Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Kakuru A, Jagannathan P, Muhindo MK, et al. Dihydroartemisinin–piperaquine for the prevention of malaria in pregnancy. N Engl J Med 2016;374:928-39. DOI: 10.1056/NEJMoa1509150

Supplemental Appendix

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Figure S1

Title: Histological outcomes stratified by treatment arm and gravidity

Legend A: Prevalence of any evidence of placental malaria by histopathology

Legend B: Prevalence of moderate-high grade pigment deposition

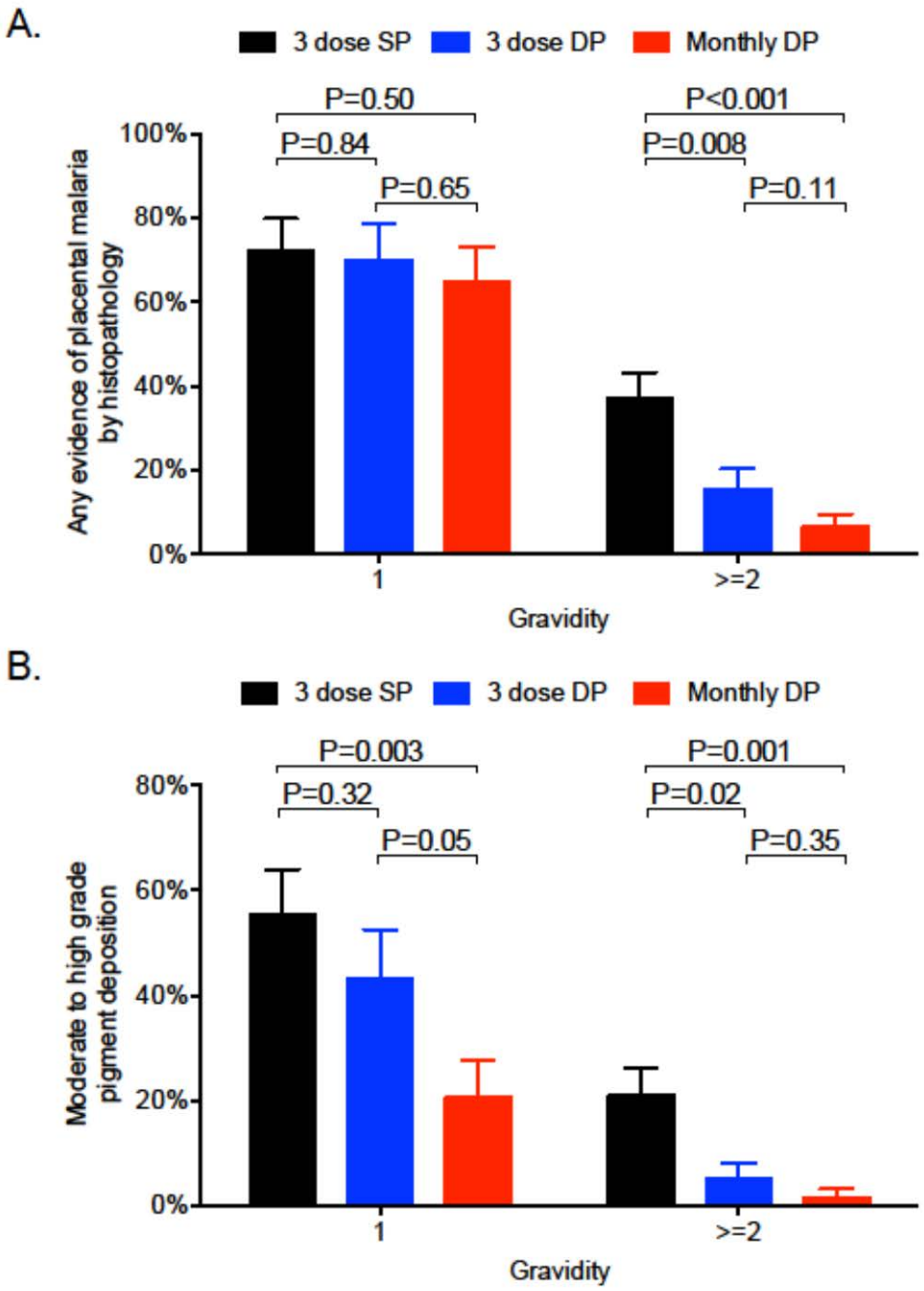

Table S1. Histopathological findings of placental malaria

Outcomes	Treatment arm		
	3 dose SP (n=98)	3 dose DP (n=88)	Monthly DP (n=96)
Rogerson classification system – no. (%)			
No parasites or pigment	49 (50.0)	58 (65.9)	70 (72.9)
Parasites, pigment in monocytes and fibrin	5 (5.1)	1 (1.14)	0 (0.0)
Parasites, pigment in fibrin only	0 (0.0)	1 (1.14)	0 (0.0)
No parasite, pigment only	44 (44.9)	28 (31.8)	26 (27.1)
Moderate-high grade pigment deposition [a] – no. (%)	33 (33.7)	16 (18.2) [b]	8 (8.3) [c]

