No		2 (1.11%)	88 (97.78%)	4 (100.00%)	94 (34.31%)
Yes		178 (98.89%)	2 (2.22%)	0 (0.00%)	180 (65.69%)
Recommended		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
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	119 (100.00%)	180 (100.00%)	90 (100.00%)	4 (100.00%)	393 (100.00%)
DP	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Transmission intensity of the site					
Low	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Moderate	0 (0.00%)	6 (3.33%)	0 (0.00%)	0 (0.00%)	6 (1.53%)
High	119 (100.00%)	174 (96.67%)	90 (100.00%)	4 (100.00%)	387 (98.47%)
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	119 (100.00%)	180 (100.00%)	90 (100.00%)	4 (100.00%)	393 (100.00%)
Asia-Pacific	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Relapse Peridocity					
Low periodicity	119 (100.00%)	180 (100.00%)	90 (100.00%)	4 (100.00%)	393 (100.00%)
High periodicity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
G6PD categories (Qualitative test)					
<30%	0 (0.00%)	0 (0.00%)	2 (2.22%)	0 (0.00%)	2 (0.51%)
>=30%	107 (89.92%)	167 (92.78%)	88 (97.78%)	4 (100.00%)	366 (93.13%)
Unknown	12 (10.08%)	13 (7.22%)	0 (0.00%)	0 (0.00%)	25 (6.36%)
G6PD categories (Quantitative test)					
<30%	0 (0.00%)	0 (0.00%)	2 (2.22%)	0 (0.00%)	2 (0.51%)
30-<70%	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
>=70%	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Unknown	119 (100.00%)	180 (100.00%)	88 (97.78%)	4 (100.00%)	391 (99.49%)

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	119 (100.0 %)	180 (100.0 %)	85 (96.6 %)	4 (100.0 %)	388 (99.2 %)
Yes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	0 (0%)	0 (0%)	3 (3.4%)	0 (0%)	3 (0.8%)
Drop in haemoglobin of >5 g/dL from baseline between days 1-14					
No	119 (100.0 %)	180 (100.0 %)	84 (95.5 %)	4 (100.0 %)	387 (99.0 %)
Yes	0 (0.0 %)	0 (0.0 %)	1 (1.1 %)	0 (0.0 %)	1 (0.3 %)
Missing	0 (0%)	0 (0%)	3 (3.4%)	0 (0%)	3 (0.8%)
Drop in haemoglobin to <5 g/dL between days 1 and 14					
No	119 (100.0 %)	180 (100.0 %)	85 (96.6 %)	4 (100.0 %)	388 (99.2 %)
Yes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	0 (0%)	0 (0%)	3 (3.4%)	0 (0%)	3 (0.8%)
Anaemia developed at days 2 or 3					
Nil (Hb: >=11 g/dL)	91 (76.5 %)	143 (79.4 %)	62 (70.5 %)	3 (75.0 %)	299 (76.5 %)
Mild (Hb: >=8 g/dL & <11 g/dL)	13 (10.9 %)	17 (9.4 %)	8 (9.1 %)	1 (25.0 %)	39 (10.0 %)
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	15 (12.6%)	20 (11.1%)	18 (20.5%)	0 (0%)	53 (13.6%)
Anaemia developed at days 5-7					
Nil (Hb: >=11 g/dL)	103 (86.6 %)	148 (82.2 %)	57 (64.8 %)	3 (75.0 %)	311 (79.5 %)
Mild (Hb: >=8 g/dL & <11 g/dL)	4 (3.4 %)	10 (5.6 %)	3 (3.4 %)	0 (0.0 %)	17 (4.3 %)
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	12 (10.1%)	22 (12.2%)	28 (31.8%)	1 (25.0%)	63 (16.1%)
Change in haemoglobin on days 2-3 from day 0					
Mean (SD)	-0.373 (0.854)	-0.556 (0.966)	-0.434 (1.12)	-0.100 (0.762)	-0.469 (0.971)
Missing	8 (6.7%)	5 (2.8%)	4 (4.5%)	0 (0%)	17 (4.3%)
Change in haemoglobin on days 5-7 from day 0					
Mean (SD)	-0.297 (0.873)	-0.347 (1.00)	-0.0812 (1.09)	0.433 (0.306)	-0.274 (0.981)
Missing	4 (3.4%)	7 (3.9%)	19 (21.6%)	1 (25.0%)	31 (7.9%)
Relative percentage (%) change in haemoglobin on days 2-3 from day 0					
Mean (SD)	2.78 (6.58)	4.04 (7.62)	2.76 (8.29)	0.926 (6.58)	3.35 (7.48)
Missing	8 (6.7%)	5 (2.8%)	4 (4.5%)	0 (0%)	17 (4.3%)
Relative percentage (%) change in haemoglobin on days 5-7 from day 0					
Mean (SD)	1.95 (6.87)	2.20 (8.20)	0.181 (8.12)	-3.72 (2.64)	1.68 (7.78)
Missing	4 (3.4%)	7 (3.9%)	19 (21.6%)	1 (25.0%)	31 (7.9%)

