SUPPLEMENTAL MATERIAL

Dose	24 h-interval		36 h-interval		48 h-interval		72 h-interval	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
Proportion of patient with target trough concentrations ≥ 1 mg/L								
4 mg/kg	40	49	8	15	1	4	0	0
7.5 mg/kg	75	77	35	40	13	17	1	3
Proportion of patients with target trough concentrations ≥ 2 mg/L								
4 mg/kg	4	16	0	2	0	0	0	0
7.5 mg/kg	36	46	6	13	0	3	0	0

Table S1: Proportion of patients with target trough concentrations of ≥ 1 mg/L and ≥ 2 mg/L for dosing intervals after first dose first and after one week of treatment. The same dosing regimen is given to the entire population.

AUC/MIC ratio	% Neonates achieving ratio after 4 mg/kg per 24h/36h (MIC 0.5 mg/L)	% Neonates achieving ratio after 7.5 mg/kg per 36h/48h (MIC 1.0 mg/L)
≥ 37	99.8	99.8
≥ 67	94.4	94.6
≥ 80	88.2	89.1

Table S2: Proportion of patients achieving AUC/MIC ratios, as proposed by Nielsen et al. (1) or Turnidge et al. (2) after 4 mg/kg or 7.5 mg/kg dose according to different subgroups based on PNA and GA. AUC; area under the curve, MIC; minimum inhibition concentration, PNA; postnatal age, GA; gestational age.

Pathogen	MIC breakpoint (mg/L)
Enterobacteriaceae	2.0
Pseudomonas spp.	4.0
Acinetobacter spp.	4.0
Staphylococcus spp. (s. aureus)	1.0
Staphylococcus spp. (CoNS)	1.0

Table S3: Pathogens with their corresponding minimum inhibitory concentrations breakpoints (MIC). Source: EUCAST; Clinical breakpoints, (Update 2017-03-13).

Germovsek *et al.* model prediction comparison according to two other models:

Concentration predictions based on Germovsek *et al.* model were compared to two other model predictions. The model of Nielsen *et al.* 2009 and Fuchs *et al.* 2014 were chosen as they included gestational age on volume of distribution. A two-compartmental model was used (Fuchs *et al.*) vs. three-compartmental model (Germovsek et *al.* and Nielsen et *al.*) to investigate whether the difference in distribution characterization could have influenced the predictions. Model description is presented in Table S4 and results are illustrated in figures S6-S8.

Author	Germovsek et al.	Nielsen et al.	Fuchs et al.
Data	Multi-center (3), prospective data collection. MB datasets with 1325 serum concentrations & ME dataset with 483 serum concentrations.	Single center, prospective data collection. 894 serum concentrations	Single center, retrospective data collection. MB dataset with 3039 serum concentrations. Not specified for ME.
Structure	3 CMT, linear elimination.	3 CMT, linear elimination.	2 CMT, linear elimination.
Population (median, [min, max])	205 neonates (MB) 163 neonates (ME) † WT; 2.12 [0.53-5.05]* GA; 34 [23.3-42.1]* PNA; 5.4 [1-66]* PMA; 33 [23.3-43.8]*	61 newborns WT; 1.4 [0.495- 5.05] GA; 28.9 [23.3-42.1] PNA; 1 [0-45] PMA; not specified	1449 neonates (MB) 69 neonates (ME) WT; 2.17 [4.4-5.51]* GA; 34 [24-42]* PNA; 1 [1-94]* PMA; 34.4 [24.2-42.4]*
Covariates included	WT, PMA, PNA, SCr on CL. WT on V.	WT, GA, PNA on CL. WT, GA on V.	WT, GA, PNA, DOPA on CL. WT, GA on V.
Identified IIV (CV %)	CL (41.8), V (33.5), V2 (36.3), V3 (42.1)	CL (21.6).	CL (28), V (18).
Parameter estimates ARPEC dataset (median, [min, max])	CL; 0.098 [0.008, 0.899] V1; 0.8 [0.1, 3.3] Cmax; 15.6 [5.7, 35.6] ‡ Cmin; 0.5 [0.009, 2.898] ‡	CL; 0.098 [0.005, 0.618]) V1; 0.8 [0.2, 1.8] Cmax; 16.1 [11.4, 19.6] ‡ Cmin; 0.3 [0.005, 1.944] ‡	CL; 0.12 [0.006, 0.761] V1; 0.9 [0.2, 3.0] Cmax; 14.2 [6.9, 34.8] ‡ Cmin; 0.4 [0.005, 4.452] ‡
Notes	Data from Nielsen et al., Thomson et al. and Methsvaht et al. (unpublished) used for MB	Data used in the MB of Germovsek et al.	

