## Supplementary Information

**Table S1.** Summary of the characteristics of the evaluated PopPK models.

| Model | Cmpt | Cov | Error | ɵCL | $IIV_{CL}$ (%) | ɵV or $V_1$ | $IIV_{V\ or\ V1}$ (%) | ɵQ | $IIV_Q$ (%) | ɵ$V_2$ | $IIV_{V2}$ (%) | Residual variability | | Model equations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | Proportional (%) | Additive (mg/L) | |
| Rea RS et al. [13] | 1 | GFR, BW | Mixed | 3.14 | 83.7 | 53 | 64.4 | - | - | - | - | 24.3 | 0.381 | $CL = (3.14 \times GFR^{1.2}) / (54.8^{1.2} + GFR^{1.2})$<br>$V_1 = 53 \times (BW/70)$ |
| Bos JC et al.[14] | 1 | CrCl | Mixed | 5.7 | 74 | 19 | 49 | - | - | - | - | 32 | 0.056 | $CL = 5.7 \times (1 + 0.0091 \times (CrCl - 74))$ |
| Hodiamont et al.[15] | 2 | IBW, ALBM | Proportional | 1.15 | 42.5 | 21.2 | 17.2 | 1.96 | - | 18.4 | - | | | $CL = 1.15 \times (IBW/70)^{0.75}$<br>$V_1 = 21.2 \times (IBW/70) \times (ALBM/22)^{-0.833}$ |
| Hodiamont et al. [16] | 2 | - | Mixed | 2.3 | 75.0 | 21.6 | 27.0 | 1.3 | - | 10.2 | - | 19.4 | 0.13 | $CL = 2.3 \times (BW/70)^{0.75}$<br>$Q = 1.3 \times (BW/70)^{0.75}$<br>$V_1 = 21.6 \times (BW/70)$ |

*Cmpt*, compartment; *Cov*, covariates, *CL*, clearance; *V*, central volume of distribution; $V_1$, volume of distribution of the first compartment; *Q*, inter-compartmental clearance; $V_2$, volume of distribution of the second compartment; *IIV*, interindividual variability, *ALBM*, Albumin, *CrCl*, creatinine clearance; *GFR*, glomerular filtration rate, *BW*, bodyweight, *IBW*, ideal bodyweight.

**Table S2.** Summary of the characteristics of the re-estimated PopPK models.

| Model | Cmpt | Cov | Error | ɵCL | $IIV_{CL}$ (%) | ɵV or $V_1$ | $IIV_{V\ or\ V1}$ (%) | ɵQ | $IIV_Q$ (%) | ɵ$V_2$ | $IIV_{V2}$ (%) | Model equations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rea RS et al. [13] | 1 | GFR, BW | Mixed | 9.31[a] 129[b] | 36.9[a] 18.3[b] | 21.7 | 28.8 | - | - | - | - | $CL = (ɵ_{CL,a} \times GFR^{1.2}) / (ɵ_{CL,b}{}^{1.2} + GFR^{1.2})$ $V_1 = ɵ_V \times (BW/70)$ |
| Bos JC et al.[14] | 1 | CrCl | Mixed | 3.44 | 27.1 | 22.4 | 39.4 | - | - | - | - | $CL = 3.44 \times (1 + 0.00925 \times (CrCl - 92))$ |
| Hodiamont et al.[15] | 2 | IBW, ALBM | Proportional | 2.12 | 49.1 | 23.9 | 45.7 | 1.95 | - | 18.1 | - | $CL = 2.11 \times (IBW/70)^{0.75}$ $V_1 = 21.2 \times (IBW/70) \times (ALBM/22)^{-0.833}$ |
| Hodiamont et al. [16] | 2 | - | Mixed | 1.63 | 54.8 | 8.67 | 45.7 | 0.943 | - | 6.78 | - | $CL = 1.63 \times (BW/70)^{0.75}$ $Q = 0.943 \times (BW/70)^{0.75}$ $V_1 = 8.67 \times (BW/70)$ |

*Cmpt*, compartment; *Cov*, covariates, *CL*, clearance; *V*, central volume of distribution; $V_1$, volume of distribution of the first compartment; *Q*, inter-compartmental clearance; $V_2$, volume of distribution of the second compartment; *IIV*, interindividual variability, *ALBM*, Albumin, *CrCl*, creatinine clearance; *GFR*, glomerular filtration rate, *BW*, bodyweight, *IBW*, ideal bodyweight.

