

# Standard report for Vivax Malaria

WWARN Vivax Primaquine Study Group

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

08 May, 2025

## Introduction

This report has been produced for countries: Vietnam, Philippines, Cambodia, Malaysia, Myanmar

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 supervision	Patients available
Llanos-Cuentas-2019	Vietnam	2015 - 2017	19 - 58	180	Cq_Pq_3.5_14d_D1	<50% supervised	15
Taylor-2019	Vietnam	2014 - 2017	4 - 94.3	365	Cq_Pq_7.0_14d_D0, Cq, Cq_Pq_7.0_7d_D0	Fully supervised	324
Lacerda-2019	Philippines, Cambodia	2014 - 2016	15 - 55	180	Cq_Pq_3.5_14d_D1, Cq	<50% supervised	22
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
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
Thanh-2015	Vietnam	2009 - 2010	3 - 60	28	Cq_Pq_5.0_10d_D0	Fully supervised	260

\* 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 1013 patients across 9 study sites, from 6 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				Total (N=1013)
	No primaquine (N=103)	Very low dose total primaquine (<2 mg/kg)(N=6)	Low dose total primaquine (2 - <5 mg/kg)(N=618)	High dose total primaquine (≥ 5 mg/kg)(N=286)	
<b>Age (years)</b>					
Mean (SD)	24 (12)	21 (8.5)	15 (13)	26 (12)	19 (14)
<b>Age Category</b>					
<5	3 (3%)	0 (0%)	64 (10%)	4 (1%)	71 (7%)
5-<15	13 (13%)	1 (17%)	373 (60%)	43 (15%)	430 (42%)
≥15	87 (84%)	5 (83%)	181 (29%)	239 (84%)	512 (51%)
<b>Gender</b>					
Male	89 (86%)	3 (50%)	336 (54%)	238 (83%)	666 (66%)
Female	14 (14%)	3 (50%)	282 (46%)	48 (17%)	347 (34%)
<b>Weight (kg)</b>					
Mean (SD)	50 (15)	50 (20)	58 (9.1)	51 (13)	51 (14)
Missing	4 (3.9%)	0 (0%)	588 (95.1%)	2 (0.7%)	594 (58.6%)
<b>Malnutrition</b>					
No	4 (4%)	0 (0%)	0 (0%)	3 (1%)	7 (1%)
Yes	1 (1%)	0 (0%)	0 (0%)	1 (0%)	2 (0%)
Missing	98 (95.1%)	6 (100%)	618 (100%)	282 (98.6%)	1004 (99.1%)
<b>Fever day 0</b>					
No	6 (6%)	0 (0%)	63 (10%)	14 (5%)	83 (8%)
Yes	97 (94%)	6 (100%)	349 (56%)	272 (95%)	724 (71%)
Missing	0 (0%)	0 (0%)	206 (33.3%)	0 (0%)	206 (20.3%)
<b>P. vivax baseline parasitaemia</b>					
Median (IQR)	10000 [3206, 20000]	3467 [1227, 4796]	1920 [700, 5554]	8492 [2530, 17500]	3380 [1000, 10000]
<b>Haemoglobin day 0 (g/dL)</b>					
Mean (SD)	13 (2.1)	11 (1.2)	13 (1.5)	13 (1.7)	13 (1.8)
<b>PQ daily dose (mg/kg)</b>					
Mean (SD)		0.79 (0.32)	3.0 (0.19)	7.5 (0.95)	4.4 (2.2)
Missing		0 (0%)	0 (0%)	0 (0%)	0(0%)
7 days		0 (0%)	589 (95%)	126 (44%)	715 (79%)
14 days		2 (33%)	27 (4%)	131 (46%)	160 (18%)
Missing		4 (66.7%)	2 (0.3%)	29 (10.1%)	35 (3.8%)
Per actual dose		6 (100%)	5 (1%)	283 (99%)	294 (32%)
Per dosing protocol		0 (0%)	613 (99%)	3 (1%)	616 (68%)
Missing		0 (0%)	0 (0%)	0 (0%)	0(0%)
<b>Start day of PQ treatment</b>					
Day 0		4 (67%)	591 (96%)	269 (94%)	864 (95%)
Day 1		1 (17%)	26 (4%)	9 (3%)	36 (4%)
Day 2		1 (17%)	1 (0%)	4 (1%)	6 (1%)
Day 3		0 (0%)	0 (0%)	1 (0%)	1 (0%)

(continued)