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.

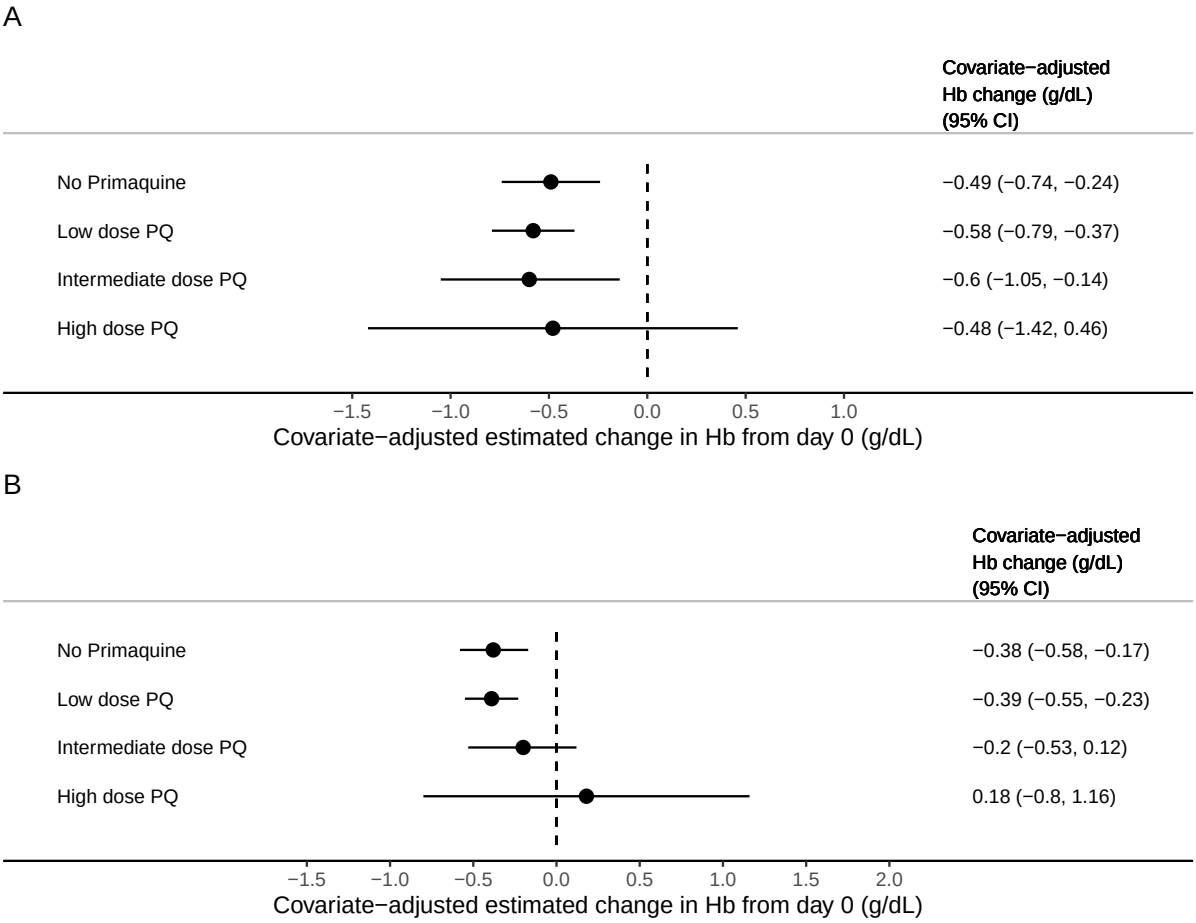


Figure 1_saf: The covariate-adjusted estimated change in Hb between primaquine daily dose groups on (A) days 2-3 and (B) days 5-7, in patients with ≥ 30% G6PD activity.

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 417 patients across 12 study sites, from 5 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				Total **(N=417)**
	No primaquine (N=0)	Low dose daily primaquine (<0.375 mg/kg/day) (N=244)	Intermediate dose daily primaquine (>=0.375 & <0.75 mg/kg/day) (N=169)	High dose daily primaquine (>= 0.75 mg/kg/day) (N=4)	
Age (years)	**NA**				
Mean (SD)	NA	34 (16)	30 (15)	12 (2.0)	32 (16)
Age Category	**NA**				
<5	NA	5 (2%)	0 (0%)	0 (0%)	5 (1%)
5-<15	NA	23 (9%)	32 (19%)	3 (75%)	58 (14%)
>=15	NA	216 (89%)	137 (81%)	1 (25%)	354 (85%)
Gender	**NA**				
Male	NA	150 (61%)	111 (66%)	2 (50%)	263 (63%)
Female	NA	94 (39%)	58 (34%)	2 (50%)	154 (37%)