**Table S3.** Typical value of PK parameters and variability used during external evaluation and following the re-estimation of PopPK models.

| Model | External evaluation | | | | | | | | Following re-estimation | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **CL** | **IIV$_{CL}$ (%)** | **V or V$_1$** | **IIV$_{V\ or\ V1}$ (%)** | **Q** | **IIV$_Q$ (%)** | **V$_2$** | **IIV$_{V2}$ (%)** | **CL** | **IIV$_{CL}$ (%)** | **V or V$_1$** | **IIV$_{V\ or\ V1}$ (%)** | **Q** | **IIV$_Q$ (%)** | **V$_2$** | **IIV$_{V2}$ (%)** |
| Rea RS et al. [13] | 1.45 | 83.7 | 53 | 64.4 | - | - | - | - | 2.26 | 60.7 | 21.7 | 42.8 | - | - | - | - |
| Bos JC et al. [14] | 5.7 | 74 | 19 | 49 | - | - | - | - | 4.01 | 27.0 | 22.4 | 39.4 | - | - | - | - |
| Hodiamont et al. [15] | 1.90 | 42.5 | 21.2 | 17.2 | 1.96 | - | 18.4 | - | 2.12 | 49.1 | 23.9 | 45.7 | 1.95 | - | 18.1 | - |
| Hodiamont et al. [16] | 2.3 | 75.0 | 21.6 | 27.0 | 1.3 | - | 10.2 | - | 1.63 | 54.8 | 8.67 | 45.7 | 0.943 | - | 6.78 | - |

*CL*, clearance; *V*, central volume of distribution; $V_1$, volume of distribution of the first compartment; *Q*, inter-compartmental clearance; $V_2$, volume of distribution of the second compartment; *IIV*, interindividual variability.

**Table S4.** Bootstrap Results of the Re-estimated Model from Rea et al.

| | Bootstrap of re-estimated model | |
|---|---|---|
| Parameter | Mean | 95% CI |
| ɵCL,a (L/h) | 9.74 | 9.62 – 9.87 |
| ɵCL,b | 136 | 134 – 138 |
| ɵV (L) | 21.8 | 21.7 – 21.9 |
| Interindividual variability (IIV) | | |
| CL[a] (CV%) | 35.9 | 35.6 – 36.2 |
| CL[b] (CV%) | 16.6 | 16.3 – 16.9 |
| V (CV%) | 27.9 | 27.5 – 28.2 |
| Residual Error | | |
| Additive (mg/L) | 0.279 | 0.275 – 0.282 |
| Proportional (CV%) | 34.4 | 34.1 – 34.6 |

*Cmpt*, compartment; *Cov*, covariates, *CL*, clearance; *V*, central volume of distribution; $V_1$, volume of distribution of the first compartment; *Q*, inter-compartmental clearance; $V_2$, volume of distribution of the second compartment; *IIV*, interindividual variability, *ALBM*, Albumin, *CrCl*, creatinine clearance; *GFR*, glomerular filtration rate, *BW*, bodyweight, *IBW*, ideal bodyweight.

