Supplemental Material

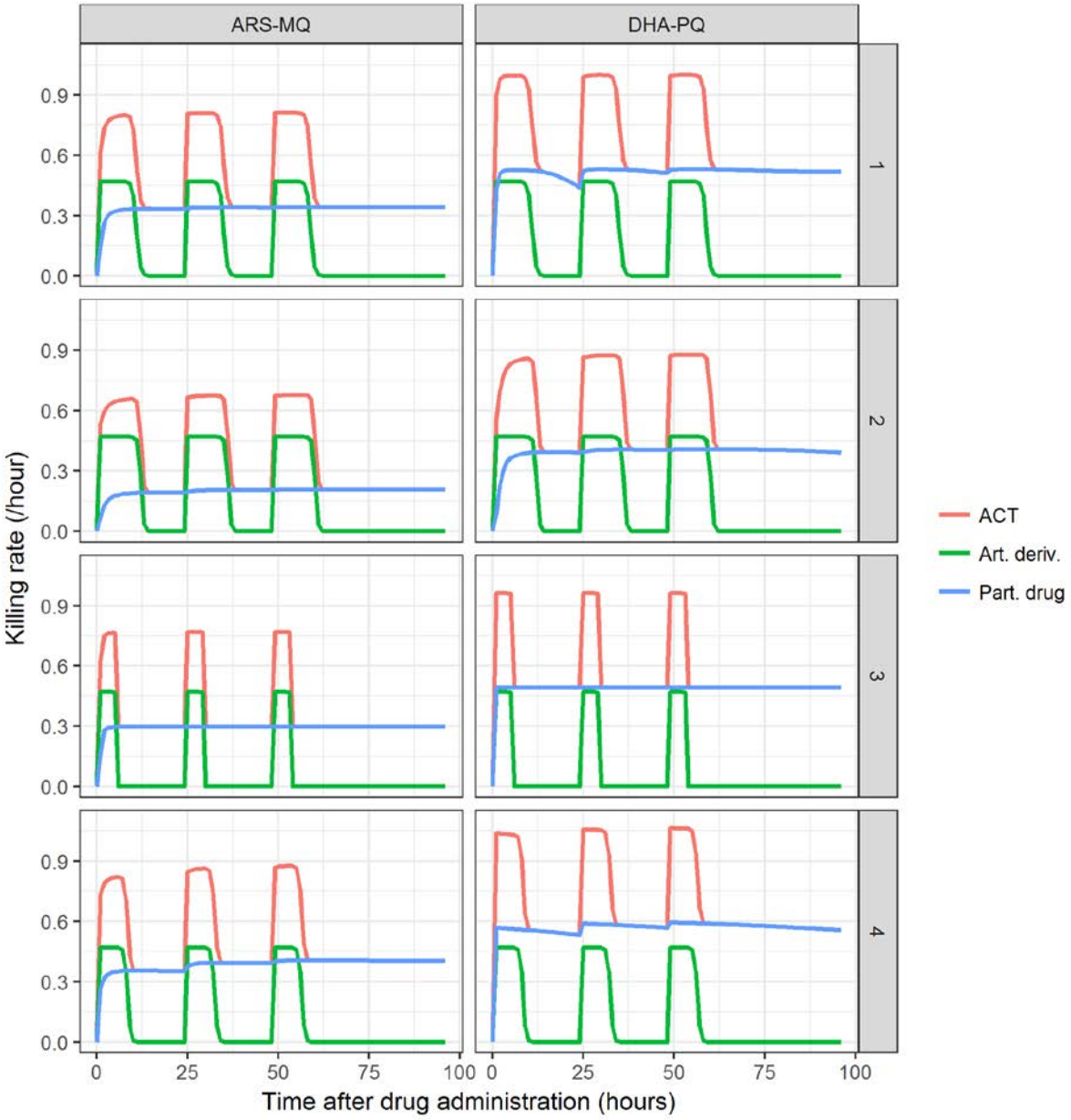


Fig. S1 A subset of four simulated killing rate versus time profiles for artesunate-mefloquine (ARS-MQ) and dihydorartemisinin-piperaquine (DHA-PQ). The killing rate for PQ (blue line in DHA-PQ panels) are higher than MQ (blue line in ARS-MQ panels) at saturating drug concentrations because the parasite reduction ratio (*PRR*) ($=10^{4.6}$) for PQ is higher than the *PRR* ($=10^{2.25}$) for MQ. The killing rate versus time profiles differ between the 1000 hypothetical patients for each artemisinin combination therapy (ACT) because there is between-subject variability in the pharmacokinetic profiles. The ARS and DHA profiles

