

Supplemental Information

The main text describes the results of different dihydroartemisinin-piperaquine (DHA-PPQ) dosing regimens assuming the ratio of DHA to PPQ matches the World Health Organization (WHO) recommended ratio of 1:4.5 (1). The predicted cure rates and parasite clearance times for each model calibration can be found in Table S1.

Here we show the results are consistent when simulating the DHA to PPQ ratio of 1:8 (2); typical of the commercially available co-formulations routinely used as first-line therapies. The commercial dosing regimens tested are described in Table S2 and the corresponding treatment outcomes are given in Table S3 and Figure S1.

References

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Table S1. Predicted cure rate and parasite clearance times following five dosing regimens, and a poor adherence scenario, of dihydroartemisinin-piperaquine (DHA-PPQ). The regimens are described in the main text and summarised on Table 1. Cure rates were simulated using either one-compartment (calibration 1), two-compartment (calibration 2a-c) or three-compartment (calibration 3a-c) PK models as explained in the main text and in the caption to Figure 1.

	SR _{3/3}	eSTD _{5/5}	pa[eSTD _{5/5}]	eITD _{5/5}	sSTD _{6/3}	sITD _{6/3}
Calibration 1 (3)						
TCR (%)	98.0	99.4	92.8	99.7	99.7	99.9
ACR (%) day 28	99.4	99.8	96.3	99.9	99.9	100.0
ACR (%) day 42	99.0	99.6	94.1	99.9	99.8	100.0
ACR (%) day 63	98.3	99.4	93.1	99.8	99.7	99.9
PCT (days)	0.9	1.1	1.1	0.9	0.9	0.7
(mean (min, max))	(0.5, 11)	(0.5, 9)	(0.5, 17)	(0.5, 21)	(0.5, 26)	(0.5, 13)
Calibration 2a (4)						
TCR (%)	64.9	83.3	41.3	93.8	90.8	97.8
ACR (%) day 28	66.8	84.4	42.1	94.6	91.4	98.1
ACR (%) day 42	65.1	83.5	41.4	94.0	90.9	97.9
ACR (%) day 63	64.9	83.4	41.3	93.8	90.8	97.8
PCT (days)	1.1	1.3	1.2	1.1	0.9	0.8
(mean (min, max))	(0.5, 16)	(0.5, 11)	(0.5, 7)	(0.5, 8)	(0.5, 8.0)	(0.5, 8.0)
Calibration 2b (5)						
TCR (%)	67.5	86.0	46.4	94.7	92.0	97.7
ACR (%) day 28	68.1	86.3	46.5	95.1	92.1	98.1
ACR (%) day 42	67.5	86.1	46.4	94.8	92.0	97.8
ACR (%) day 63	67.5	86.0	46.4	94.7	92.0	97.8
PCT (days)	1.0	1.2	1.1	1.0	0.9	0.8
(mean (min, max))	(0.5, 7)	(0.5, 5)	(0.5, 8)	(0.5, 5)	(0.5, 3.5)	(0.5, 3.0)
Calibration 2c (6)						
TCR (%)	74.4	90.1	58.2	96.1	94.4	98.2
ACR (%) day 28	75.6	90.4	59.0	96.4	94.6	98.4
ACR (%) day 42	74.7	90.2	58.3	96.1	94.5	98.3
ACR (%) day 63	74.5	90.1	58.2	96.1	94.4	98.2
PCT (days)	0.9	1.1	1.0	0.9	0.8	0.7
(mean (min, max))	(0.5, 6)	(0.5, 5.5)	(0.5, 7.0)	(0.5, 5.5)	(0.5, 5.5)	(0.5, 4.5)