	No primaquine (N=103)	Very low dose total primaquine (<2 mg/kg)(N=6)	Low dose total primaquine (2 - <5 mg/kg)(N=618)	High dose total primaquine (≥ 5 mg/kg)(N=286)	Total (N=1013)
Day 5		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Day 6		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing		0 (0%)	0 (0%)	0 (0%)	0(0%)
<b>Level of PQ supervision</b>					
Partially supervised		0 (0%)	613 (99%)	1 (0%)	614 (67%)
Fully supervised		2 (33%)	3 (0%)	255 (89%)	260 (29%)
Missing		0 (0%)	0 (0%)	0 (0%)	0(0%)
<b>Was PQ taken with food?</b>					
No		4 (67%)	0 (0%)	12 (4%)	16 (2%)
Yes		0 (0%)	25 (4%)	1 (0%)	26 (3%)
Recommended		2 (33%)	593 (96%)	273 (95%)	868 (95%)
<b>Other treatment given</b>					
AL	20 (19%)	0 (0%)	0 (0%)	14 (5%)	34 (3%)
AsAq	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AsMf	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (0%)
Cq	83 (81%)	5 (83%)	618 (100%)	272 (95%)	978 (97%)
DP	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Transmission intensity of the site</b>					
Low	92 (89%)	6 (100%)	20 (3%)	285 (100%)	403 (40%)
Moderate	11 (11%)	0 (0%)	598 (97%)	1 (0%)	610 (60%)
High	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not available	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Geographical region</b>					
Africa	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Americas	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asia-Pacific	103 (100%)	6 (100%)	618 (100%)	286 (100%)	1013 (100%)
<b>Relapse Periodicity</b>					
Low periodicity	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
High periodicity	103 (100%)	6 (100%)	618 (100%)	286 (100%)	1013 (100%)
<b>G6PD categories (Qualitative test)</b>					
<30%	4 (4%)	0 (0%)	0 (0%)	1 (0%)	5 (0%)
≥30%	97 (94%)	6 (100%)	30 (5%)	284 (99%)	417 (41%)
Missing	2 (1.9%)	0 (0%)	588 (95.1%)	1 (0.3%)	591 (58.3%)
<b>G6PD categories (Quantitative test)</b>					
<30%	4 (4%)	0 (0%)	0 (0%)	1 (0%)	5 (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	99 (96.1%)	6 (100%)	618 (100%)	285 (99.7%)	1008 (99.5%)

### 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 (≥ 5 mg/kg). Very low total dose primaquine (<2 mg/kg) was not presented due to low numbers of patients treated with this dose.

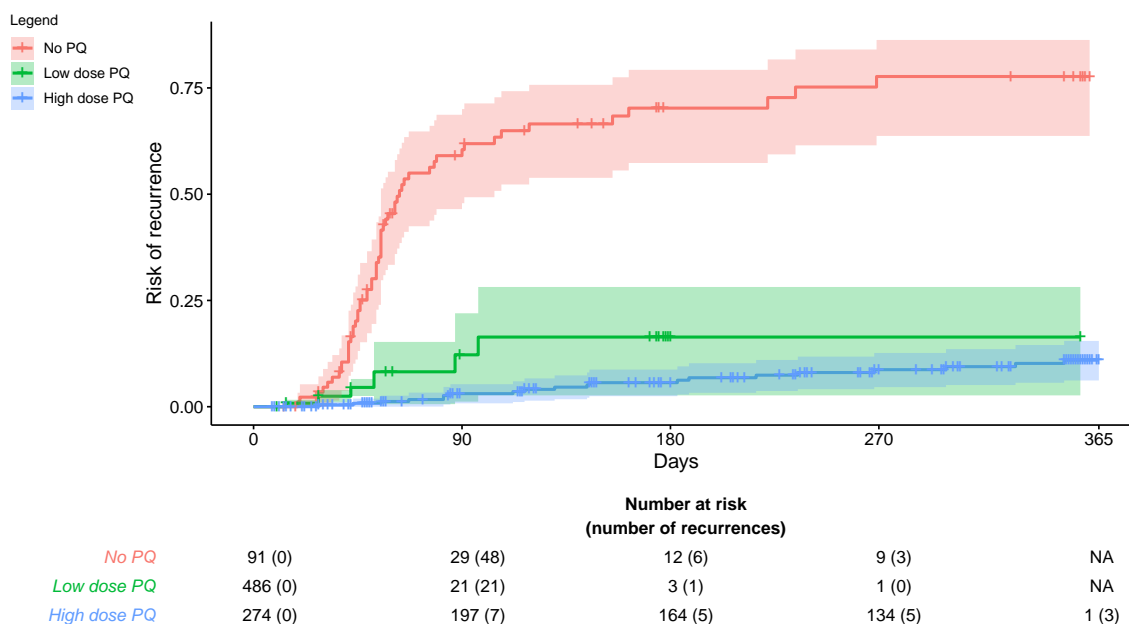


Figure 0\_eff: Kaplan-Meier figure of cumulative risk of recurrence between day 7 and day 365 for primaquine treatment category. Please interpret the results of this figure with caution as there may not always be paired treatment comparisons in the original studies contributing to these pooled results.