Weight (kg)	**NA**				
Mean (SD)	NA	62 (16)	60 (15)	38 (1.5)	61 (16)
Malnutrition	**NA**				
No	NA	7 (3%)	0 (0%)	0 (0%)	7 (2%)
Yes	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	NA	237 (97.1%)	169 (100%)	4 (100%)	410 (98.3%)
Fever day 0	**NA**				
No	NA	7 (3%)	5 (3%)	0 (0%)	12 (3%)
Yes	NA	237 (97%)	164 (97%)	4 (100%)	405 (97%)
P. vivax baseline parasitaemia	**NA**				
Median (IQR)	NA	3598 [1225, 7004])	2800 [1472, 4440])	3565 [2560, 6552])	3190 [1320, 6060])
Haemoglobin day 0 (g/dL)	**NA**				
Mean (SD)	NA	13 (1.5)	13 (1.7)	12 (0.33)	13 (1.6)
Missing	NA	163 (66.8%)	12 (7.1%)	0 (0%)	175 (42.0%)
PQ daily dose (mg/kg)	**NA**				
Mean (SD)		3.5 (0.70)	3.4 (0.55)	3.4 (1.3)	3.5 (0.65)
Duration of PQ treatment	**NA**				
7 days		20 (8%)	156 (92%)	4 (100%)	180 (43%)
14 days		224 (92%)	13 (8%)	0 (0%)	237 (57%)
Method to calculate PQ dose	**NA**				
Per actual dose		164 (67%)	99 (59%)	4 (100%)	267 (64%)

(continued)