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Table S1. – Continued

	SR _{3/3}	eSTD _{5/5}	pa[eSTD _{5/5}]	eITD _{5/5}	sSTD _{6/3}	sITD _{6/3}
Calibration 3a (7)						
TCR (%)	79.0	92.0	57.3	97.9	95.5	99.1
ACR (%) day 28	80.5	92.8	58.4	98.4	96.0	99.3
ACR (%) day 42	79.4	92.1	57.5	98.1	95.6	99.2
ACR (%) day 63	79.1	92.0	57.3	97.9	95.5	99.1
PCT (days) (mean (min, max))	0.9 (0.5, 5.5)	1.1 (0.5, 5.5)	1.1 (0.5, 7.0)	0.9 (0.5, 5.0)	0.9 (0.5, 4.5)	0.7 (0.5, 3.0)
Calibration 3b (8)						
TCR (%)	96.3	99.1	91.6	99.5	99.3	99.7
ACR (%) day 28	97.8	99.5	93.4	99.8	99.5	99.9
ACR (%) day 42	97.0	99.2	92.1	99.7	99.4	99.8
ACR (%) day 63	96.5	99.1	91.7	99.5	99.3	99.8
PCT (days) (mean (min, max))	0.8 (0.5, 5.0)	0.9 (0.5, 11)	0.9 (0.5, 6.0)	0.8 (0.5, 9.0)	0.8 (0.5, 9.0)	0.7 (0.5, 6.0)
Calibration 3c (9)						
TCR (%)	91.3	96.8	73.0	99.3	98.2	99.7
ACR (%) day 28	93.8	97.8	75.6	99.7	98.8	99.9
ACR (%) day 42	91.8	96.9	73.3	99.4	98.3	99.8
ACR (%) day 63	91.4	96.8	73.0	99.3	98.2	99.7
PCT (days) (mean (min, max))	0.9 (0.5, 9.0)	1.1 (0.5, 10)	1.1 (0.5, 7.0)	0.9 (0.5, 7.0)	0.9 (0.5, 8.0)	0.7 (0.5, 7.0)

TCR: true cure rate (i.e. parasite number <1); ACR: apparent cure rate (i.e. parasite number <10⁸);

PCT: parasite clearance time; SR_{3/3}: standard regimen; eSTD_{5/5}: extended regimen; pa[eSTD_{5/5}]: extended regimen with poor adherence; eITD_{5/5}: increased and extended regimen; sSTD_{6/3}: split standard regimen; sITD_{6/3}: twice daily standard regimen.

Table S2. Dosing regimens, and a poor adherence scenario, for dihydroartemisinin-piperaquine (DHA-PPQ) using commercial co-formulations of the drug. This table has the same format as Table 1 of the main text which presented the analogous results for treatment with the World Health Organization’s (WHO) recommended ratio of DHA:PPQ. The commercial co-formulations of DHA-PPQ contain less DHA than recommend by WHO so the DHA doses shown here are consistently lower than those given on Table 1 of the main text.

Regimen *	Dosing interval	Single dose DHA/PPQ [mg/kg]	Total dose DHA/PPQ [mg/kg]
SR _{3/3} (Standard regimen)	Once daily for three days	2/18	6/54
eSTD _{5/5} (Extended regimen)	Once daily for five days	1.2/10.8	6/54
pa[eSTD _{5/5}] (eSTD _{5/5} with poor adherence)	Once daily for three days (doses 4 and 5 missed)	1.2/10.8	3.6/32.4
eITD _{5/5} (Increased and extended regimen)	Once daily for five days	2/18	10/90
sSTD _{6/3} (Split SR _{3/3})	Twice daily for three days	1/9	6/54
sITD _{6/3} (Twice SR _{3/3})	Twice daily for three days	2/18	12/108

* The ratio of DHA-PPQ in the combination is 1:8 and corresponds to the ratio of the commercially available fix-dose combination.

Table S3. Predicted cure rate and parasite clearance times following six different dosing regimens of dihydroartemisinin-piperazine (DHA-PPQ) using commercial co-formulations of the drug. This table has the same format as Table S1 which presented the analogous results for treatment with the World Health Organization's recommended ratio of DHA:PPQ. The regimens are described in Table S2. Cure rates were simulated using either one-compartment (calibration 1), two-compartment (calibration 2a-c) or three-compartment (calibration 3a-c) pharmacokinetic models (see main text).