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.

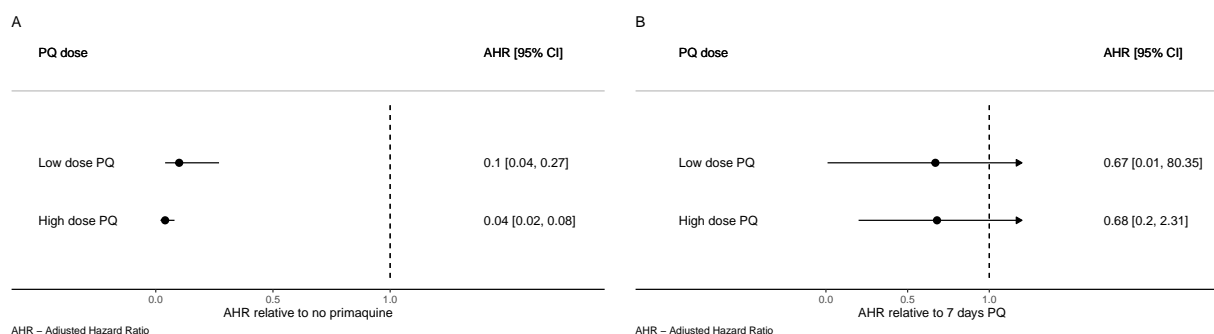


Figure 1\_eff: Hazard ratio between day 7 and day 180 for A: total dose of primaquine and B: 14-day vs 7-day primaquine duration, stratified by total dose of primaquine

## 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 388 patients across 8 study sites, from 5 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				Total (N=388)
	No primaquine (N=103)	Low dose daily primaquine (<0.375 mg/kg/day) (N=28)	Intermediate dose daily primaquine (≥ 0.375 & <0.75 mg/kg/day) (N=132)	High dose daily primaquine (≥ 0.75 mg/kg/day) (N=125)	
<b>Age (years)</b>					
Mean (SD)	24 (12)	31 (12)	26 (11)	25 (12)	26 (12)
<b>Age Category</b>					
<5	3 (2.91%)	0 (0.00%)	0 (0.00%)	1 (0.80%)	4 (1.03%)
5-<15	13 (12.62%)	0 (0.00%)	15 (11.36%)	22 (17.60%)	50 (12.89%)
≥15	87 (84.47%)	28 (100.00%)	117 (88.64%)	102 (81.60%)	334 (86.08%)
<b>Gender</b>					
Male	90 (87.38%)	23 (82.14%)	116 (87.88%)	101 (80.80%)	330 (85.05%)
Female	13 (12.62%)	5 (17.86%)	16 (12.12%)	24 (19.20%)	58 (14.95%)
<b>Weight (kg)</b>					
Mean (SD)	51 (15)	60 (11)	51 (12)	52 (12)	52 (13)
Missing	3 (2.9%)	0 (0%)	0 (0%)	0 (0%)	3 (0.8%)
<b>Malnutrition</b>					
No	4 (3.88%)	0 (0.00%)	0 (0.00%)	1 (0.80%)	5 (1.29%)
Yes	1 (0.97%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.26%)
Missing	98 (95.1%)	28 (100%)	132 (100%)	124 (99.2%)	382 (98.5%)
<b>Fever day 0</b>					
No	6 (5.83%)	3 (10.71%)	7 (5.30%)	7 (5.60%)	23 (5.93%)
Yes	97 (94.17%)	25 (89.29%)	125 (94.70%)	118 (94.40%)	365 (94.07%)
<b>P. vivax baseline parasitaemia</b>					
Median (IQR)	10000 [3130, 20000]	7508 [2686, 15285]	7500 [2590, 17500]	10000 [3802, 20000]	9591 [3130, 17500]
<b>Haemoglobin day 0 (g/dL)</b>					
Mean (SD)	13 (2.1)	14 (1.6)	13 (1.4)	13 (1.6)	13 (1.7)
<b>PQ daily dose (mg/kg)</b>					
Missing		0 (0%)	0 (0%)	0 (0%)	0(0%)
<b>Duration of PQ treatment</b>					
Mean (SD)		14 (0)	14 (0.61)	7.0 (0)	11 (3.5)
<b>Method to calculate PQ dose</b>					

(continued)

