THE LANCET Infectious Diseases

Supplementary webappendix

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The safety, tolerability and efficacy of repeated doses of dihydroartemisinin-piperaquine for the prevention and treatment of malaria: A systematic review and meta-analysis

Supplementary Web Appendix

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Supplemental Text

We conducted our search, analyses, and reporting adhering to the PRISMA guidelines for systematic reviews and meta-analyses. An electronic literature search applying the PICOTS framework was conducted of the following clinical databases: MEDLINE, EMBASE, Web of Science, Scopus, CINAHL Plus, the Cochrane Library databases, WHO Global Health Library and the Malaria in Pregnancy Consortium (MiPc) Library. A multi-concept Boolean search strategy was applied using keywords and MeSH terms. We additionally searched 'gray literature' databases, conference abstracts, manually reviewed reference lists of selected publications as well as records recommended by contacting experts so as to encompass a broad range of available literature. We imported all into EndNote Web (Thompson Reuters, NY), removed duplicates, and screened each record against the eligibility criteria.

Data on the study population, including age, severity of malaria, drug exposures, treatment outcomes (including protective efficacy and the incidence of any parasitemia after treatment with DP), tolerability, and all serious adverse events were abstracted. We also used measures of lost to follow-up, drop-outs and adherence as surrogates of tolerability.

Supplemental References

- 1. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700.
- 2. van Eijk AM, Hill J, Povall S, Reynolds A, Wong H, Ter Kuile FO. The Malaria in Pregnancy Library: a bibliometric review. *Mal J* 2012; **11**: 362.

Table S1. PICOTS framework

Components	Characteristics						
Population	All persons at risk for malaria or with malaria infections						
	-Subgroup analyses:						
	Malaria transmission intensity						
	Geography (Southeast Asia, Sub-Saharan Africa)						
	Target groups (infants, children, pregnant women, and						
	adults)						
	Number of doses						
Intervention	Exposed to repeat DP for treatment or prevention of malaria						
Control	Exposed to another ACT or antimalarial for treatment, to SP for						
	prevention, or placebo						
Outcomes	Serious Adverse Events including but not limited to:						
	1. Death						
	2. Any event leading to hospitalization						
	3. QT prolongation						
	4. Adverse pregnancy outcomes (stillbirth, miscarriage,						
	congenital anomalies)						
	Tolerability:						
	1. Vomiting						
	2. Nausea						
	3. Dizziness						
	4. Lost to follow-up, drop-outs or poor adherence						
Timing	No time limits will be placed on the search						
Setting	Any study in which participants were exposed to DP including case						
	series						
	Limit to English Language						