(green line) are the same across ACTs because the same random seed was used for the DHA-PQ and ARS-MQ simulations.

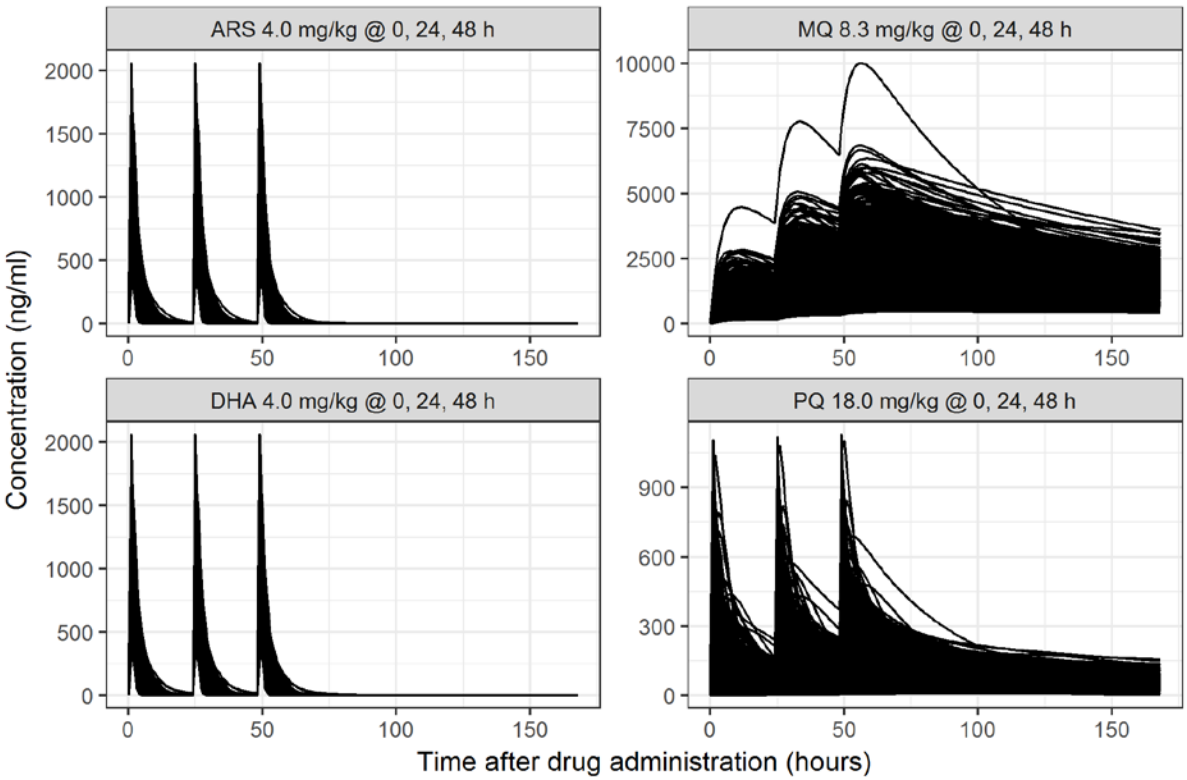


Fig. S2 The 1000 PK profiles simulated based on the LHS sampled PK parameters for each artemisinin combination therapy (artesunate-mefloquine (ARS-MQ) and dihydroartemisinin-piperaquine (DHA-PQ). The dosing information is provided in the heading of each panel. Dihydroartemisinin profiles were simulated for artesunate, since dihydroartemisinin is the primary active metabolite of artesunate and artesunate is considered the pro-drug.