	No primaquine (N=103)	Low dose daily primaquine ( $<0.375$ mg/kg/day) (N=28)	Intermediate dose daily primaquine ( $\geq 0.375$ & $<0.75$ mg/kg/day) (N=132)	High dose daily primaquine ( $\geq 0.75$ mg/kg/day) (N=125)	Total (N=388)
Per actual dose		3 (10.71%)	131 (99.24%)	125 (100.00%)	259 (90.88%)
Per dosing protocol		25 (89.29%)	1 (0.76%)	0 (0.00%)	26 (9.12%)
<b>Start day of PQ treatment</b>					
Day 0		3 (10.71%)	131 (99.24%)	125 (100.00%)	259 (90.88%)
Day 1		25 (89.29%)	1 (0.76%)	0 (0.00%)	26 (9.12%)
Day 2		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
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%)
<b>Level of PQ supervision</b>					
Unsupervised		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Partially supervised		25 (89.29%)	1 (0.76%)	0 (0.00%)	26 (9.12%)
Fully supervised		3 (10.71%)	131 (99.24%)	125 (100.00%)	259 (90.88%)
No		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Yes		25 (89.29%)	1 (0.76%)	0 (0.00%)	26 (9.12%)
Recommended		3 (10.71%)	131 (99.24%)	125 (100.00%)	259 (90.88%)
<b>Other treatment given</b>					
AL	20 (19.42%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	20 (5.15%)
AsAq	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cq	83 (80.58%)	28 (100.00%)	132 (100.00%)	125 (100.00%)	368 (94.85%)
DP	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
<b>Transmission intensity of the site</b>					
Low	92 (89.32%)	18 (64.29%)	131 (99.24%)	125 (100.00%)	366 (94.33%)
Moderate	11 (10.68%)	10 (35.71%)	1 (0.76%)	0 (0.00%)	22 (5.67%)
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%)
<b>Geographical region</b>					
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	103 (100.00%)	28 (100.00%)	132 (100.00%)	125 (100.00%)	388 (100.00%)
<b>Relapse Periodicity</b>					
Low periodicity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
High periodicity	103 (100.00%)	28 (100.00%)	132 (100.00%)	125 (100.00%)	388 (100.00%)
<b>G6PD categories (Qualitative test)</b>					
$<30\%$	4 (3.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (1.03%)
$\geq 30\%$	98 (95.15%)	27 (96.43%)	131 (99.24%)	125 (100.00%)	381 (98.20%)
Unknown	1 (0.97%)	1 (3.57%)	1 (0.76%)	0 (0.00%)	3 (0.77%)
<b>G6PD categories (Quantitative test)</b>					
$<30\%$	4 (3.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (1.03%)
$30-<70\%$	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
$\geq 70\%$	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Unknown	99 (96.12%)	28 (100.00%)	132 (100.00%)	125 (100.00%)	384 (98.97%)

