

Figure S1: Observed plasma concentration versus (hours) (A: normal scale, B: log-normal scale). Time after dose could be up to 60 hours as some patients only received benzylpenicillin for 2 days, after which it was discontinued while samples were still drawn according to protocol on following study days.

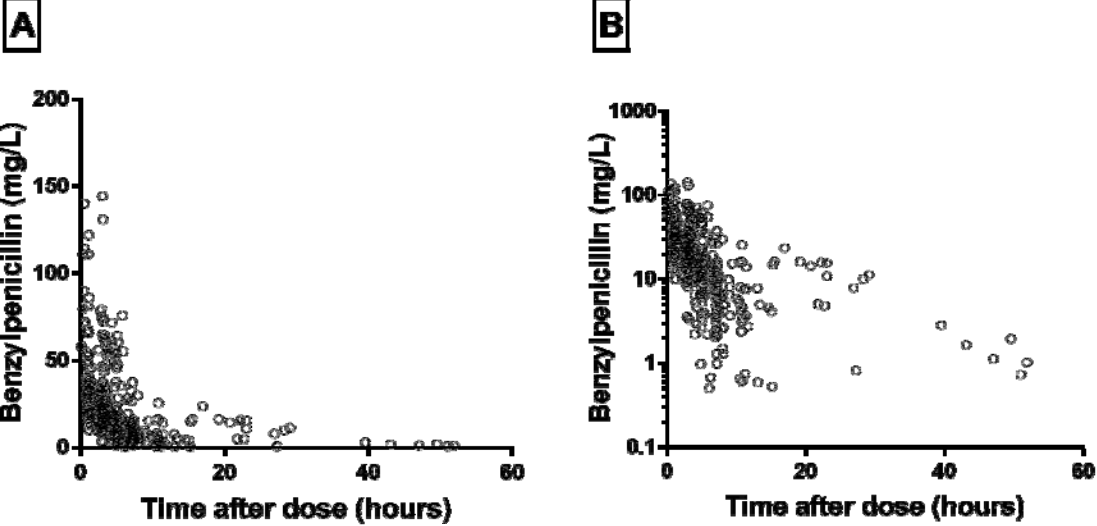


Figure S2: Visual predictive check of the system-specific model (A) and the reference-model (B) with observed benzylpenicillin concentrations (blue circles) and population prediction (red solid line) with the corresponding 95% prediction interval (dotted red lines). Pink and blue fields represent the model-based percentile confidence interval.

