Risk of bias assessment

Supplementary Table 13. Risk of bias assessment

Study ID	Study design[1]	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants, personnel (performance bias) Hb Day 7, AEs	Blinding of outcomes assessment (detection bias) Hb Day 7, AEs	Incomplete outcome data (attrition bias) Hb Day 7		Other bias AE elicitation method
				Primary outcome Hb D7	Primary outcome Hb D7	n	%	
1	MDA	Not applicable	Not applicable	Open label	Open label	295	78%	Open questions
2	RCT	Computer generated	Sealed, opaque envelopes	Open label	Open label, not clear if Hb staff blinded	692	89%	Open questions, direct for dark/'coke' urine
3	RCT	Computer generated	Sealed, opaque envelopes	Staff unblinded, participants blinded	Open label	220	97%	Checklist questions, incl. for dark urine
4	RCT	Envelope draw	Sealed, opaque envelopes	Open label	Not reported	231	71%	Checklist
5	RCT	Envelope draw	Sealed, opaque envelopes	Only pharmacist, unblinded	Blinded	357	97%	Open, some checklist items, incl. dark urine
6	RCT	Computer generated	Sealed, opaque envelopes	Open label	Open label	86	92%	Not reported
7	RCT	Computer generated	Sealed, opaque envelopes	Open label	Open label	50	92%	Checklist questions, Hillman for dark urine
8	RCT	Computer generated	Sealed, opaque envelopes	Only pharmacist, unblinded	Blinded	461	100%	Checklist questions, incl. dark urine
9	RCT	Envelope draw	Sealed, opaque envelopes	Open label	Open label	78	88%	Question dark urine
10	RCT	Computer generated	Sealed, opaque envelopes	Open label	Open label	61	69%	Not reported
11	RCT	Computer generated	Sealed, opaque envelopes	Open label	Hb lab staff blinded, clinical staff unblinded	267	89%	Not reported except Hillman for dark urine
12	Cohort	Not applicable	Not applicable	Open label	Open label	94	66%	Open questions, Hillmen for dark urine
13	RCT	Computer generated	Sealed, opaque envelopes	Open label	Hb lab staff blinded, clinical staff unblinded	103	98%	Checklist questions, incl. for dark urine
14	MDA	Not applicable	Not applicable	Open label	Open label	843	70%	Not reported
15	RCT	Computer generated	Sealed, opaque envelopes	Open label	Open label	373	98%	Checklist
16	RCT	Computer generated	Sealed, opaque envelopes	Open label	Open label	139	60%	Open and some checklist items
17	RCT	Computer generated	Sealed, opaque envelopes	Only pharmacist, unblinded	Blinded	114	100%	Not reported

18	Cohort	Not applicable	Not applicable	Open label	Open label			Checklist questions, incl. for dark urine
19	RCT	Computer generated	Sealed, opaque envelopes	Staff blinded, participants unblinded on request by non-investigator	Blinded	81	95%	Open and some checklist questions
20	MDA	Not applicable	Not applicable	Open label	Open label			Not reported

[1]MDA = mass drug administration, RCT = randomised controlled trial; D7 = Day 7

Supplementary Table 14. Individual participant data not available

Author, date	PubMed ID	Study Design	Location	Year	ACT	Follow up (days)	Age	G6PD exclusion	Target primaquine dose (mg/kg)	N	Summary of haemoglobin outcome	Summary of adverse events
Arroyo-Arroyo, 2	28749756	3 sequential dose groups ACT plus primaquine	Colombia	2010-2014	AL	7	All	Not tested	1) 0.75 day 3, 2) 0.50 day 1 and 0.25 day 3, 3) 0.25 days 1, 2 and 3	60	Not applicable	No volunteers had adverse events possibly associated with the antimalarial treatment. The signs and symptoms observed in all patients were indistinguishable from the common malaria symptoms
Lin,2017*	28591198	Randomised controlled trial, ACT with/without primaquine	Cambodia	2012-2014	DP	42	18-65	Severe	0.75 day 3	101	Among 8/101 with mild or moderate G6PD deficiency, a greater drop in haemoglobin at day 7 was seen with primaquine but not statistically significant: median fractional reduction in haemoglobin 24.8% (range 0.9% to 29.8%) in 6 given primaquine versus 7.1% (-4.4% and 18.7%) in 2 not given primaquine (p = 0.14). The largest drop was 9.9 g/dL from a baseline of 14.1; all Hgb values were >11.0 g/dL by day 14. In G6PD normal subjects, haemoglobin was only measured to day 3, at which time there was no change in the fractional drop between arms (9.8% versus 9.3% in the primaquine and non-primaquine groups, respectively, p = 0.79).	
Shah, 2013*	23587943	Meta-analysis of sites with / without primaquine	India	2009-2010	ASSP	28	> 1 year	Not tested	0.75 day 2	1372	Not applicable	Adverse events reported included vomiting (8) and fever (2) in the AS+SP-alone arm and vomiting (14) and jaundice (1) in the primaquine arm. Only 5/14 patients who experienced vomiting did so on the day of primaquine administration. The jaundice occurred in a 5-year-old on day 14 and self-resolved
Smithius 1010	20832366	Randomised controlled trial, ACT with/without primaquine	Myanmar	2008-2009	AM, ASAQ, DP, AL	63	> 1 year	Not tested	0.75 day	808**	No day 7 data	599 (74%) reported adverse events. 13 (1.6%) vomited within the first hour, none after treatment. The ony side-effect attributed to primaquine was abdominal pain.
Tun, 2016	27036739	Single arm	Myanmar	2013-2014	DP	42	6 months to 65 years	Not tested	0.25mg/kg day 0	116	There were no clinically significant falls in haemoglobin, or haemoglobinuria	Study medications generally well tolerated although 6 vomited day 0 medication, and 1 vomited on day 2. One serious adverse event, a death through road traffic accident 2 weeks after the last visit