	No primaquine (N=0)	Low dose daily primaquine (<0.375 mg/kg/day) (N=244)	Intermediate dose daily primaquine (>=0.375 & <0.75 mg/kg/day) (N=169)	High dose daily primaquine (>= 0.75 mg/kg/day) (N=4)	Total **(N=417)**
Per dosing protocol		80 (33%)	70 (41%)	0 (0%)	150 (36%)
Start day of PQ treatment	**NA**				
Day 0		183 (75%)	168 (99%)	4 (100%)	355 (85%)
Day 1		61 (25%)	1 (1%)	0 (0%)	62 (15%)
Day 2		0 (0%)	0 (0%)	0 (0%)	0 (0%)
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	**NA**				
Partially supervised		79 (32%)	69 (41%)	0 (0%)	148 (35%)
Fully supervised		165 (68%)	100 (59%)	4 (100%)	269 (65%)
Was PQ taken with food?	**NA**				
No		2 (1%)	88 (52%)	4 (100%)	94 (23%)
Yes		61 (25%)	1 (1%)	0 (0%)	62 (15%)
Recommended		181 (74%)	80 (47%)	0 (0%)	261 (63%)
Other treatment given	**NA**				
AL	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AsAq	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cq	NA	244 (100%)	169 (100%)	4 (100%)	417 (100%)
DP	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Transmission intensity of the site	**NA**				
Low	NA	83 (34%)	5 (3%)	0 (0%)	88 (21%)
Moderate	NA	86 (35%)	7 (4%)	0 (0%)	93 (22%)
High	NA	75 (31%)	157 (93%)	4 (100%)	236 (57%)
Not available	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Geographical region	**NA**				
Africa	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Americas	NA	244 (100%)	169 (100%)	4 (100%)	417 (100%)
Asia-Pacific	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Relapse Peridocity	**NA**				
Low periodicity	NA	244 (100%)	169 (100%)	4 (100%)	417 (100%)
High periodicity	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
G6PD categories (Qualitative test)	**NA**				
<30%	NA	0 (0%)	2 (1%)	0 (0%)	2 (0%)
>=30%	NA	63 (26%)	87 (51%)	4 (100%)	154 (37%)
Missing	NA	181 (74.2%)	80 (47.3%)	0 (0%)	261 (62.6%)
G6PD categories (Quantitative test)	**NA**				
<30%	NA	0 (0%)	2 (1%)	0 (0%)	2 (0%)
30-<70%	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
>=70%	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	NA	244 (100%)	167 (98.8%)	4 (100%)	415 (99.5%)

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=0)	**(N=244)**	**(N=169)**	**(N=4)**	**(N=417)**
Composite on day 0					
No	NA	61 (25.0 %)	51 (30.2 %)	3 (75.0 %)	115 (27.6 %)
Yes	NA	183 (75.0 %)	118 (69.8 %)	1 (25.0 %)	302 (72.4 %)
Composite between days 1-2					
No	NA	128 (72.7 %)	84 (51.2 %)	2 (50.0 %)	214 (62.2 %)
Yes	NA	48 (27.3 %)	80 (48.8 %)	2 (50.0 %)	130 (37.8 %)
Missing	NA	68 (27.9%)	5 (3.0%)	0 (0%)	73 (17.5%)
Composite between days 5-7					
No	NA	161 (99.4 %)	151 (97.4 %)	4 (100.0 %)	316 (98.4 %)
Yes	NA	1 (0.6 %)	4 (2.6 %)	0 (0.0 %)	5 (1.6 %)
Missing	NA	82 (33.6%)	14 (8.3%)	0 (0%)	96 (23.0%)
Vomiting between days 5-7					
No	NA	160 (100.0 %)	70 (97.2 %)	0 (NaN %)	230 (99.1 %)
Yes	NA	0 (0.0 %)	2 (2.8 %)	0 (NaN %)	2 (0.9 %)
Missing	NA	84 (34.4%)	97 (57.4%)	4 (100%)	185 (44.4%)
Anorexia between days 5-7					
No	NA	77 (100.0 %)	89 (98.9 %)	4 (100.0 %)	170 (99.4 %)
Yes	NA	0 (0.0 %)	1 (1.1 %)	0 (0.0 %)	1 (0.6 %)
Missing	NA	167 (68.4%)	79 (46.7%)	0 (0%)	246 (59.0%)
Diarrhoea between days 5-7					
No	NA	93 (98.9 %)	148 (98.7 %)	4 (100.0 %)	245 (98.8 %)
Yes	NA	1 (1.1 %)	2 (1.3 %)	0 (0.0 %)	3 (1.2 %)
Missing	NA	150 (61.5%)	19 (11.2%)	0 (0%)	169 (40.5%)
Outcomes restricted to participants >5 years old					
	(N=0)	**(N=237)**	**(N=169)**	**(N=4)**	**(N=410)**
Nausea between days 5-7*					
No	NA	90 (100.0 %)	65 (97.0 %)	0 (NaN %)	155 (98.7 %)
Yes	NA	0 (0.0 %)	2 (3.0 %)	0 (NaN %)	2 (1.3 %)
Missing	NA	147 (62.0%)	102 (60.4%)	4 (100%)	253 (61.7%)
Abdominal pain between days 5-7*					
No	NA	89 (96.7 %)	145 (97.3 %)	4 (100.0 %)	238 (97.1 %)
Yes	NA	3 (3.3 %)	4 (2.7 %)	0 (0.0 %)	7 (2.9 %)
Missing	NA	145 (61.2%)	20 (11.8%)	0 (0%)	165 (40.2%)
Dizziness between days 5-7*					
No	NA	2 (100.0 %)	82 (94.3 %)	4 (100.0 %)	88 (94.6 %)
Yes	NA	0 (0.0 %)	5 (5.7 %)	0 (0.0 %)	5 (5.4 %)
Missing	NA	235 (99.2%)	82 (48.5%)	0 (0%)	317 (77.3%)