Table S2. PubMed search strategy

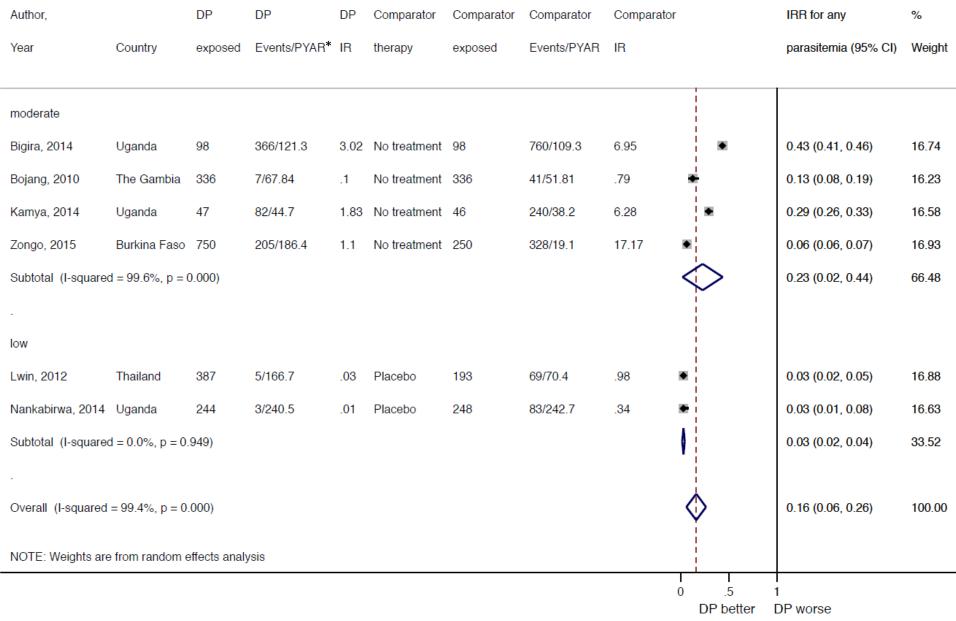
Search date Sept 1, 2016

	Framework	Search terms	Number of articles
Р	Population	Human	
ı	Intervention	AND	P + I: 252
		Dihydroartemisinin piperaquine OR	
		DHA-PPQ	
С	Control	-	
0	Outcome	-	
Т	Timing	-	
S	Setting	AND (English [la])	P+I+O+T+S: 244
	Limit to English language		

Figure S1: Bias assessment of randomized-controlled trials using the Cochrane Collaboration tool

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome efficacy assessment	Blinding of safety outcomes	Incomplete outcome data
Bigira, 2014						
Bojang, 2010						
Cisse, 2009						
Desai, 2015						
Kakuru, 2015						
Kamya, 2014						
Lwin, 2012						
Nankabirwa, 2014						
Wanzira, 2009						
Zongo 2015						

Figure S2: Pooled incidence rate ratio for any parasitemia, monthly dihydroartemisinin-piperaquine versus placebo stratified by bias assessment



DP dihydroartemisinin-piperaquine, PYAR person years at risk, IR incidence rate, IRR incidence rate ratio *Two studies, Lwin et al. and Zongo et al., did not report PYAR

Figure S3: Pooled incidence rate ratio for any parasitemia, monthly dihydroartemisinin-piperaquine versus placebo stratified by geography

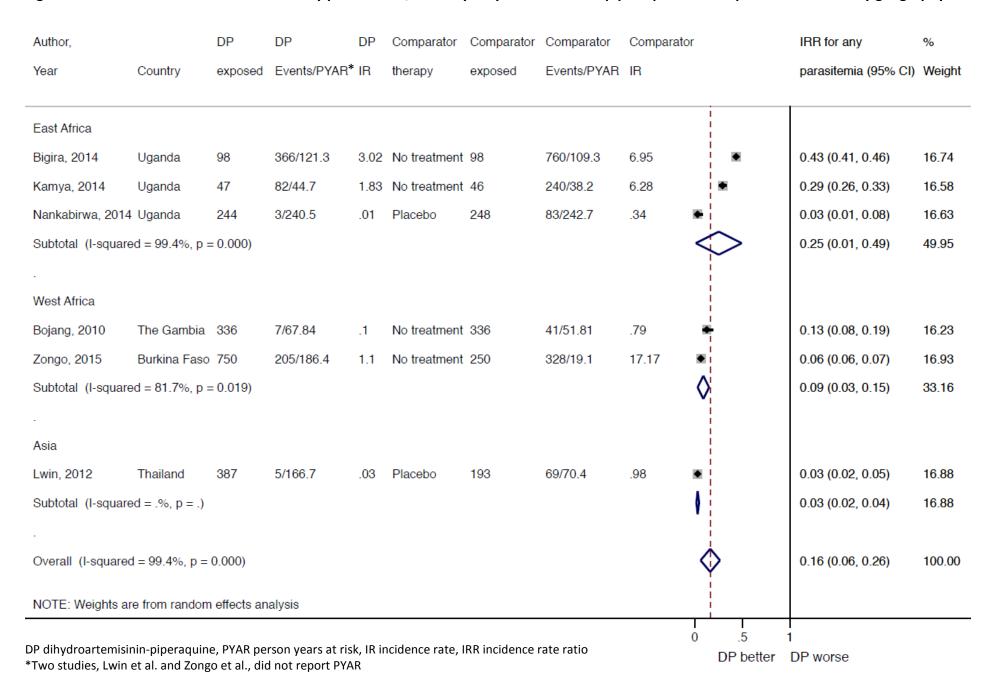
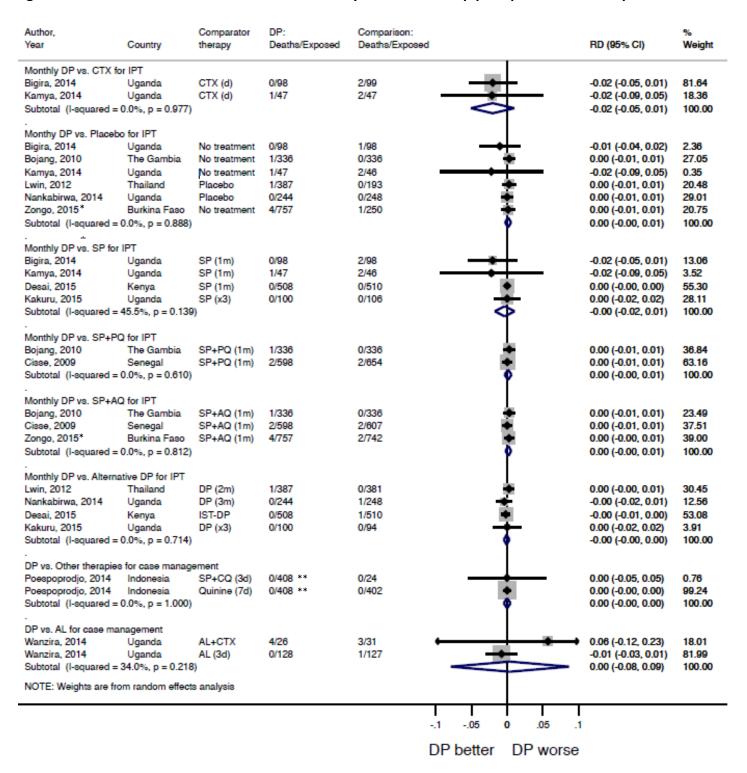