	SR _{3/3}	eSTD _{5/5}	pa[eSTD _{5/5}]	eITD _{5/5}	sSTD _{6/3}	sITD _{6/3}
Calibration 1 (3)						
TCR (%)	97.4	98.9	90.9	99.6	99.4	99.8
ACR (%) day 28	99.3	99.7	95.5	99.9	99.8	99.9
ACR (%) day 42	98.5	99.5	92.5	99.8	99.7	99.9
ACR (%) day 63	97.8	99.1	91.2	99.7	99.5	99.9
PCT (days)	1.0	1.2	1.3	1.0	0.9	0.8
(mean (min, max))	(0.5, 13)	(0.5, 12)	(0.5, 20)	(0.5, 25)	(0.5, 8.0)	(0.5, 18)
Calibration 2a (4)						
TCR (%)	57.3	76.7	32.4	91.1	85.7	96.9
ACR (%) day 28	59.5	78.0	33.5	92.4	86.6	97.3
ACR (%) day 42	57.5	76.9	32.5	91.3	85.9	97.0
ACR (%) day 63	57.3	76.8	32.4	91.1	85.7	96.9
PCT (days)	1.2	1.5	1.3	1.3	1.0	0.9
(mean (min, max))	(0.5, 19)	(0.5, 13)	(0.5, 7.0)	(0.5, 9)	(0.5, 10)	(0.5, 9)
Calibration 2b (5)						
TCR (%)	58.1	79.6	36.9	92.2	87.7	96.2
ACR (%) day 28	58.9	80.1	37.0	92.8	88.0	96.7
ACR (%) day 42	58.2	79.7	36.9	92.3	87.8	96.2
ACR (%) day 63	58.2	79.7	36.9	92.2	87.8	96.2
PCT (days)	1.1	1.4	1.3	1.1	1.0	0.8
(mean (min, max))	(0.5, 8)	(0.5, 5.5)	(0.5, 8)	(0.5, 6)	(0.5, 4.5)	(0.5, 4.0)
Calibration 2c (6)						
TCR (%)	67.1	85.6	49.1	93.8	91.0	97.2
ACR (%) day 28	68.8	86.2	50.2	94.2	91.4	97.5
ACR (%) day 42	67.5	85.7	49.3	93.9	91.0	97.2
ACR (%) day 63	67.2	85.6	49.2	93.8	91.0	97.2
PCT (days)	1.0	1.2	1.2	1.0	0.9	0.8
(mean (min, max))	(0.5, 6)	(0.5, 5.5)	(0.5, 11)	(0.5, 5.5)	(0.5, 5.5)	(0.5, 4.5)

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Table S3. – *Continued*

	SR _{3/3}	eSTD _{5/5}	pa[eSTD _{5/5}]	eITD _{5/5}	sSTD _{6/3}	sITD _{6/3}
Calibration 3a (7)						
TCR (%)	72.3	88.0	47.2	96.7	92.2	98.7
ACR (%) day 28	74.5	89.1	48.5	97.5	92.9	99.1
ACR (%) day 42	72.8	88.2	47.5	96.9	92.3	98.8
ACR (%) day 63	72.4	88.1	47.2	96.7	92.2	98.7
PCT (days)	1.1	1.3	1.2	1.1	1.0	0.8
(mean (min, max))	(0.5, 15)	(0.5, 6.0)	(0.5, 7.0)	(0.5, 12)	(0.5, 5.0)	(0.5, 3.5)
Calibration 3b (8)						
TCR (%)	95.0	98.6	88.2	99.3	98.9	99.5
ACR (%) day 28	97.1	99.3	91.0	99.7	99.4	99.8
ACR (%) day 42	95.9	98.9	89.0	99.6	99.1	99.7
ACR (%) day 63	95.3	98.7	88.5	99.4	99.0	99.6
PCT (days)	0.9	1.1	1.1	0.9	0.9	0.8
(mean (min, max))	(0.5, 15)	(0.5, 4.5)	(0.5, 13)	(0.5, 10)	(0.5, 11)	(0.5, 8.0)
Calibration 3c (9)						
TCR (%)	88.3	95.4	66.1	98.9	96.9	99.5
ACR (%) day 28	91.6	96.8	69.4	99.6	97.9	99.8
ACR (%) day 42	88.7	95.6	66.5	99.1	97.0	99.6
ACR (%) day 63	88.3	95.4	66.2	98.9	96.9	99.5
PCT (days)	1.1	1.3	1.3	1.1	1.0	0.8
(mean (min, max))	(0.5, 10)	(0.5, 11)	(0.5, 11)	(0.5, 7)	(0.5, 8.0)	(0.5, 7.0)