## 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**

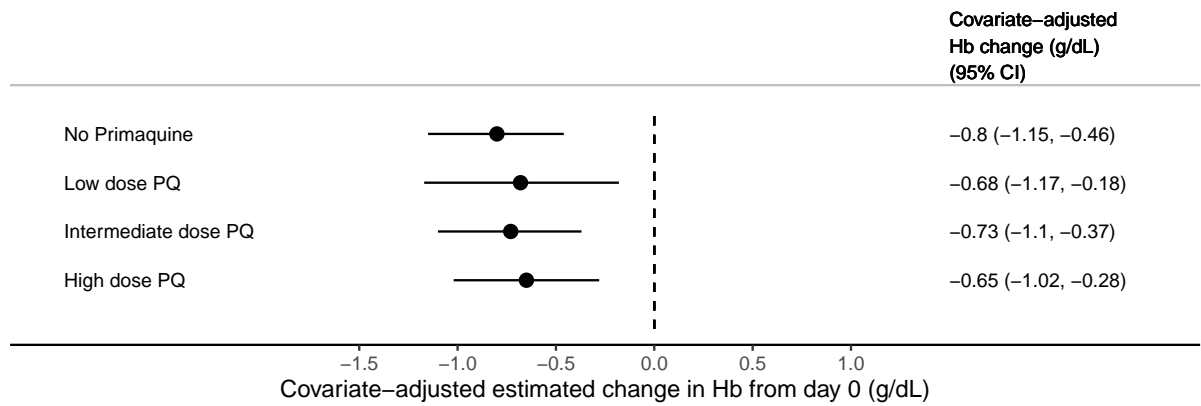
	Primaquine Treatment				Total
	No primaquine	Low dose daily primaquine (<0.375 mg/kg/day)	Intermediate dose daily primaquine (0.375 & <0.75 mg/kg/day)	High dose daily primaquine (0.75 mg/kg/day)	
<b>Drop in haemoglobin of &gt;25% AND Hb below 7 g/dL</b>					
No	95 (96.9 %)	28 (100.0 %)	130 (98.5 %)	125 (100.0 %)	378 (98.7 %)
Yes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	3 (3.1%)	0 (0%)	2 (1.5%)	0 (0%)	5 (1.3%)
<b>Drop in haemoglobin of &gt;5 g/dL from baseline between days 1-14</b>					
No	95 (96.9 %)	28 (100.0 %)	130 (98.5 %)	125 (100.0 %)	378 (98.7 %)
Yes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	3 (3.1%)	0 (0%)	2 (1.5%)	0 (0%)	5 (1.3%)
<b>Drop in haemoglobin to &lt;5 g/dL between days 1 and 14</b>					
No	95 (96.9 %)	28 (100.0 %)	130 (98.5 %)	125 (100.0 %)	378 (98.7 %)
Yes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Missing	3 (3.1%)	0 (0%)	2 (1.5%)	0 (0%)	5 (1.3%)
<b>Anaemia developed at days 2 or 3</b>					
Nil (Hb: >=11 g/dL)	72 (73.5 %)	25 (89.3 %)	113 (85.6 %)	105 (84.0 %)	315 (82.2 %)
Mild (Hb: >=8 g/dL & <11 g/dL)	5 (5.1 %)	2 (7.1 %)	8 (6.1 %)	2 (1.6 %)	17 (4.4 %)
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	21 (21.4%)	1 (3.6%)	11 (8.3%)	18 (14.4%)	51 (13.3%)
<b>Anaemia developed at days 5-7</b>					
Nil (Hb: >=11 g/dL)	67 (68.4 %)	23 (82.1 %)	110 (83.3 %)	97 (77.6 %)	297 (77.5 %)
Mild (Hb: >=8 g/dL & <11 g/dL)	0 (0.0 %)	2 (7.1 %)	1 (0.8 %)	2 (1.6 %)	5 (1.3 %)
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	31 (31.6%)	3 (10.7%)	21 (15.9%)	26 (20.8%)	81 (21.1%)
<b>Change in haemoglobin on days 2-3 from day 0</b>					
Mean (SD)	-0.560 (0.898)	-0.564 (0.795)	-0.486 (1.04)	-0.399 (0.994)	-0.482 (0.974)
Missing	10 (10.2%)	0 (0%)	6 (4.5%)	9 (7.2%)	25 (6.5%)
<b>Change in haemoglobin on days 5-7 from day 0</b>					
Mean (SD)	-0.0282 (1.20)	0.123 (0.811)	-0.0155 (1.08)	0.196 (1.22)	0.0638 (1.14)
Missing	27 (27.6%)	2 (7.1%)	16 (12.1%)	18 (14.4%)	63 (16.4%)
<b>Relative percentage (%) change in haemoglobin on days 2-3 from day 0</b>					
Mean (SD)	4.06 (6.72)	3.89 (5.79)	3.35 (7.77)	2.72 (7.43)	3.36 (7.26)
Missing	10 (10.2%)	0 (0%)	6 (4.5%)	9 (7.2%)	25 (6.5%)
<b>Relative percentage (%) change in haemoglobin on days 5-7 from day 0</b>					
Mean (SD)	-0.0743 (9.21)	-1.09 (5.81)	-0.264 (8.25)	-1.83 (9.22)	-0.813 (8.64)
Missing	27 (27.6%)	2 (7.1%)	16 (12.1%)	18 (14.4%)	63 (16.4%)

## 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.*

A



B

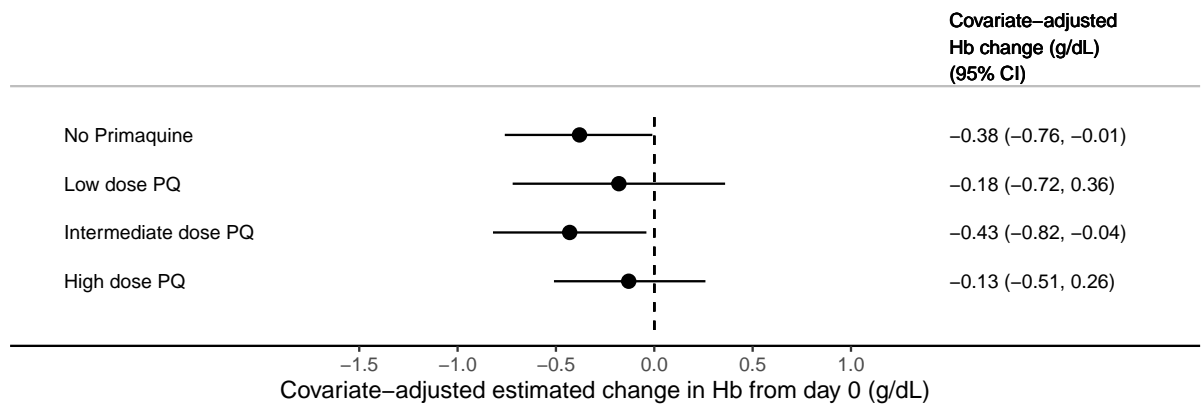


Figure 1\_saf: The covariate-adjusted estimated change in Hb between primaquine daily dose groups on (A) days 2-3 and (B) days 5-7, in patients with  $\geq 30\%$  G6PD activity.



