THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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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.[1] 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.[2] 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

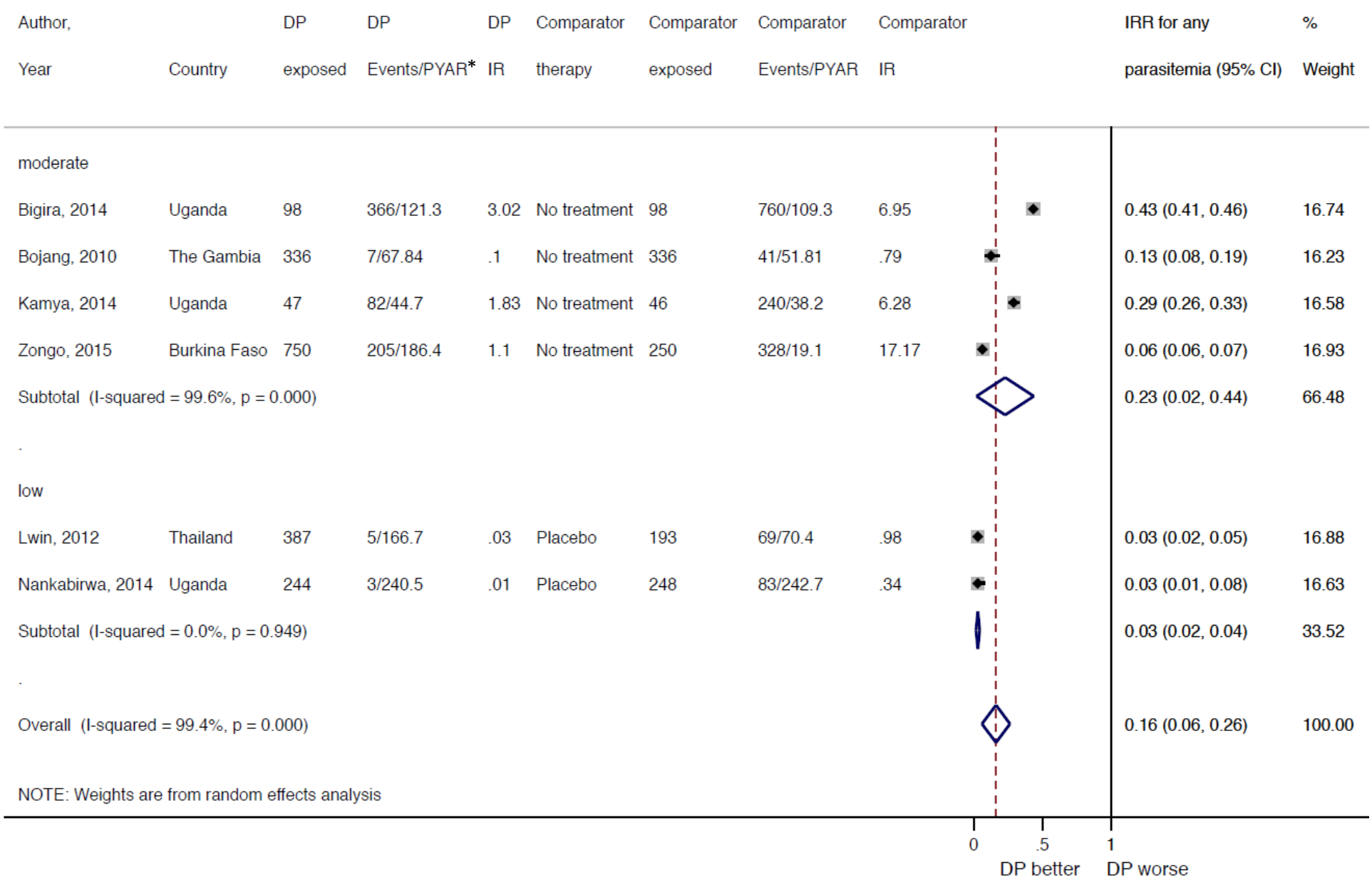
Search date Sept 1, 2016

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