Figure S4: Pooled odds ratio for any hospitalization, dihydroartemisinin-piperaquine compared to other drugs and placebo

Author, Year	Country	Comparator therapy	DP: Hospitalizations/ Exposed	Comparator: Hospitalizations/ Exposed		OR (95% CI)	% Weight
Monthly DP vs	. CTX for IPT						
Bigira, 2014	Uganda	CTX (d)	13/98	12/99		1.11 (0.48, 2.57)	59.74
Kamya, 2014	Uganda	CTX (d)	6/47	8/47		0.71 (0.23, 2.24)	40.26
Subtotal (I-squ	uared = 0.0%,	p = 0.543)			\Diamond	0.95 (0.48, 1.86)	100.00
Monthy DP vs.	Placebo for IF	РТ					
Bojang, 2010	The Gambia	No treatment	3/336	8/336		0.37 (0.10, 1.40)	47.35
Kamya, 2014	Uganda	No treatment	6/47	10/46		0.53 (0.17, 1.59)	52.65
Subtotal (I-squ	uared = 0.0%,	p = 0.688)			\Diamond	0.45 (0.19, 1.06)	100.00
Monthly DP vs	. SP for IPT						
Bigira, 2014	Uganda	SP (1m)	13/98	25/98	-	0.45 (0.21, 0.94)	59.13
Kamya, 2014	Uganda	SP (1m)	6/47	17/46	*	0.25 (0.09, 0.71)	40.87
Subtotal (I-squ	uared = 0.0%,	p = 0.373)			\Diamond	0.37 (0.20, 0.67)	100.00
Monthly DP vs	. SP+PQ for IF	РΤ					
Bojang, 2010	The Gambia	SP+PQ (1m)	3/336	1/336		3.02 (0.31, 29.16)	100.00
Subtotal (I-squ	uared = .%, p :	= .)				3.02 (0.31, 29.16)	
Monthly DP vs	. SP+AQ for IF	РΤ					
Bojang, 2010			3/336	2/336	-	1.50 (0.25, 9.06)	100.00
Subtotal (I-squ	uared = .%, p :	= .)				1.50 (0.25, 9.06)	100.00
DP vs. AL for o	ase managem	nent					
Wanzira, 2014	Uganda	AL (3d)	13/154	42/158	-	0.25 (0.13, 0.50)	100.00
Subtotal (I-squ	uared = .%, p =	= .)			\Diamond	0.25 (0.13, 0.50)	100.00
				Т		Τ	
				.1	•	30	
	- 11 I .				DP better DP worse		