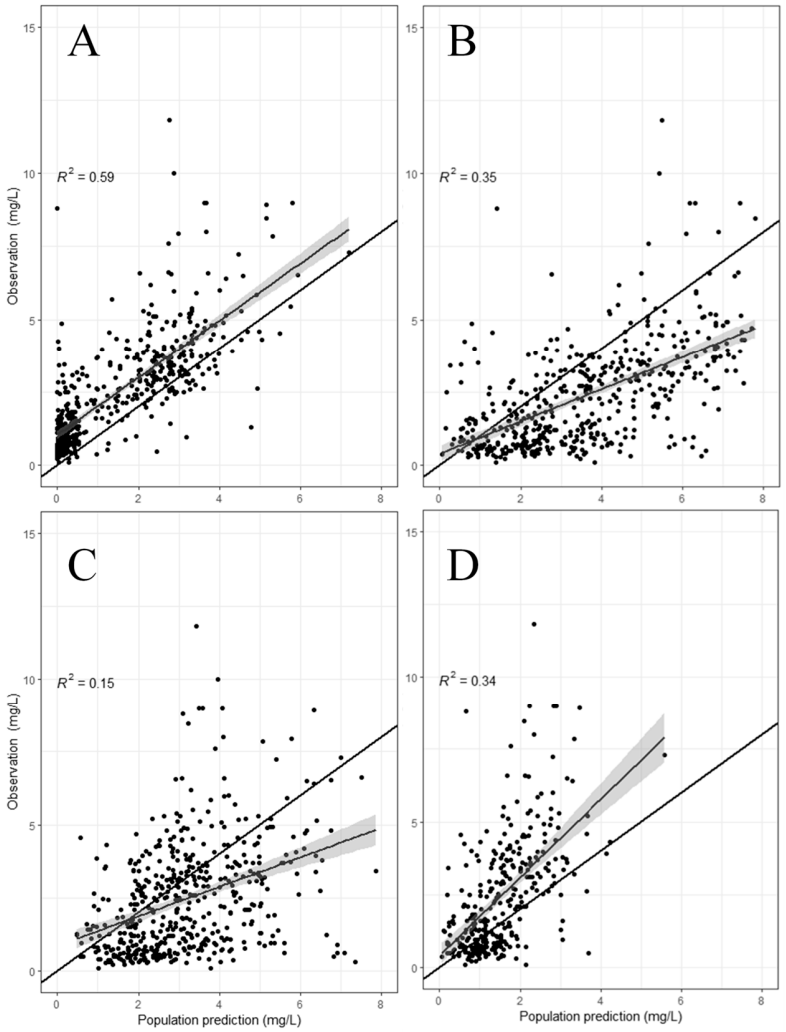


**Figure S1.** Population-predicted concentration versus observed concentrations for gentamicin models. A. Bos et al. [14], B. Hodiamont et al. [15], C. Rea et al. [13], D. Hodiamont et al [16]. Black line with shaded area represents the trendline from the scatter points.

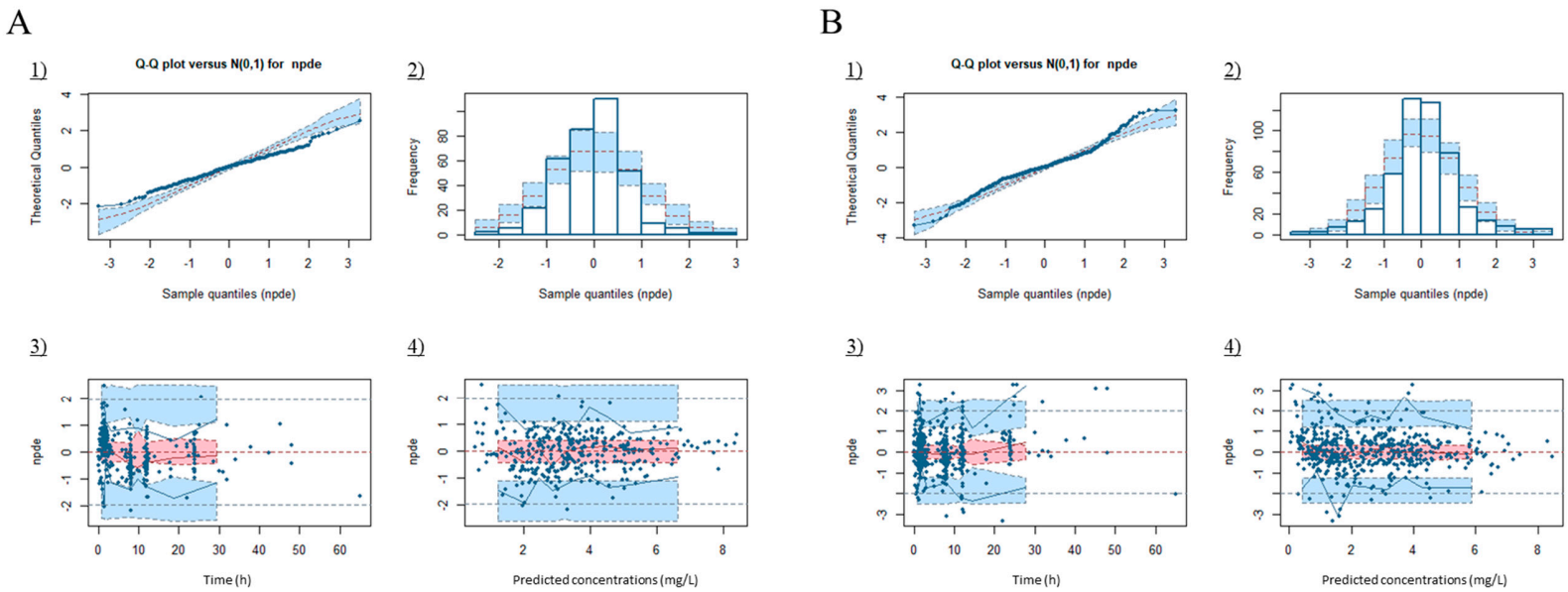


**Figure S2.** Normalized prediction distribution errors (NPDE) plots of (A) the external evaluation and (B) following model re-estimation for Rea et al. 1) Q-Q plot of the NPDE, 2) Histogram of the NPDE, 3) NPDE versus time, 4) NPDE versus predicted concentrations.