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

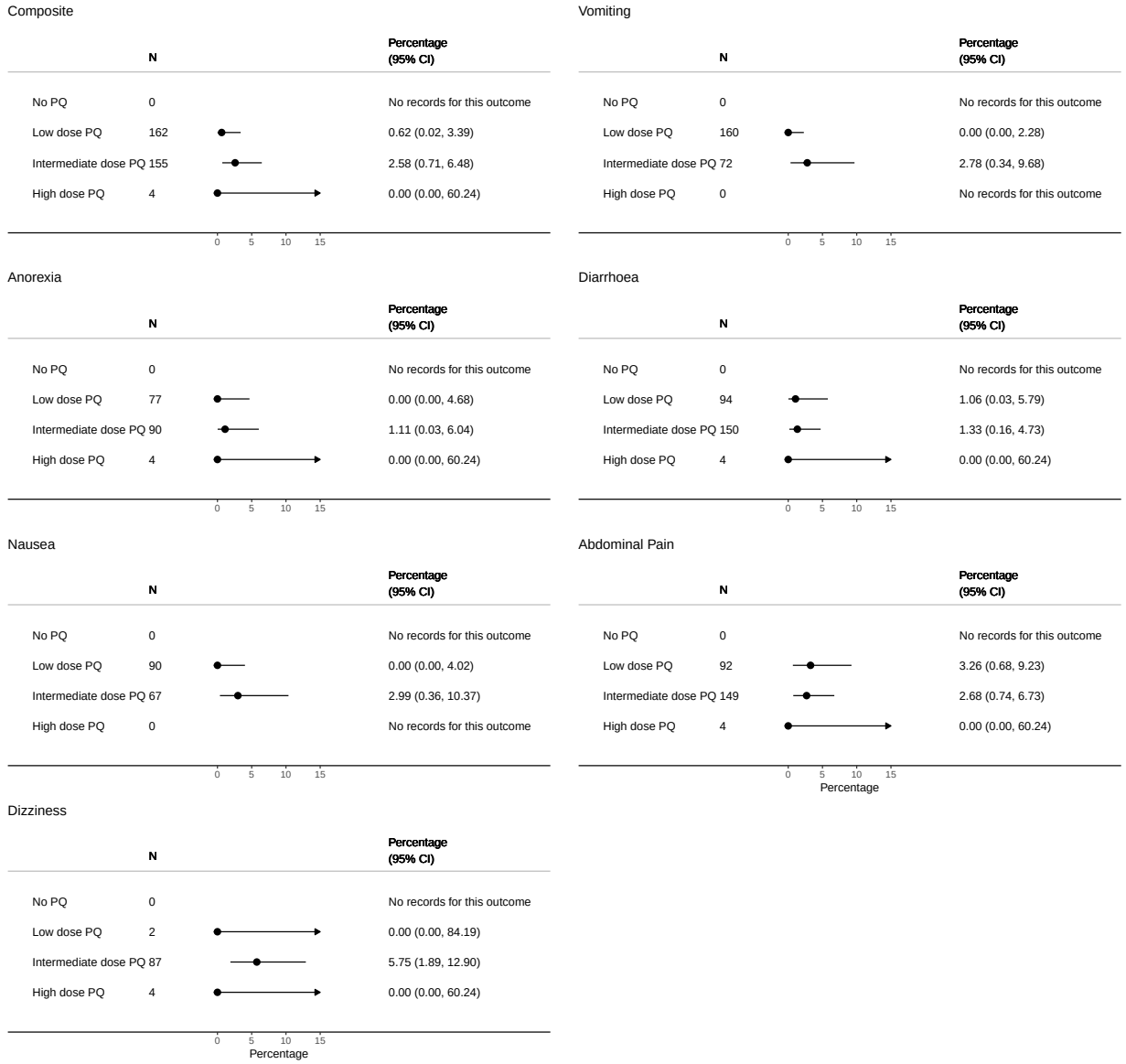


Figure 2_tol: Risk of gastrointestinal intolerance by symptoms. For each outcome the risk was estimated as the number of individuals experiencing the symptom as a proportion of the number of individuals asked about the symptom on any day between days 5-7. The confidence intervals (CIs) are exact binomial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

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