OR odds ratio, DP dihydroartemisinin-piperaquine, CTX co-trimoxazole, IPT intermittent preventative treatment, SP sulfadoxine-pyrimethamine, SP+PQ sulfadoxine-pyrimethamine piperaquine, SP+AQ sulfadoxine-pyrimethamine amodiaquine, AL artemether-lumefantrine

Figure S5: Pooled risk difference for death with dihydroartemisinin-piperaquine versus comparators



RD risk difference, DP dihydroartemisinin-piperaquine, CTX co-trimoxazole, SP sulfadoxine-pyrimethamine, SP+PQ sulfadoxine-pyrimethamine piperaquine, SP+AQ sulfadoxine-pyrimethamine amodiaquine, AL artemether-lumefantrine, IPT intermittent preventative treatment, IST intermittent screening and treatment

^{*}Zongo et al: Numbers are based on actual drug exposures

^{**} Poespoprodjo, et al: Only 64 of 408 DP recipients received ≥ 2 courses of DP

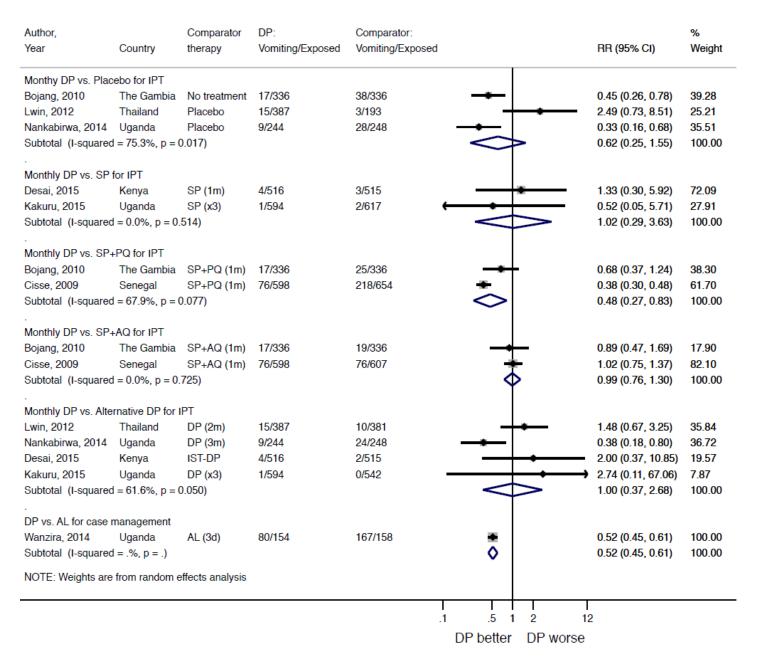
Figure S6: Pooled relative risk for loss to follow-up for dihydroartemisinin-piperaquine versus comparators