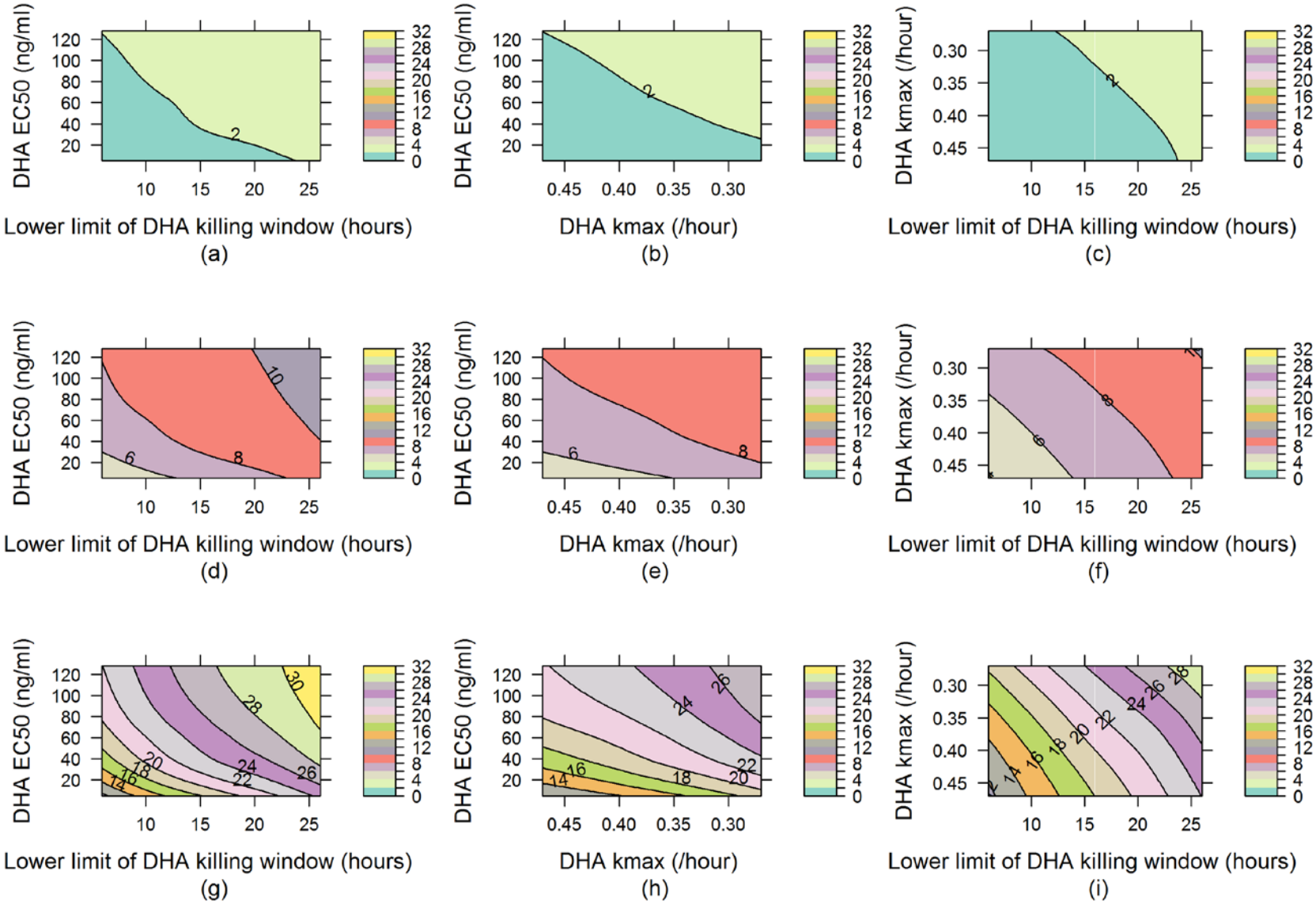