Covariate-adjusted estimated proportion of patients with gastrointestinal symptoms on days 5–7 cannot be presented as there were no records for any gastrointestinal intolerances (experienced or not experienced) for the refrence group (no primaquine)

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)	1/61 (1.6%)	0/0 (NaN%)
Intermediate dose daily primaquine (>=0.375 & <0.75 mg/kg/day)	0/1 (0.0%)	0/0 (NaN%)
High dose daily primaquine (>=0.75 mg/kg/day)	0/0 (NaN%)	0/0 (NaN%)

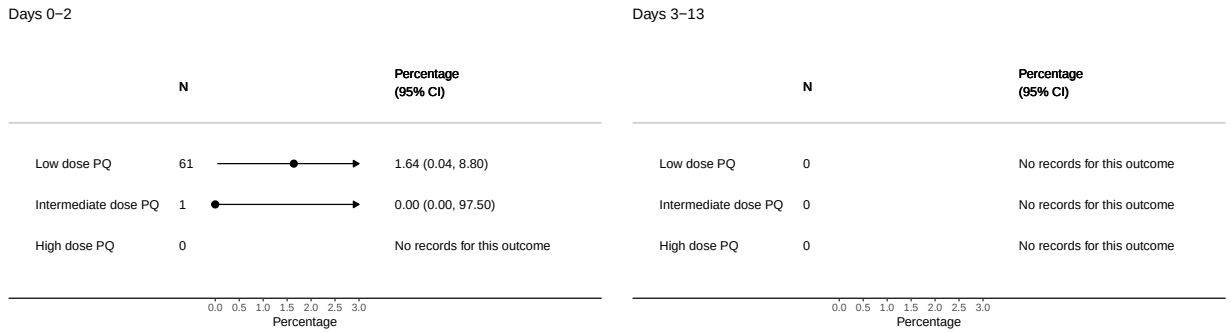


Figure 3_tol: Risk of acute vomiting on days 0-2 and 3-13 by primaquine daily dose categories. The confidence intervals (CIs) are exact binomial CIs.