### 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 599 patients across 5 study sites, from 3 studies.

#### Characteristics of Study Population

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

	Primaquine Treatment				Total (N=599)
	No primaquine (N=64)	Low dose daily primaquine ( $<0.375$ mg/kg/day) (N=18)	Intermediate dose daily primaquine ( $\geq 0.375$ & $<0.75$ mg/kg/day) (N=132)	High dose daily primaquine ( $\geq 0.75$ mg/kg/day) (N=385)	
<b>Age (years)</b>					
Mean (SD)	25 (11)	34 (11)	26 (11)	18 (13)	21 (13)
<b>Age Category</b>					
$<5$	0 (0%)	0 (0%)	1 (1%)	43 (11%)	44 (7%)
5- $<15$	6 (9%)	0 (0%)	15 (11%)	140 (36%)	161 (27%)
$\geq 15$	58 (91%)	18 (100%)	116 (88%)	202 (52%)	394 (66%)
<b>Gender</b>					
Male	58 (91%)	14 (78%)	117 (89%)	260 (68%)	449 (75%)
Female	6 (9%)	4 (22%)	15 (11%)	125 (32%)	150 (25%)
<b>Weight (kg)</b>					
Mean (SD)	53 (13)	63 (12)	51 (12)	37 (18)	43 (18)
<b>Malnutrition</b>					
No	1 (2%)	0 (0%)	0 (0%)	30 (8%)	31 (5%)
Yes	0 (0%)	0 (0%)	1 (1%)	27 (7%)	28 (5%)
Missing	63 (98.4%)	18 (100%)	131 (99.2%)	328 (85.2%)	540 (90.2%)
<b>Fever day 0</b>					
No	3 (5%)	2 (11%)	6 (5%)	7 (2%)	18 (3%)
Yes	61 (95%)	16 (89%)	126 (95%)	378 (98%)	581 (97%)
<b>P. vivax baseline parasitaemia</b>					
Median (IQR)	12500 [5000, 25000]	11250 [3338, 16143]	7500 [2849, 17500]	4840 [1840, 12500]	6520 [2260, 15000]
<b>Haemoglobin day 0 (g/dL)</b>					
Mean (SD)	14 (1.5)	14 (1.9)	13 (1.5)	12 (2.2)	13 (2.1)
<b>PQ daily dose (mg/kg)</b>					
Mean (SD)		3.8 (0.67)	7.4 (1.4)	5.6 (1.5)	6.0 (1.7)
<b>Duration of PQ treatment</b>					
7 days		0 (0%)	2 (2%)	385 (100%)	387 (72%)
14 days		18 (100%)	130 (98%)	0 (0%)	148 (28%)
<b>Method to calculate PQ dose</b>					
Per actual dose		3 (17%)	132 (100%)	385 (100%)	520 (97%)
Per dosing protocol		15 (83%)	0 (0%)	0 (0%)	15 (3%)

(continued)

	No primaquine (N=64)	Low dose daily primaquine ( $<0.375$ mg/kg/day) (N=18)	Intermediate dose daily primaquine ( $\geq 0.375$ & $<0.75$ mg/kg/day) (N=132)	High dose daily primaquine ( $\geq 0.75$ mg/kg/day) (N=385)	Total (N=599)
<b>Start day of PQ treatment</b>					
Day 0		3 (17%)	132 (100%)	385 (100%)	520 (97%)
Day 1		15 (83%)	0 (0%)	0 (0%)	15 (3%)
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%)
<b>Level of PQ supervision</b>					
Unsupervised		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Partially supervised		15 (83%)	0 (0%)	0 (0%)	15 (3%)
Fully supervised		3 (17%)	132 (100%)	385 (100%)	520 (97%)
<b>Was PQ taken with food?</b>					
No		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Yes		15 (83%)	1 (1%)	259 (67%)	275 (51%)
Recommended		3 (17%)	131 (99%)	126 (33%)	260 (49%)
<b>Other treatment given</b>					
AL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AsAq	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cq	64 (100%)	18 (100%)	132 (100%)	385 (100%)	599 (100%)
DP	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Transmission intensity of the site</b>					
Low	64 (100%)	18 (100%)	132 (100%)	385 (100%)	599 (100%)
Moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
High	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not available	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Geographical region</b>					
Africa	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Americas	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asia-Pacific	64 (100%)	18 (100%)	132 (100%)	385 (100%)	599 (100%)
<b>Relapse Periodicity</b>					
Low periodicity	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
High periodicity	64 (100%)	18 (100%)	132 (100%)	385 (100%)	599 (100%)
<b>G6PD categories (Qualitative test)</b>					
$<30\%$	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
$\geq 30\%$	64 (100%)	18 (100%)	131 (99%)	126 (33%)	339 (57%)
Missing	0 (0%)	0 (0%)	1 (0.8%)	259 (67.3%)	260 (43.4%)
<b>G6PD categories (Quantitative test)</b>					
$<30\%$	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
$30- <70\%$	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
$\geq 70\%$	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	64 (100%)	18 (100%)	132 (100%)	385 (100%)	599 (100%)