TCR: true cure rate (i.e. parasite number <1); ACR: apparent cure rate (i.e. parasite number <10⁸);

PCT: parasite clearance time; SR_{3/3}: standard regimen; eSTD_{5/5}: extended regimen; pa[eSTD_{5/5}]:

extended regimen with poor adherence; eITD_{5/5}: increased and extended regimen; sSTD_{6/3}: split

standard regimen; sITD_{6/3}: twice daily standard regimen.

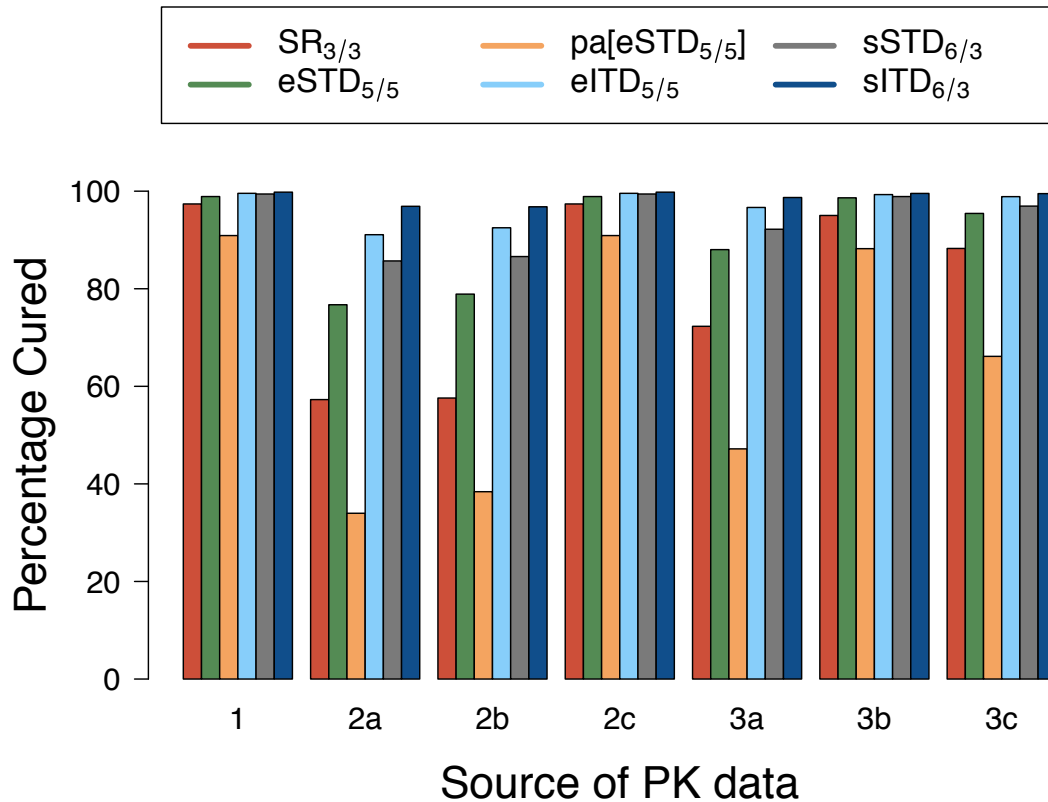


Figure S1. The percentage of individuals predicted to be cured by five dihydroartemisinin-piperavaquine (DHA-PPQ) dosing regimens and one poor adherence scenario. This figure has the same format as Figure 1 of the main text which presented the analogous results for treatment with the World Health Organization’s recommended ratio of DHA:PPQ. Cure rates were estimated across seven different pharmacokinetic (PK) calibrations for PPQ. The regimens and poor adherence scenario are detailed in Table S2. The PK calibrations are as follows (see main text for more details). Calibration 1 is the one-compartment PK model described in (3). Calibrations 2a-c are two-compartment models calibrated using data from (4-6) respectively. Calibration 3a-c are three-compartment models calibrated using data from (7-9) respectively.