[a] Malaria pigment detected in $\geq$ 5% of high power fields

[b] Significant difference between 3 dose DP and 3 dose SP arms (P=0.02)

[c] Significant differences between monthly DP and 3 dose SP (P<0.001) and 3 dose DP arms (P=0.05)

Table S2. Description of all women with any adverse birth outcome

Treatment arm	Gestational age (weeks)	Birth weight (gm)	Spontaneous abortion	Stillbirth	Low birth weight	Preterm delivery	Congenital anomaly
3 dose SP	N/A	N/A	X				
3 dose SP	N/A	N/A	X				
3 dose SP	N/A	N/A	X				
3 dose SP	38	2390			X		
3 dose SP	39	2130			X		
3 dose SP	39	2480			X		
3 dose SP	40	2180			X		
3 dose SP	36	3000				X	
3 dose SP	38	2420			X		
3 dose SP	36	2800				X	
3 dose SP	35	2350			X	X	
3 dose SP	38	2230			X		
3 dose SP	35	2410			X	X	polydactyl
3 dose SP	31	1490			X	X	club foot
3 dose SP	40	2470			X		
3 dose SP	33	2210			X	X	
3 dose SP	34	2180			X	X	
3 dose SP	38	950		X	X		
3 dose SP	33	2160			X	X	
3 dose DP	31	1430			X	X	
3 dose DP	40	2910					undescended testis
3 dose DP	41	2940					polydactyl
3 dose DP	34	2180		X	X	X	
3 dose DP	36	2650				X	
3 dose DP	41	2490			X		
3 dose DP	39	3150					hypospadias
3 dose DP	32	1710			X	X	
3 dose DP	38	2450			X		
3 dose DP	36	2210			X	X	
3 dose DP	36	1320			X	X	
3 dose DP	29	1240			X	X	
3 dose DP	40	2450			X		
3 dose DP	33	2300			X	X	
3 dose DP	31	1320			X	X	
3 dose DP	34	1740			X	X	
3 dose DP	39	2870					polydactyl
3 dose DP	40	1850			X		
3 dose DP	35	2440			X	X	
Monthly DP	35	2140			X	X	
Monthly DP	35	2500				X	
Monthly DP	39	2300			X		
Monthly DP	39	2240			X		
Monthly DP	34	1600			X	X	
Monthly DP	37	2420			X		
Monthly DP	38	2000			X		
Monthly DP	32	1970			X	X	
Monthly DP	32	2000		X	X	X	

Table S3. Comparison of efficacy outcomes between 3 dose DP and monthly DP arms

Incidence measures during pregnancy	IRR (95% CI) [a]	P-value
Symptomatic malaria	0 (0-0.16)	<0.001
Prevalence measures during pregnancy	**RR (95% CI) [a]**	**P-value**
Detection of malaria parasites by LAMP [b]	0.33 (0.20-0.54)	<0.001
Anemia (Hb < 11 g/dL) [b]	0.76 (0.50-1.15)	0.19
Outcomes assessed at delivery	**RR (95% CI) [a]**	**P-value**
Malaria positivity, by test		
Histopathology	0.79 (0.51-1.23)	0.30
Placental blood by microscopy	0 (0-0.80)	0.11
Placental blood by LAMP	0.61 (0.10-3.57)	0.67
Maternal blood by microscopy	0 (0-5.30)	0.48
Maternal blood by LAMP	0.30 (0.03-2.86)	0.35
Cord blood by microscopy	N/A	N/A
Cord blood by LAMP	N/A	N/A
Birth outcomes		
Spontaneous abortion	N/A	N/A
Stillbirth [c]	0.91 (0.06-14.3)	1.0
Low birth weight [c]	0.52 (0.23-1.18)	0.11
Preterm delivery [c]	0.41 (0.15-1.14)	0.08
Congenital anomaly [c]	0 (0-0.56)	0.05
Composite adverse birth outcome	0.43 (0.21-0.90)	0.02

[a] Reference group 3 dose DP

[b] Repeated measures assessed at the time of all routine visits following administration of study drugs

[c] Only includes those who delivered after at least 28 weeks gestational age

Table S4. ECG measurements before and after study drugs administered at 28 weeks gestational age

Characteristic	Treatment arm		
	3 dose SP (n=12)	**3 dose DP (n=17)**	**Monthly DP (n=13)**
Day 0 QTc interval in msec, median (range)	385 (340-410)	390 (360-410)	380 (350-430)
Day 2 QTc interval in msec, median (range)	390 (360-450)	410 (370-450)	390 (380-420)
Change in QTc interval in msec, median (range)	5 (-40-60)	20 (-10-50)	30 (-30-50)