**Table S5.** Probability of target attainment of $C_{max}$/MIC >8 on the 3rd dose based on different MIC values and MDD and ODD dosing regimens of gentamicin.

| MIC | 3 mg/kg/day (%) | | | 4 mg/kg/day (%) | | | 5 mg/kg/day (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 mg/kg/q8h | 1.5 mg/kg/q12h | 3 mg/kg/q24h | 1.33 mg/kg/q8h | 2 mg/kg/q12h | 4 mg/kg/q24h | 1.67 mg/kg/q8h | 2.5 mg/kg/q12h | 5 mg/kg/q24h |
| 0.25 | 91.6 | 94.6 | 99.2 | 95.5 | 97.7 | 99.1 | 97.7 | 98.1 | 99.4 |
| 0.5 | 57.3 | 75.7 | 93.8 | 77 | 88.6 | 97.2 | 87.3 | 93.5 | 98.0 |
| 1 | 8.6 | 20.9 | 62.3 | 25.1 | 47.0 | 80.7 | 41.0 | 64.8 | 90.5 |
| 2 | 0.1 | 0.3 | 13.3 | 0.8 | 3.5 | 30.7 | 2.6 | 13.2 | 51.3 |
| 4 | 0 | 0 | 0.5 | 0 | 0 | 2.0 | 0 | 0 | 6.5 |

**Table S5.** Continued.

| MIC | 6 mg/kg/day (%) | | | 7 mg/kg/day (%) | | | 8 mg/kg/day (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2 mg/kg/q8h | 3 mg/kg/q12h | 6 mg/kg/q24h | 2.33 mg/kg/q8h | 3.5 mg/kg/q12h | 7 mg/kg/q24h | 2.66 mg/kg/q8h | 4 mg/kg/q12h | 8 mg/kg/q24h |
| 0.25 | 99.1 | 98.6 | 99.3 | 99.0 | 99.4 | 100.0 | 98.7 | 99.5 | 99.4 |
| 0.5 | 92.6 | 96.7 | 98.5 | 95.5 | 97.5 | 99.1 | 95.8 | 98.3 | 99.3 |
| 1 | 57.9 | 75.4 | 93.2 | 69.2 | 82.5 | 96.4 | 76.2 | 87.2 | 97.3 |
| 2 | 8.1 | 21.4 | 61.7 | 14.5 | 33.5 | 74.8 | 24.4 | 44.7 | 82.8 |
| 4 | 0.1 | 1 | 14.1 | 0.4 | 2.5 | 22.5 | 0.8 | 4.6 | 33.8 |

**Table S5.** Continued.

| MIC | 10 mg/kg/day (%) | | | 12 mg/kg/day (%) | | |
|---|---|---|---|---|---|---|
| | 3.33 mg/kg/q8h | 5 mg/kg/q12h | 10 mg/kg/q24h | 3 mg/kg/q8h | 4 mg/kg/q12h | 12 mg/kg/q24h |
| 0.25 | 99.1 | 99.5 | 99.7 | 99.7 | 99.6 | 99.9 |
| 0.5 | 97.4 | 98.8 | 99.5 | 97.9 | 99.5 | 99.8 |
| 1 | 87.4 | 94.1 | 98.6 | 90.5 | 96.4 | 98.8 |
| 2 | 37.7 | 62.2 | 89.5 | 54.5 | 77.4 | 94.2 |
| 4 | 2.7 | 11.3 | 49.4 | 8.2 | 20.2 | 65.8 |

*MIC*, Minimum inhibitory concentration; *q8h*, every 8 hours; *q12h*, every 12 hours, *q24h*, every 24 hours.