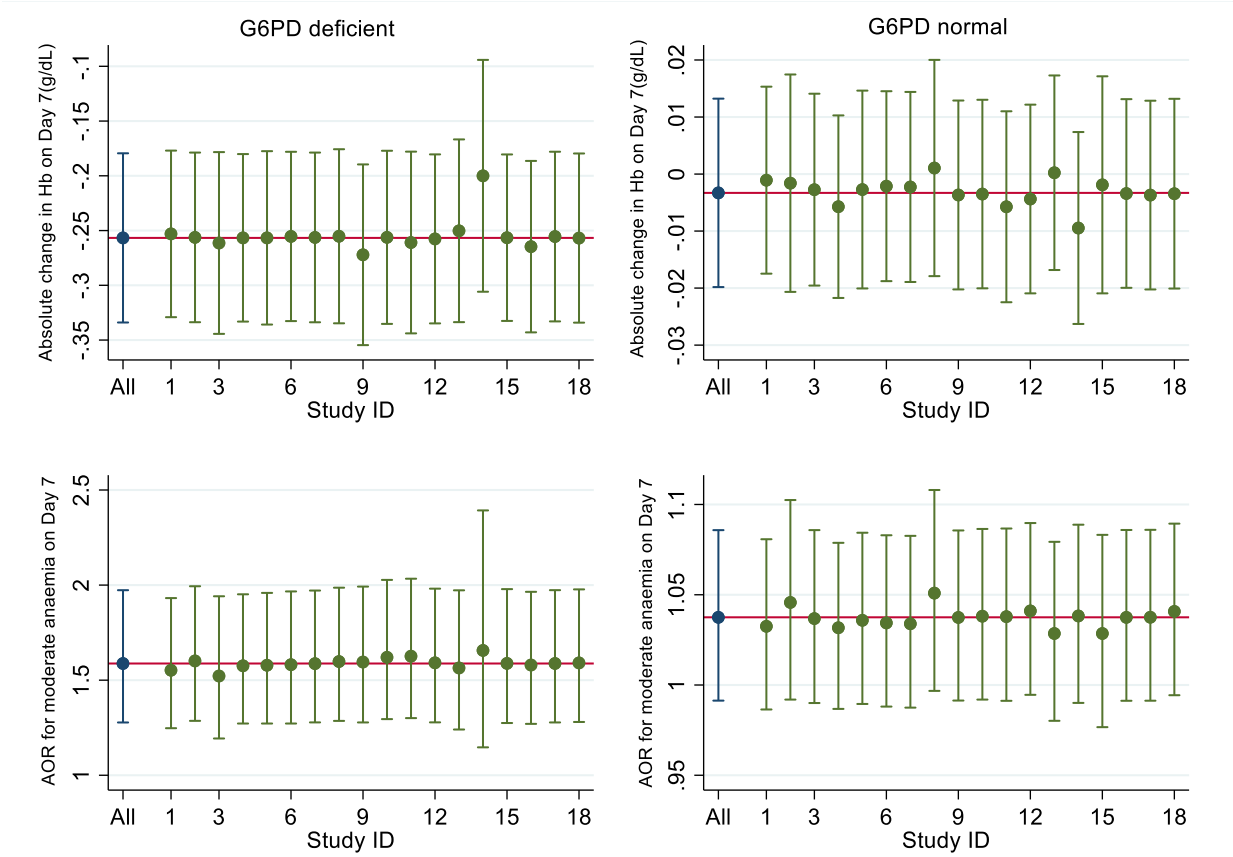
AL: artemether-lumefantrine, ASAQ:artesunate amodiaquine, AM:artesuate-mefloquine, ASSP:artesunate sulphadoxine-pyrimthamine, DP:dihydroartemisinin piperaquine,

*Unclear if requested

**Included mixed infections

Supplementary Figure 12. Sensitivity analysis for the main haematological results

Figures show estimates and their 95% CI for the effect of primaquine dose (in G6PD deficient subjects in the left-hand-side panels and in G6PD normal subjects in the right-hand panels) from the final multivariable model (in blue) and in the same model re- fitted after exclusion of each study in turn (in green). Two endpoints are presented: absolute change in haemoglobin on Day 7 (upper panels) and risk of moderate anaemia on Day 7 (lower panels). Red line show the effect estimated in the final model.



Coefficient of variation for the estimates was (from top left, clockwise) 5.7%, 75.8%, 3.9% and 14.5%.

Large variability for the second model was due to the estimates being very close to 0, nonetheless the results were very consistent throughout.