Author, Year	Country	Comparator therapy	DP: LTFU/Exposed	Comparison: LTFU/Expose			RR (95% CI)	% Weight
Monthly DP vs. CT. Bigira, 2014 Kamya, 2014 Subtotal (I-squared	Uganda Uganda	CTX (d) CTX (d) 490)	13/98 2/47	14/99 4/47	-	<u>+</u>	0.94 (0.47, 1.89) 0.50 (0.10, 2.60) 0.85 (0.45, 1.62)	84.67 15.33 100.00
Monthy DP vs. Place Bigira, 2014 Bojang, 2010 Kamya, 2014 Lwin, 2012 Nankabirwa, 2014 Zongo, 2015* Subtotal (I-squared	Uganda The Gambia Uganda Thailand Uganda Burkina Faso	No treatment No treatment No treatment Placebo Placebo No treatment 397)	13/98 7/336 2/47 135/387 8/244 27/757	11/98 11/336 3/46 48/193 5/248 3/250		•	1.18 (0.56, 2.51) 0.64 (0.25, 1.62) 0.65 (0.11, 3.73) 1.40 (1.06, 1.86) 1.63 (0.54, 4.90) 2.97 (0.91, 9.71) 1.33 (1.03, 1.73)	11.55 7.57 2.22 68.44 5.47 4.76 100.00
Monthly DP vs. SP Bigira, 2014 Kamya, 2014 Desai, 2015 Kakuru, 2015 Subtotal (I-squared	Uganda Uganda Kenya Uganda	SP (1m) SP (1m) SP (1m) SP (x3) 376)	13/98 2/47 106/516 2/100	15/98 6/46 98/515 4/106	-	•	0.87 (0.44, 1.72) 0.33 (0.07, 1.53) 1.08 (0.84, 1.38) 0.53 (0.10, 2.83) 1.00 (0.77, 1.29)	13.36 2.73 81.58 2.33 100.00
Monthly DP vs. SP- Bojang, 2010 Cisse, 2009 Subtotal (I-squared	The Gambia Senegal	SP+PQ (1m) SP+PQ (1m) 0.250)	7/336 47/598	3/336 50/654	-	*	2.33 (0.61, 8.95) 1.03 (0.70, 1.51) 1.19 (0.64, 2.21)	17.92 82.08 100.00
Monthly DP vs. SP- Bojang, 2010 Cisse, 2009 Zongo, 2015* Subtotal (I-squared	The Gambia Senegal Burkina Faso	SP+AQ (1m) SP+AQ (1m) SP+AQ (1m)	7/336 47/598 27/757	5/336 67/607 18/742	-	-	1.40 (0.45, 4.37) 0.71 (0.50, 1.02) 1.47 (0.82, 2.65) 1.04 (0.59, 1.82)	17.20 47.22 35.57 100.00
Monthly DP vs. Alte Lwin, 2012 Nankabirwa, 2014 Desai, 2015 Kakuru, 2015 Subtotal (I-squared	Thailand Uganda Kenya Uganda	DP (2m) DP (3m) IST-DP DP (x3)	135/387 8/244 106/516 2/100	91/381 14/248 107/515 5/94	-	*	1.46 (1.17, 1.83) 0.58 (0.25, 1.36) 0.99 (0.78, 1.26) 0.38 (0.07, 1.89) 1.02 (0.68, 1.51)	40.25 14.82 39.59 5.35 100.00
DP vs. AL for case Wanzira, 2014 Subtotal (I-squared NOTE: Weights are	Uganda d = .%, p = .)	AL (3d)	5/154	3/158	_		1.71 (0.42, 7.03) 1.71 (0.42, 7.03)	100.00 100.00
					I I .1 .5 DP better	1 2 1 DP wo	rse	

RR relative risk, DP dihydroartemisinin-piperaquine, CTX co-trimoxazole, SP sulfadoxine-pyrimethamine, SP+PQ sulfadoxine-pyrimethamine piperaquine, SP+AQ sulfadoxine-pyrimethamine amodiaquine, AL artemether-lumefantrine, IPT intermittent preventative treatment, IST intermittent screening and treatment, LTFU loss to follow-up

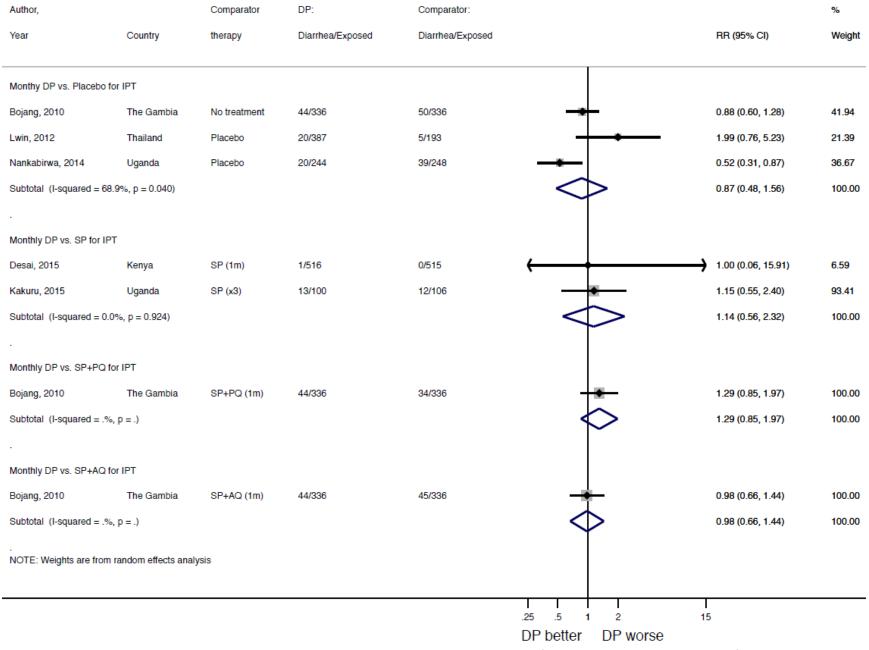
^{*}Zongo et al: Numbers are based on actual drug exposures