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

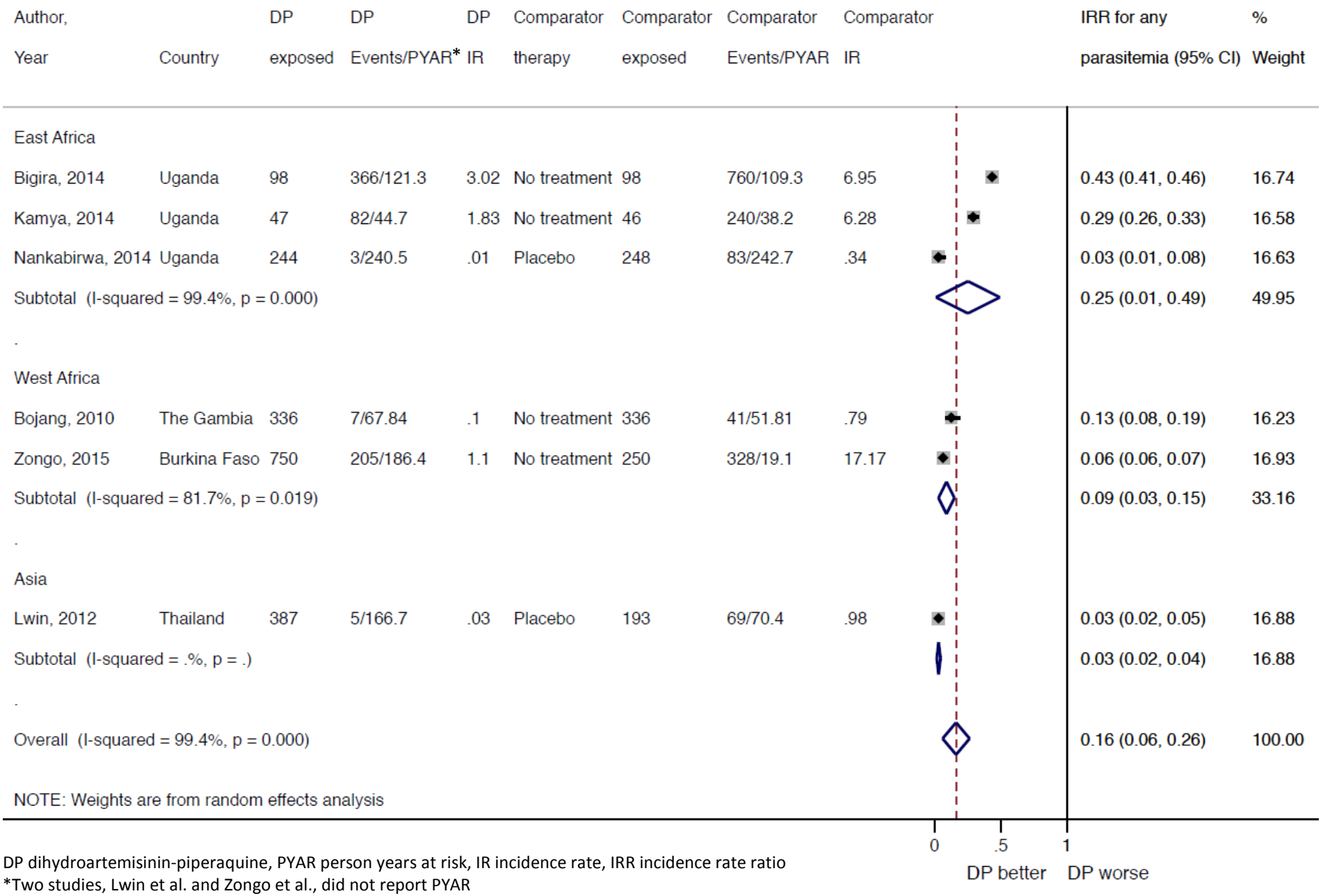
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome efficacy assessment	Blinding of safety outcomes	Incomplete outcome data
Bigira, 2014						
Bojang, 2010						
Cisse, 2009						
Desai, 2015						
Kakuru, 2015						
Kamya, 2014						
Lwin,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