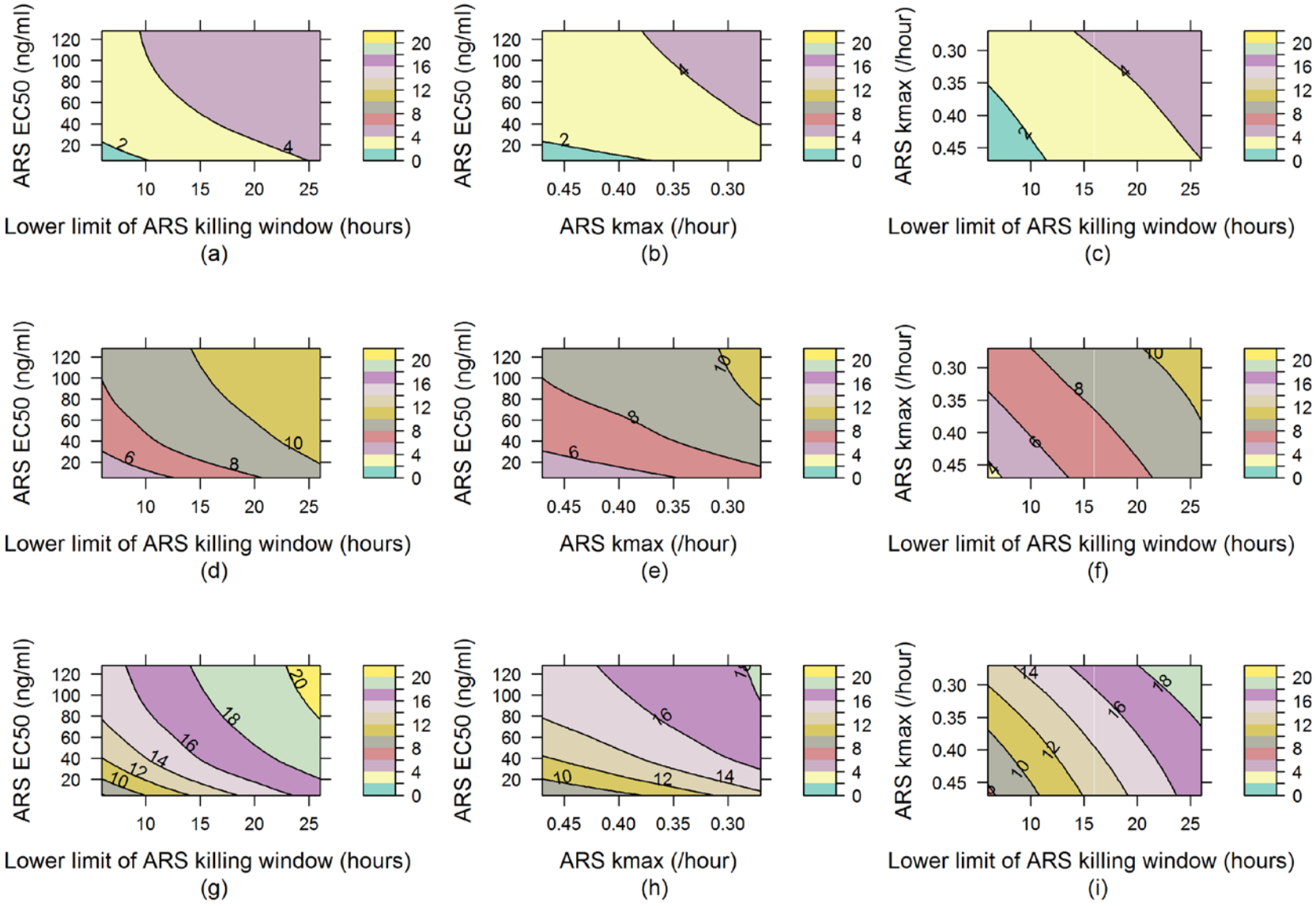