### 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<sup>1</sup>

- 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

<sup>1</sup>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				Total
	No primaquine	Low dose daily primaquine ( <b>&lt;0.375</b> mg/kg/day)	Intermediate dose daily primaquine ( <b>0.375 &amp;</b> <b>&lt;0.75</b> mg/kg/day)	High dose daily primaquine ( <b></b> <b>0.75</b> mg/kg/day)	
Outcomes include participants of all ages					
	(N=64)	(N=18)	(N=132)	(N=385)	(N=599)
Composite on day 0					
No	60 (93.8 %)	9 (50.0 %)	126 (95.5 %)	336 (87.3 %)	531 (88.6 %)
Yes	4 (6.2 %)	9 (50.0 %)	6 (4.5 %)	49 (12.7 %)	68 (11.4 %)
Composite between days 1-2					
No	61 (95.3 %)	3 (100.0 %)	127 (97.7 %)	364 (95.5 %)	555 (96.0 %)
Yes	3 (4.7 %)	0 (0.0 %)	3 (2.3 %)	17 (4.5 %)	23 (4.0 %)
Missing	0 (0%)	15 (83.3%)	2 (1.5%)	4 (1.0%)	21 (3.5%)
Composite between days 5-7					
No	63 (100.0 %)	3 (100.0 %)	124 (98.4 %)	353 (96.2 %)	543 (97.1 %)
Yes	0 (0.0 %)	0 (0.0 %)	2 (1.6 %)	14 (3.8 %)	16 (2.9 %)
Missing	1 (1.6%)	15 (83.3%)	6 (4.5%)	18 (4.7%)	40 (6.7%)
Vomiting between days 5-7					
No	63 (100.0 %)	3 (100.0 %)	125 (99.2 %)	360 (98.1 %)	551 (98.6 %)
Yes	0 (0.0 %)	0 (0.0 %)	1 (0.8 %)	7 (1.9 %)	8 (1.4 %)
Missing	1 (1.6%)	15 (83.3%)	6 (4.5%)	18 (4.7%)	40 (6.7%)
Anorexia between days 5-7					
No	63 (100.0 %)	3 (100.0 %)	126 (100.0 %)	360 (98.1 %)	552 (98.7 %)
Yes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	7 (1.9 %)	7 (1.3 %)
Missing	1 (1.6%)	15 (83.3%)	6 (4.5%)	18 (4.7%)	40 (6.7%)
Diarrhoea between days 5-7					
No	63 (100.0 %)	3 (100.0 %)	125 (99.2 %)	358 (97.5 %)	549 (98.2 %)
Yes	0 (0.0 %)	0 (0.0 %)	1 (0.8 %)	9 (2.5 %)	10 (1.8 %)
Missing	1 (1.6%)	15 (83.3%)	6 (4.5%)	18 (4.7%)	40 (6.7%)
Outcomes restricted to participants >5 years old					
	(N=63)	(N=18)	(N=131)	(N=328)	(N=540)
Nausea between days 5-7*					
No	62 (100.0 %)	3 (100.0 %)	126 (100.0 %)	305 (97.8 %)	496 (98.6 %)
Yes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	7 (2.2 %)	7 (1.4 %)
Missing	1 (1.6%)	15 (83.3%)	5 (3.8%)	16 (4.9%)	37 (6.9%)
Abdominal pain between days 5-7*					
No	62 (100.0 %)	3 (100.0 %)	125 (99.2 %)	297 (95.2 %)	487 (96.8 %)
Yes	0 (0.0 %)	0 (0.0 %)	1 (0.8 %)	15 (4.8 %)	16 (3.2 %)
Missing	1 (1.6%)	15 (83.3%)	5 (3.8%)	16 (4.9%)	37 (6.9%)
Dizziness between days 5-7*					
No	62 (100.0 %)	3 (100.0 %)	126 (100.0 %)	311 (99.7 %)	502 (99.8 %)
Yes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (0.3 %)	1 (0.2 %)
Missing	1 (1.6%)	15 (83.3%)	5 (3.8%)	16 (4.9%)	37 (6.9%)