Figure S7: Pooled relative risk for vomiting after receiving a dose of dihydroartemisinin-piperaquine compared to other drugs and placebo



RR relative risk, DP dihydroartemisinin-piperaquine, IPT intermittent preventative treatment, SP sulfadoxine-pyrimethamine, SP+PQ sulfadoxine-pyrimethamine piperaquine, SP+AQ sulfadoxine-pyrimethamine amodiaquine, AL artemether-lumefantrine

Figure S8: Pooled relative risk for any diarrhea, dihydroartemisinin-piperaquine versus comparator therapies



RR relative risk, DP dihydroartemisinin-piperaquine, IPT intermittent preventative treatment, SP sulfadoxine-pyrimethamine, SP+PQ sulfadoxine-pyrimethamine piperaquine, SP+AQ sulfadoxine-pyrimethamine amodiaquine

Figure S9: Pooled relative risk for any rash, dihydroartemisinin-piperaquine versus comparator therapies

Author,		Comparator	DP:	Comparator:			%
Year	Country	therapy	Rash/Exposed	Rash/Exposed		RR (95% CI)	Weight
Monthy DP vs. Placeb	bo for IPT						
Bojang, 2010	The Gambia	No treatment	10/36	26/336		0.38 (0.19, 0.79)	37.63
Lwin, 2012	Thailand	Placebo	4/387	2/193	-	1.00 (0.18, 5.40)	11.81
Nankabirwa, 2014	Uganda	Placebo	27/244	31/248		0.89 (0.55, 1.44)	50.56
Subtotal (I-squared =	47.4%, p = 0.149)				\Leftrightarrow	0.66 (0.35, 1.24)	100.00
-							
Monthly DP vs. SP+P	Q for IPT						
Bojang, 2010	The Gambia	SP+PQ (1m)	10/36	15/336		0.67 (0.30, 1.46)	60.81
Cisse, 2009	Senegal	SP+PQ (1m)	3/598	14/654		0.23 (0.07, 0.81)	39.19
Subtotal (I-squared =	49.5%, p = 0.159)				$\langle \rangle$	0.44 (0.16, 1.22)	100.00
-							
Monthly DP vs. SP+A	Q for IPT						
Bojang, 2010	The Gambia	SP+AQ (1m)	10/36	10/336	-+	1.00 (0.42, 2.37)	73.20
Cisse, 2009	Senegal	SP+AQ (1m)	3/598	5/607		0.61 (0.15, 2.54)	26.80
Subtotal (I-squared =	= 0.0%, p = 0.560)				\Leftrightarrow	> 0.88 (0.42, 1.83)	100.00
-							
Monthly DP vs. Altern	ative DP for IPT						
Lwin, 2012	Thailand	DP (2m)	4/387	4/381		0.98 (0.25, 3.91)	11.76
Nankabirwa, 2014	Uganda	DP (3m)	27/244	27/284	-	1.02 (0.61, 1.68)	88.24
Subtotal (I-squared =	= 0.0%, p = 0.966)				\Diamond	1.01 (0.63, 1.62)	100.00
NOTE: Weights are fr	rom random effects	analysis					
					.1 .5 1	I I 2 4	
						P worse	
					Di Dolloi D	110100	

RR relative risk, DP dihydroartemisinin-piperaquine, SP+PQ sulfadoxine-pyrimethamine piperaquine, IPT intermittent preventative treatment, SP+AQ sulfadoxine-pyrimethamine amodiaquine, IST intermittent screening and treatment