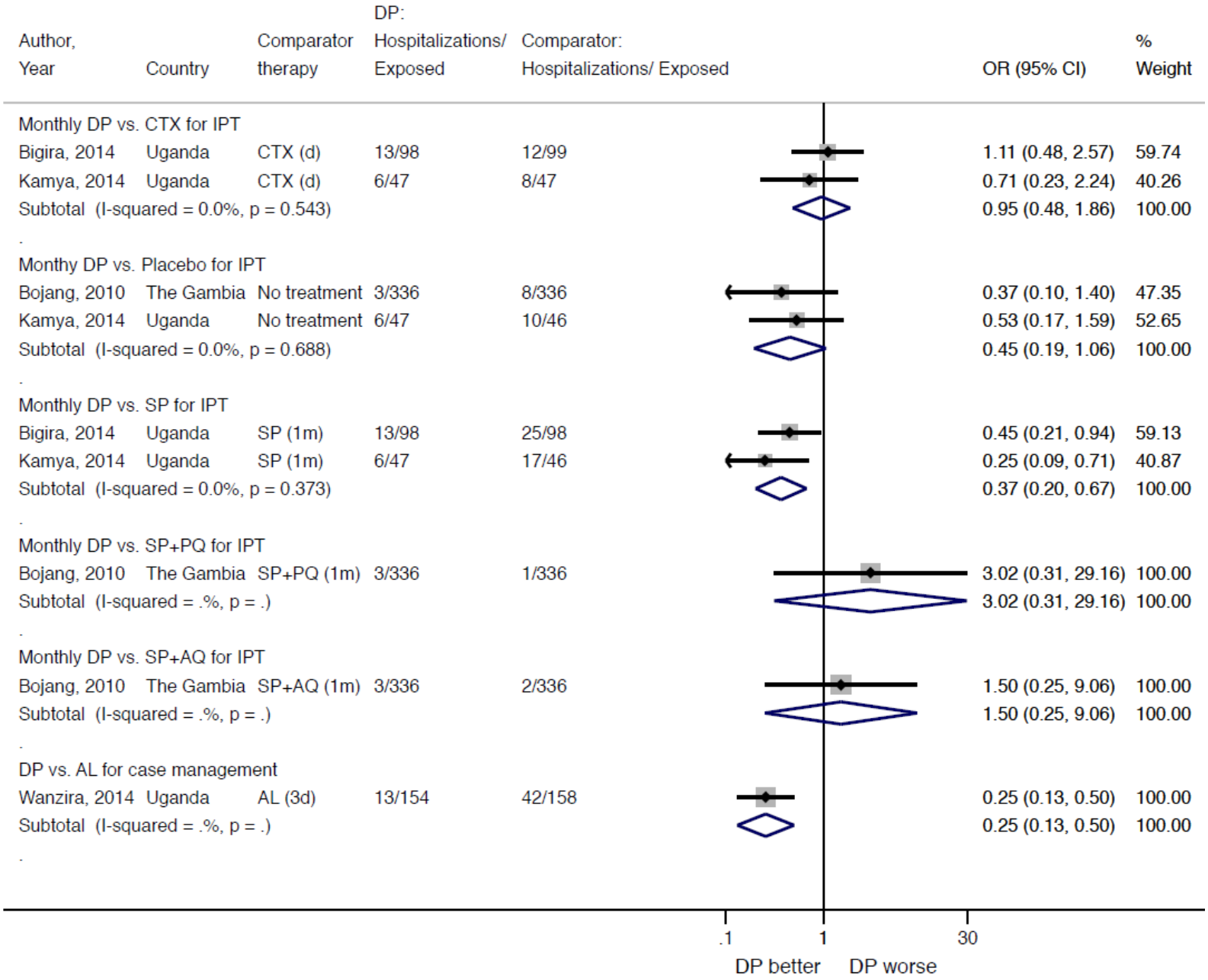
DP dihydroartemisinin-piperaquine, PYAR person years at risk, IR incidence rate, IRR incidence rate ratio
*Two studies, Lwin et al. and Zongo et al., did not report PYAR