**Table S6.** Probability of target attainment of $C_{max}$/MIC >10 on the 3rd dose based on different MIC values and MDD and ODD dosing regimens of gentamicin.

| MIC | 3 mg/kg/day (%) | | | 4 mg/kg/day (%) | | | 5 mg/kg/day (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 mg/kg/q8h | 1.5 mg/kg/q12h | 3 mg/kg/q24h | 1.33 mg/kg/q8h | 2 mg/kg/q12h | 4 mg/kg/q24h | 1.67 mg/kg/q8h | 2.5 mg/kg/q12h | 5 mg/kg/q24h |
| 0.25 | 84.7 | 91.3 | 98.2 | 92.6 | 96.9 | 98.7 | 92.6 | 97.4 | 99.4 |
| 0.5 | 37.5 | 60.1 | 89.2 | 61.1 | 78.8 | 94.2 | 61.1 | 88.4 | 97.4 |
| 1 | 2.1 | 8.5 | 46.2 | 9.5 | 27.8 | 67.2 | 22.4 | 44.7 | 82.0 |
| 2 | 0 | 0 | 5.9 | 0 | 0.6 | 15.5 | 0.2 | 4.3 | 32.8 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0.8 | 0 | 0 | 2.0 |

**Table S6.** Continued.

| MIC | 6 mg/kg/day (%) | | | 7 mg/kg/day (%) | | | 8 mg/kg/day (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2 mg/kg/q8h | 3 mg/kg/q12h | 6 mg/kg/q24h | 2.33 mg/kg/q8h | 3.5 mg/kg/q12h | 7 mg/kg/q24h | 2.66 mg/kg/q8h | 4 mg/kg/q12h | 8 mg/kg/q24h |
| 0.25 | 96.1 | 98.4 | 99.0 | 97.8 | 98.9 | 99.8 | 98.3 | 99.3 | 99.4 |
| 0.5 | 77.1 | 92.8 | 97.8 | 85.7 | 96.0 | 98.2 | 92.0 | 97.1 | 98.9 |
| 1 | 22.4 | 60.8 | 86.5 | 38.7 | 73.0 | 92.5 | 61.0 | 77.8 | 94.6 |
| 2 | 0.2 | 10.2 | 47.0 | 2.2 | 18.2 | 60.1 | 12.0 | 26.1 | 71.2 |
| 4 | 0 | 0.3 | 6.1 | 0 | 0.8 | 11.3 | 0 | 1.1 | 19.1 |

**Table S6.** Continued.

| MIC | 10 mg/kg/day (%) | | | 12 mg/kg/day (%) | | |
|---|---|---|---|---|---|---|
| | 3.33 mg/kg/q8h | 5 mg/kg/q12h | 10 mg/kg/q24h | 3 mg/kg/q8h | 4 mg/kg/q12h | 12 mg/kg/q24h |
| 0.25 | 98.9 | 99.5 | 99.7 | 99.6 | 99.6 | 99.9 |
| 0.5 | 96.2 | 98.3 | 99.1 | 97.1 | 98.7 | 99.6 |
| 1 | 76.0 | 89.2 | 97.1 | 83.7 | 92.6 | 98.5 |
| 2 | 20.5 | 43.7 | 80.6 | 35.6 | 59.7 | 90.0 |
| 4 | 0.4 | 3.9 | 31.6 | 2.7 | 9.1 | 46.3 |

*MIC*, Minimum inhibitory concentration; *q8h*, every 8 hours; *q12h*, every 12 hours, *q24h*, every 24 hours.