DHA EC50 (ng/ml)
Lower limit of DHA killing window (hours)
(a)
DHA EC50 (ng/ml)
DHA kmax (/hour)
(b)
DHA kmax (/hour)
Lower limit of DHA killing window (hours)
(c)
DHA EC50 (ng/ml)
Lower limit of DHA killing window (hours)
(d)
DHA EC50 (ng/ml)
DHA kmax (/hour)
(e)
DHA kmax (/hour)
Lower limit of DHA killing window (hours)
(f)
DHA EC50 (ng/ml)
Lower limit of DHA killing window (hours)
(g)
DHA EC50 (ng/ml)
DHA kmax (/hour)
(h)
DHA kmax (/hour)
Lower limit of DHA killing window (hours)
(i)

Fig. S3 Contour plots showing percentage of treatment failures (contour lines and colour scale) for DHA-PQ when the PQ *EC50* concentration is increased. Top panels (a)-(c) PQ *EC50* concentration is 25 ng/ml (replication of Figure 1, panels (a)-(c)). Middle panels (d)-(f) PQ *EC50* concentration is 50% increased to 37.5 ng/ml. Bottom panels (g)-(i) PQ *EC50* concentration is 100% increased to 50 ng/ml. Artemisinin derivative's *EC50* concentration is increased and its killing window shortened in panels (a), (d) and (g). Artemisinin derivative's *EC50* concentration is increased and its maximal killing effect (k_{max}) decreased in panels (b), (e) and (h). Artemisinin derivative's k_{max} decreased and its killing window shortened in panels (c), (f) and (i). Dihydroartemisinin profiles were simulated for artesunate, since dihydroartemisinin is the primary active metabolite of artesunate and artesunate is considered the pro-drug.


ARS EC50 (ng/ml)
Lower limit of ARS killing window (hours)
(a)
ARS EC50 (ng/ml)
ARS kmax (/hour)
(b)
ARS kmax (/hour)
Lower limit of ARS killing window (hours)
(c)
ARS EC50 (ng/ml)
Lower limit of ARS killing window (hours)
(d)
ARS EC50 (ng/ml)
ARS kmax (/hour)
(e)
ARS kmax (/hour)
Lower limit of ARS killing window (hours)
(f)
ARS EC50 (ng/ml)
Lower limit of ARS killing window (hours)
(g)
ARS EC50 (ng/ml)
ARS kmax (/hour)
(h)
ARS kmax (/hour)
Lower limit of ARS killing window (hours)
(i)

50

Fig. S4 Contour plots showing percentage of treatment failures (contour lines and colour scale) for ARS-MQ when the MQ *EC50* concentration is increased. Top panels (a)-(c) MQ *EC50* concentration is 280 ng/ml (replication of Figure 1, panels (d)-(f)). Middle panels (d)-(f) MQ *EC50* concentration is 50% increased to 420 ng/ml. Bottom panels (g)-(i) MQ *EC50* concentration is 100% increased to 560 ng/ml. Artemisinin derivative's *EC50* concentration is increased and its killing window shortened in panels (a), (d) and (g). Artemisinin derivative's *EC50* concentration is increased and its maximal killing effect (k_{max}) decreased in panels (b), (e) and (h). Artemisinin derivative's k_{max} decreased and its killing window shortened in panels (c), (f) and (i). Dihydroartemisinin profiles were simulated for artesunate, since dihydroartemisinin is the primary active metabolite of artesunate and artesunate is considered the pro-drug.