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



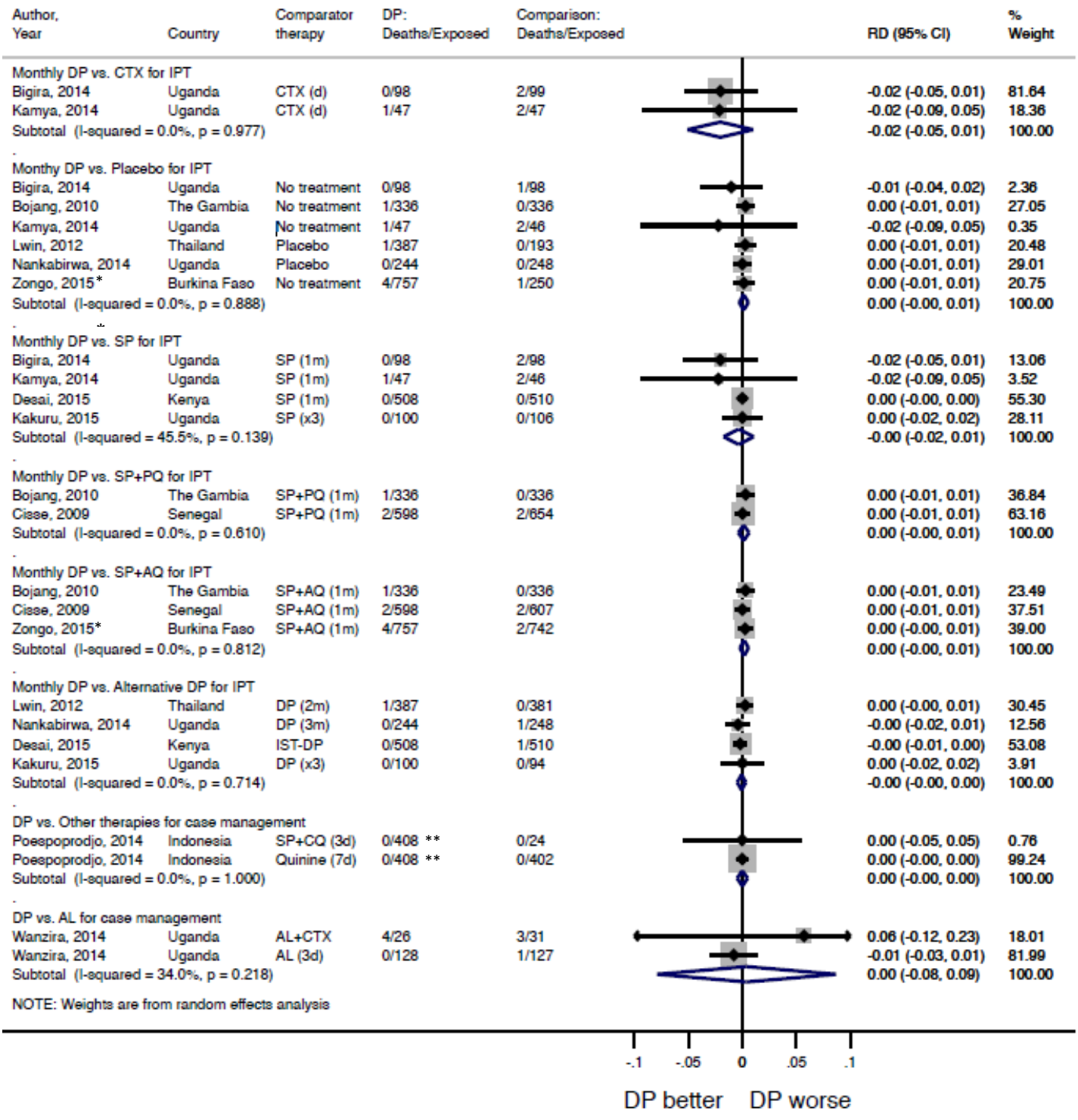
DP dihydroartemisinin-piperaquine, PYAR person years at risk, IR incidence rate, IRR incidence rate ratio
*Two studies, Lwin et al. and Zongo et al., did not report PYAR