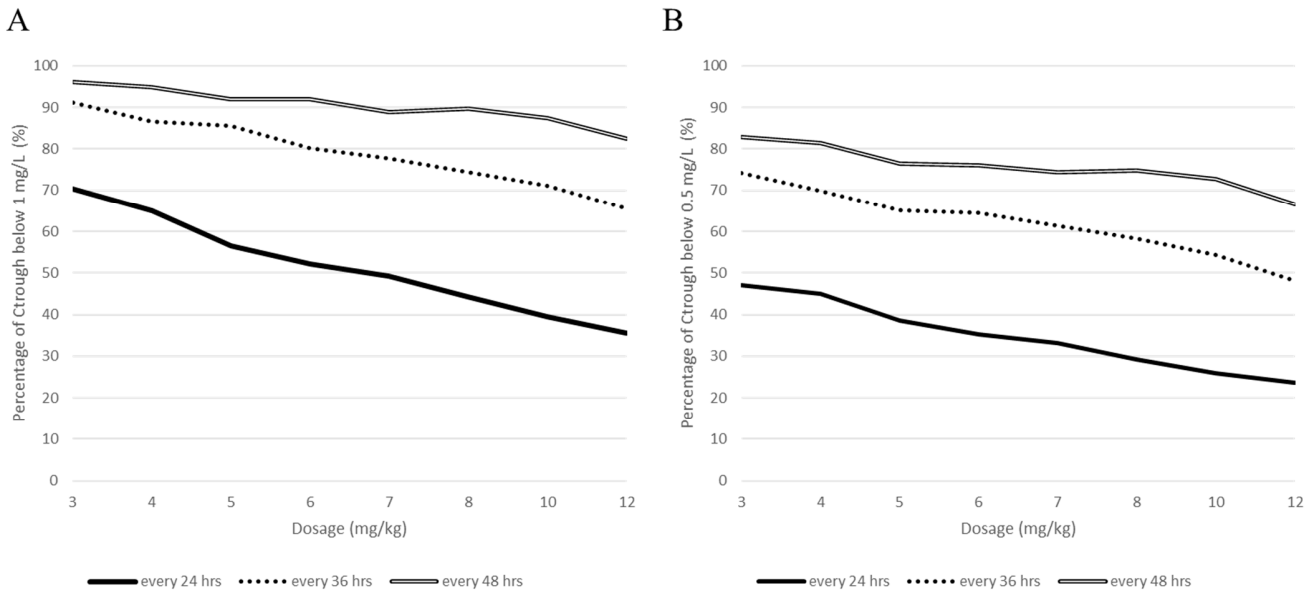


**Figure S3.** Percentage of $C_{trough}$ following different dosage regimens (every 24 hours, every 36 hours and every 48 hours) and dosing interval below **A.** 1 mg/L **B.** 0.5 mg/L.

**Table S7.** Percentage of $C_{trough}$ below 1 mg/L or 0.5 mg/L before the 4th administration following different dosage regimens and dosing interval below.

| $C_{trough}$ | 3 mg/kg (%) | | | | | 4 mg/kg (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (mg/L) | Q8h | Q12h | Q24h | Q36h | Q48h | Q8h | Q12h | Q24h | Q36h | Q48h |
| < 1 | 4.8 | 18.9 | 70.3 | 91.1 | 96.1 | 3.6 | 14.3 | 65.0 | 86.7 | 95.0 |
| < 0.5 | 1.5 | 8.9 | 47.0 | 74.2 | 82.8 | 1.7 | 6.8 | 45.0 | 69.9 | 81.5 |

**Table S7** Continued.

| | 5 mg/kg (%) | | | | | 6 mg/kg (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $C_{trough}$ (mg/L) | Q8h | Q12h | Q24h | Q36h | Q48h | Q8h | Q12h | Q24h | Q36h | Q48h |
| < 1 | 2.9 | 9 | 56.5 | 85.6 | 92.0 | 2.2 | 8.8 | 52.1 | 80.3 | 92.0 |
| < 0.5 | 1.2 | 4.5 | 38.5 | 65.1 | 76.4 | 0.9 | 3.7 | 35.2 | 64.5 | 76.0 |

**Table S7** Continued.

| $C_{trough}$ | 7 mg/kg (%) | | | | | 8 mg/kg (%) | | |
|---|---|---|---|---|---|---|---|---|
| (mg/L) | Q8h | Q12h | Q24h | Q36h | Q48h | Q24h | Q36h | Q48h |
| < 1 | 2.5 | 6.9 | 49.3 | 77.7 | 89.0 | 44.2 | 74.3 | 89.8 |
| < 0.5 | 1.3 | 3.6 | 33.1 | 61.3 | 74.4 | 29.3 | 58.3 | 74.8 |

**Table S7** Continued.

| $C_{trough}$ (mg/L) | 10 mg/kg (%) | | | 12 mg/kg (%) | | |
|---|---|---|---|---|---|---|
| | Q24h | Q36h | Q48h | Q24h | Q36h | Q48h |
| < 1 | 39.6 | 71.1 | 87.5 | 35.6 | 65.5 | 82.4 |
| < 0.5 | 25.9 | 54.4 | 72.8 | 23.6 | 48.1 | 66.6 |

*$C_{trough}$*, concentration before the 4th administration; *MIC*, Minimum inhibitory concentration; *q8h*, every 8 hours, *q12h*, every 12 hours, *q24h*, every 24 hours; *q36h*, every 36 hours; *q48h*, every 48 hours .