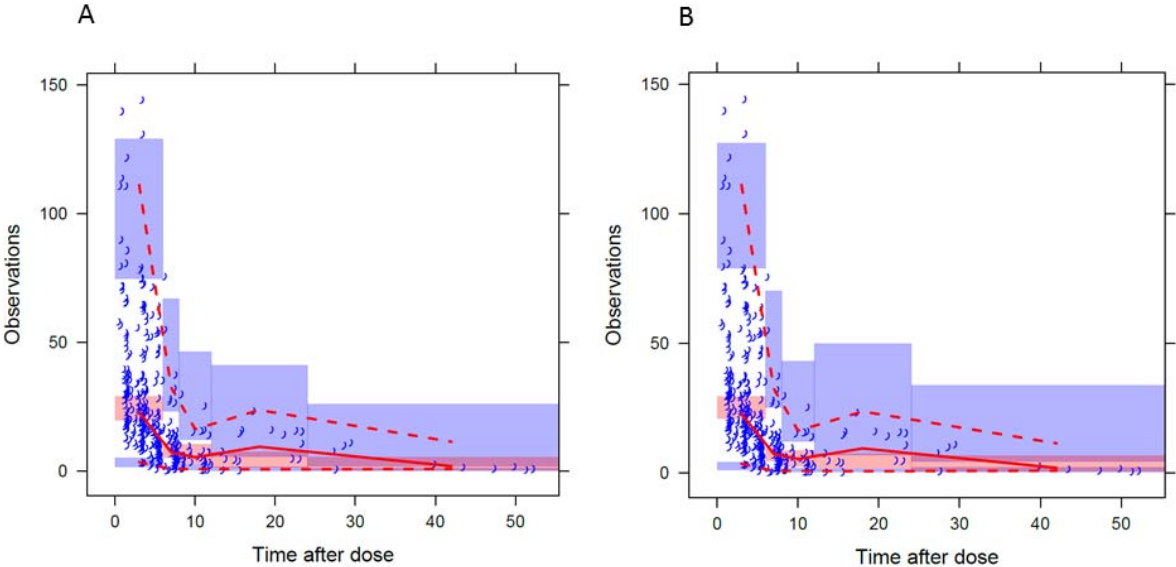


Figure S3: individual post hoc benzylpenicillin clearances (Cl, red circle) and population predicted benzylpenicillin clearances (TVCL; black triangle) versus the most predictive covariate (postnatal age, PNA) for the system-specific model (A) and the reference-model (B).

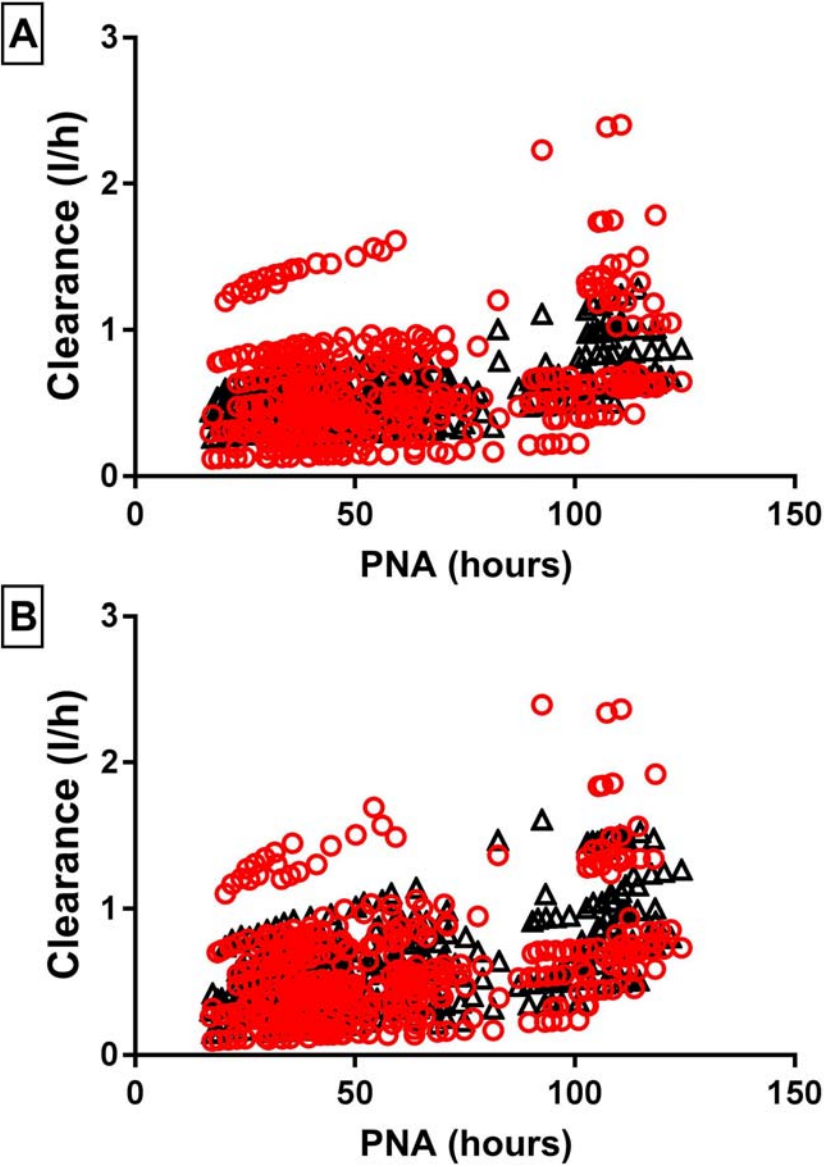


Table S1: Simulated trough and peak concentrations based on the system-specific model.