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



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

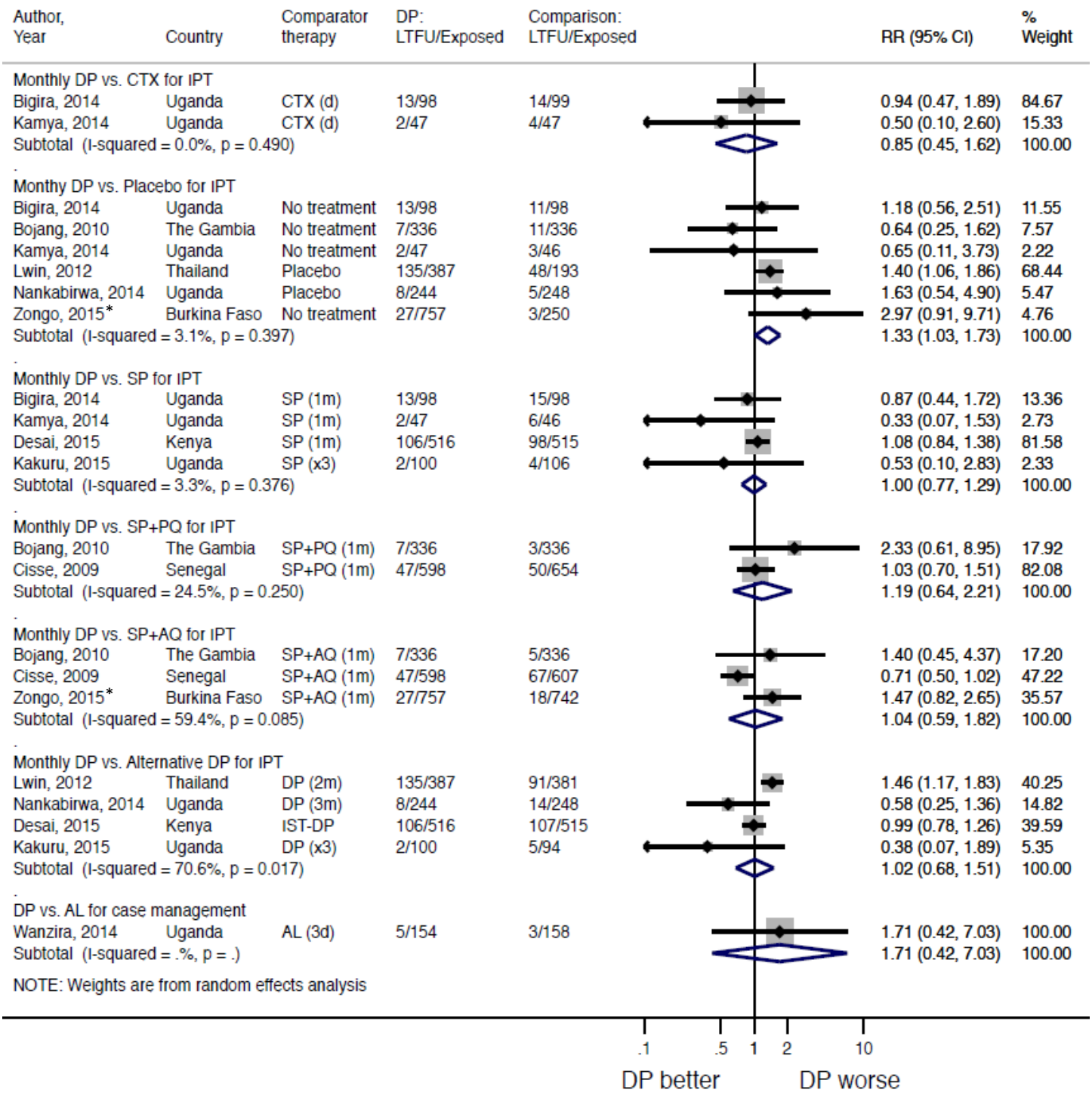


RD risk difference, DP dihydroartemisinin-piperaquine, CTX co-trimoxazole, SP sulfadoxine-pyrimethamine, SP+PQ sulfadoxine-pyrimethamine piperaquine, SP+AQ sulfadoxine-pyrimethamine amodiaquine, AL artemether-lumefantrine, IPT intermittent preventative treatment, IST intermittent screening and treatment