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

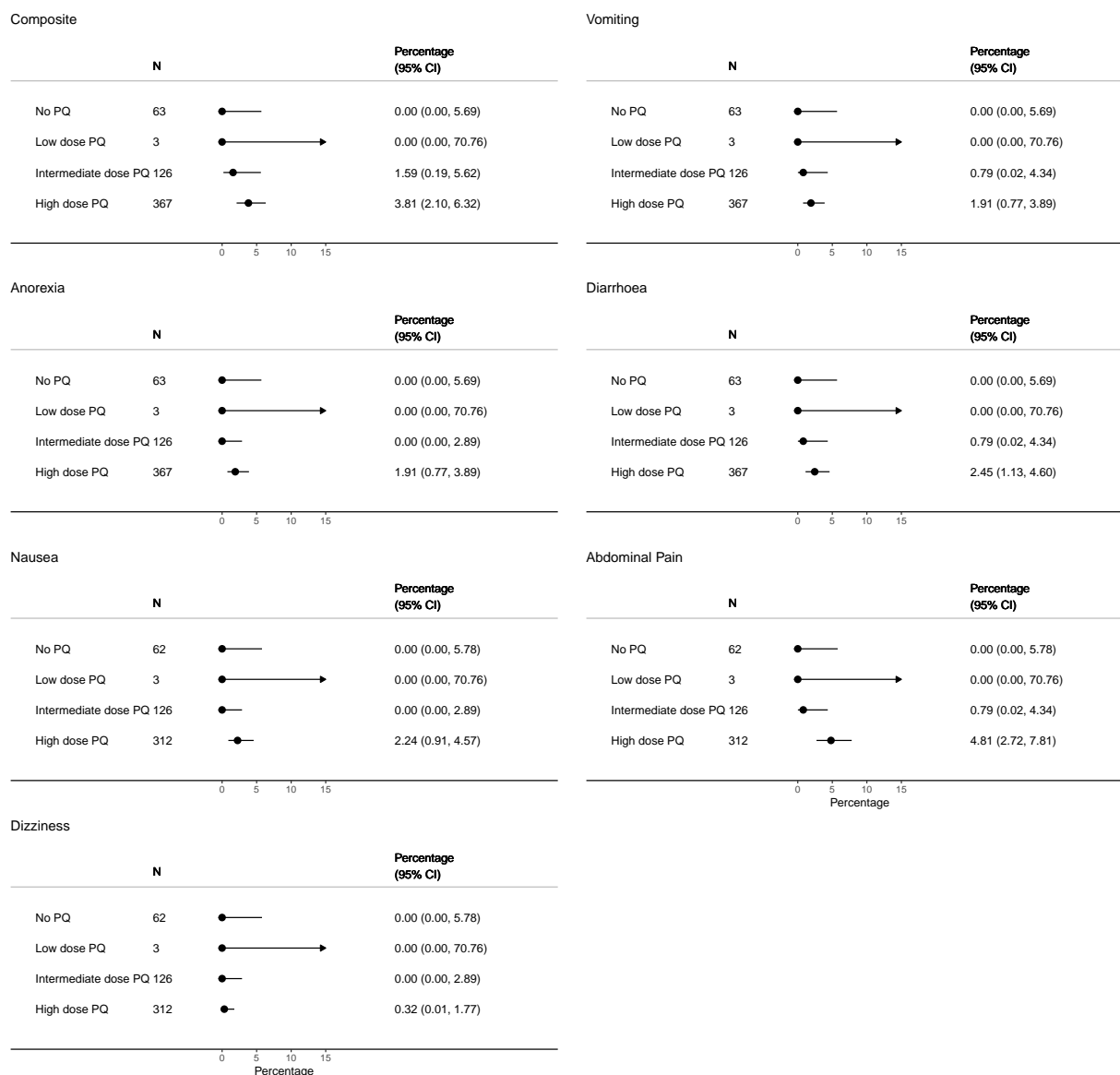


Figure 2\_tol: Risk of gastrointestinal intolerance by symptoms. For each outcome the risk was estimated as the number of individuals experiencing the symptom as a proportion of the number of individuals asked about the symptom on any day between days 5-7. The confidence intervals (CIs) are exact binomial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

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

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 reference 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**

Primaquine treatment		Risk of acute vomiting	
		Days 0-2	Days 3-13
Low dose daily primaquine (<0.375 mg/kg/day)		1/18 (5.6%)	0/3 (0.0%)
Intermediate dose daily primaquine ( $\geq 0.375$ & <0.75 mg/kg/day)		1/132 (0.8%)	1/129 (0.8%)
High dose daily primaquine ( $\geq 0.75$ mg/kg/day)		2/385 (0.5%)	1/375 (0.3%)

Days 0-2

	N	Percentage (95% CI)
Low dose PQ	18	5.56 (0.14, 27.29)
Intermediate dose PQ	132	0.76 (0.02, 4.15)
High dose PQ	385	0.52 (0.06, 1.86)

Days 3-13

	N	Percentage (95% CI)
Low dose PQ	3	0.00 (0.00, 70.76)
Intermediate dose PQ	129	0.78 (0.02, 4.24)
High dose PQ	375	0.27 (0.01, 1.48)

*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.*