Dosage regimen	GA	UO	Level	Median concentration (mg/L)	5 th percentile (mg/L)	95 th percentile (mg/L)
75,000 IU/kg/day in 3 doses	36	0.5	T	7.6	1.3	22.5
			P	25.8	12.5	50.0
		2	T	6.3	1.0	19.6
			P	24.2	11.7	46.9
		6	T	5.3	0.8	17.6
			P	23.0	11.2	44.7
	38	0.5	T	5.8	0.9	18.6
			P	23.6	11.5	46.0
		2	T	4.7	0.6	16.1
			P	22.1	10.8	43.2
		6	T	3.9	0.5	14.4
			P	21.0	10.2	41.2
	40	0.5	T	4.2	0.5	14.9
			P	21.4	10.4	41.9
		2	T	3.3	0.4	12.8
			P	20.1	9.8	39.6
		6	T	2.7	0.3	11.4
			P	19.0	9.2	37.8
	42	0.5	T	2.9	0.3	11.9
			P	19.4	9.4	38.4
		2	T	2.2	0.3	10.2
			P	18.2	8.7	36.2
		6	T	1.8	0.2	8.9
			P	17.2	8.2	34.5
150,000 IU/kg/day in 3 doses	36	0.5	T	15.2	2.6	45.0
			P	51.6	25.0	100.1
		2	T	12.5	2.0	39.3
			P	48.3	23.4	93.9
		6	T	10.7	1.5	35.2
			P	45.9	22.3	89.4
	38	0.5	T	11.6	1.7	37.2
			P	47.2	22.9	92.0
		2	T	9.4	1.3	32.3
			P	44.3	21.5	86.4
		6	T	7.9	1.0	28.8
			P	42.1	20.4	82.5
	40	0.5	T	4.2	0.5	14.9
			P	21.4	10.4	41.9
		2	T	3.3	0.4	12.8
			P	20.1	9.8	39.6
		6	T	2.7	0.3	11.4
			P	19.0	9.2	37.8

200,000 IU/kg/day in 4 doses	42	0.5	T	5.8	0.7	23.8
			P	38.8	18.8	76.8
		2	T	4.5	0.5	20.3
			P	36.3	17.4	72.4
		6	T	3.6	0.4	17.8
			P	34.5	16.3	69.0
	36	0.5	T	24.3	5.6	64.1
			P	59.0	28.5	116.8
		2	T	20.5	4.3	56.5
			P	54.8	26.5	108.6
		6	T	17.8	3.5	51.2
			P	51.7	25.0	102.5
	38	0.5	T	19.2	3.9	54.0
			P	53.4	25.8	105.8
		2	T	16.0	2.9	47.4
			P	49.5	24.0	98.5
		6	T	13.7	2.3	42.5
			P	46.7	22.6	93.2
	40	0.5	T	14.5	2.4	44.1
			P	47.7	23.1	95.0
		2	T	11.8	1.8	38.5
			P	44.3	21.4	88.5
		6	T	10.0	1.4	34.3
			P	41.8	20.1	83.6
42	0.5	T	10.6	1.5	35.8	
		P	42.7	20.6	85.5	
	2	T	8.5	1.1	30.9	
		P	39.7	19.0	79.6	
	6	T	7.1	0.8	27.5	
		P	37.3	17.8	75.3	

GA = gestational age (weeks), UO = urine output (ml/kg/hour), T = trough, P = peak. Grey cells indicate levels >100 mg/L