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

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

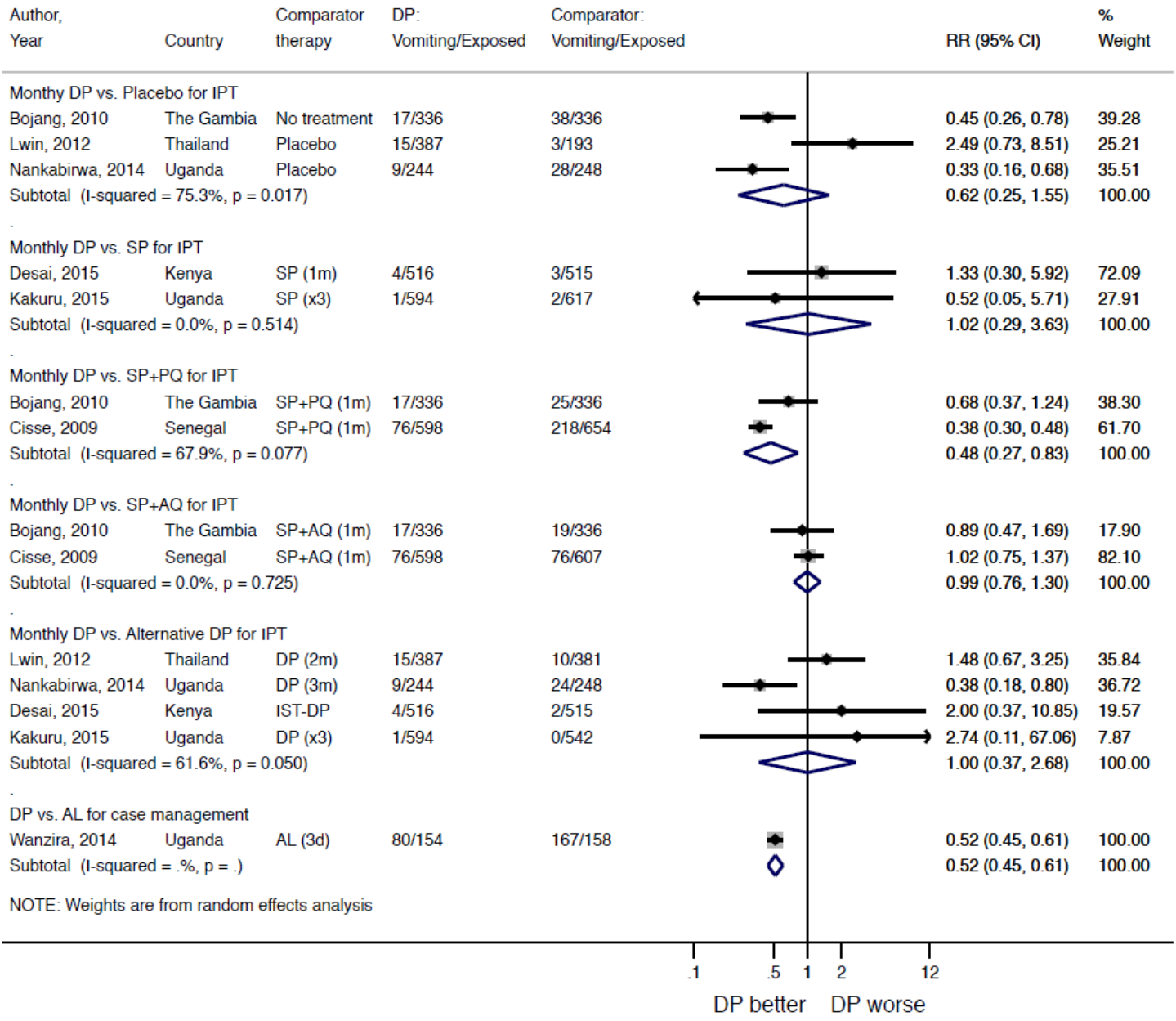
Figure S6: Pooled relative risk for loss to follow-up for dihydroartemisinin-piperaquine versus comparators



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

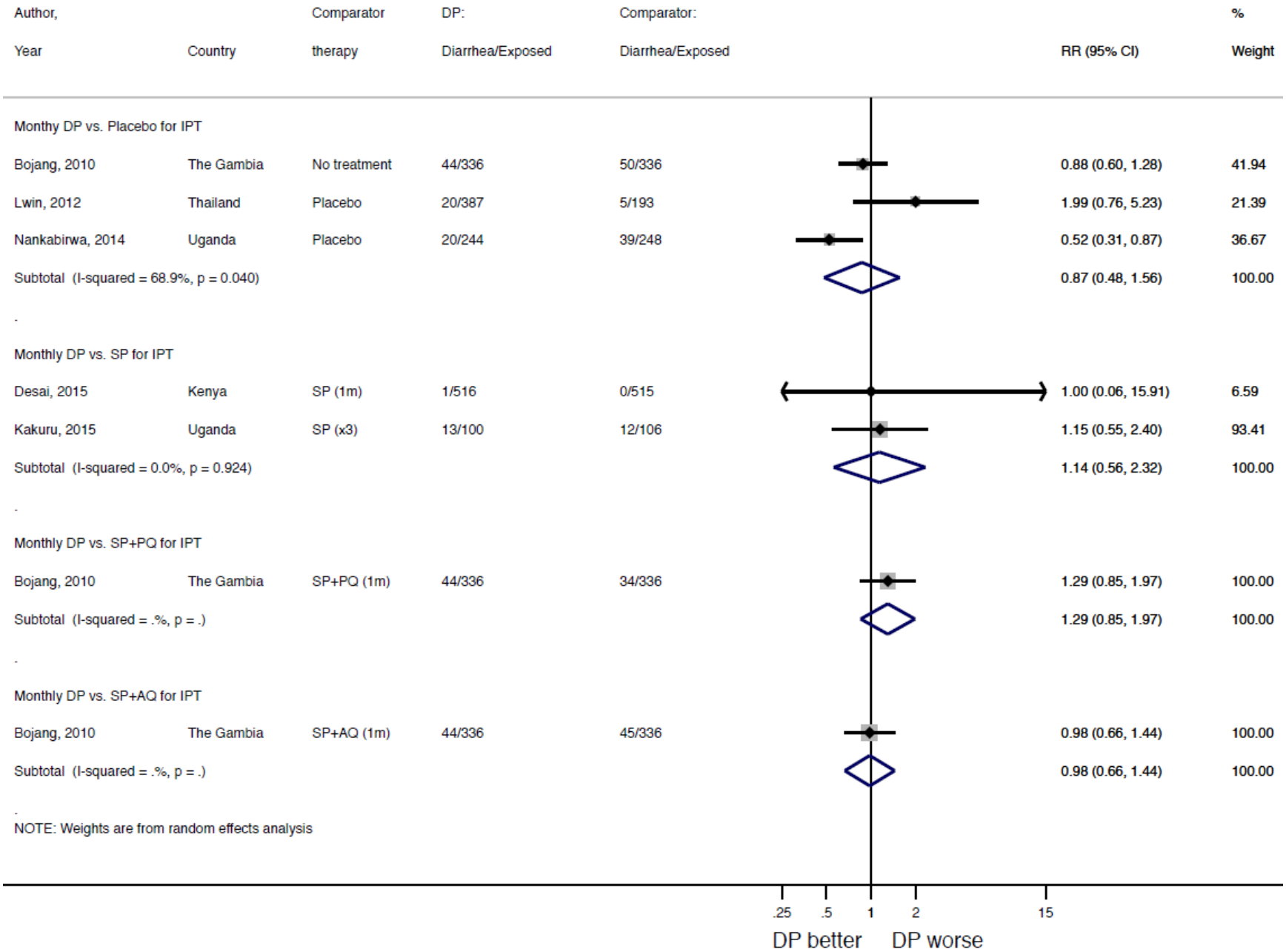
*Zongo et al: Numbers are based on actual drug exposures

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



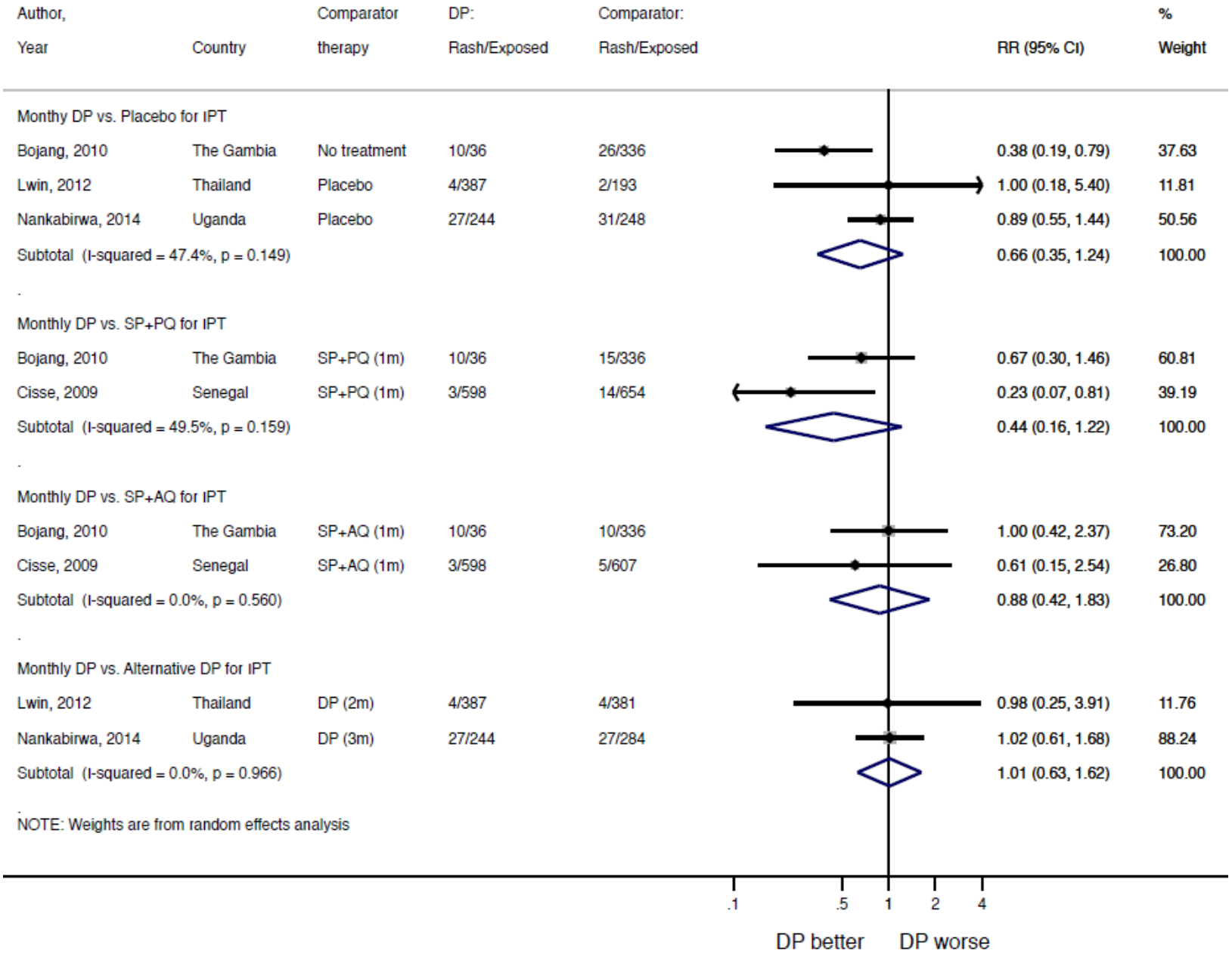
RR relative risk, DP dihydroartemisinin-piperaquine, IPT intermittent preventative treatment, SP sulfadoxine-pyrimethamine, SP+PQ sulfadoxine-pyrimethamine piperaquine, SP+AQ sulfadoxine-pyrimethamine amodiaquine, AL artemether-lumefantrine

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



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