Table S4: MB; model building, ME; model evaluation, CMT; compartment, WT; weight (kg), GA; gestational age (weeks), PNA; post-natal age (days), PMA; post menstrual age (weeks), SCr; serum creatinine concentration (µmol/L), DOPA; Dopamine, CL; Clearance (L/h), V; Volume of distribution (L), IIV; inter-individual variability. * MB population characteristics. † Prospective collection from five hospitals. ‡ Cmax and Cmin concentrations after 7.5 mg/kg dose every 36h or 48h based on PNA (7 days) and GA (28 weeks).

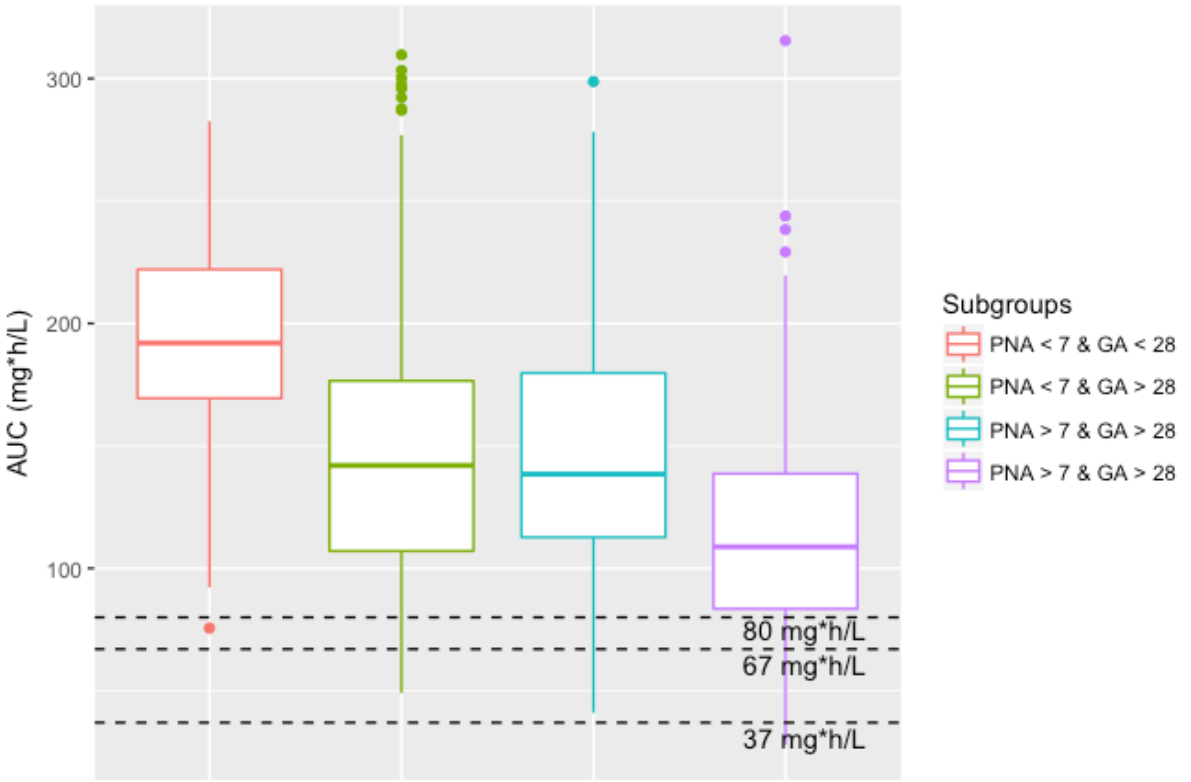

Figure S1: Distribution of area under the curve after single 7.5 mg/kg gentamicin dose over 48h interval (PNA < 7 days or PNA ≥ 7 days & GA ≤ 28 weeks) or 36h interval (PNA ≥ 7 days & GA > 28 weeks). AUC; area under the curve, PNA; post-natal age, GA; gestational age. Boxes represent the interquartile range (IQR) solid lines are the median, 25th and 75th quantile and whiskers equal 25th quantile - 1.5 IQR and 75th quantile +1.5 IQR.

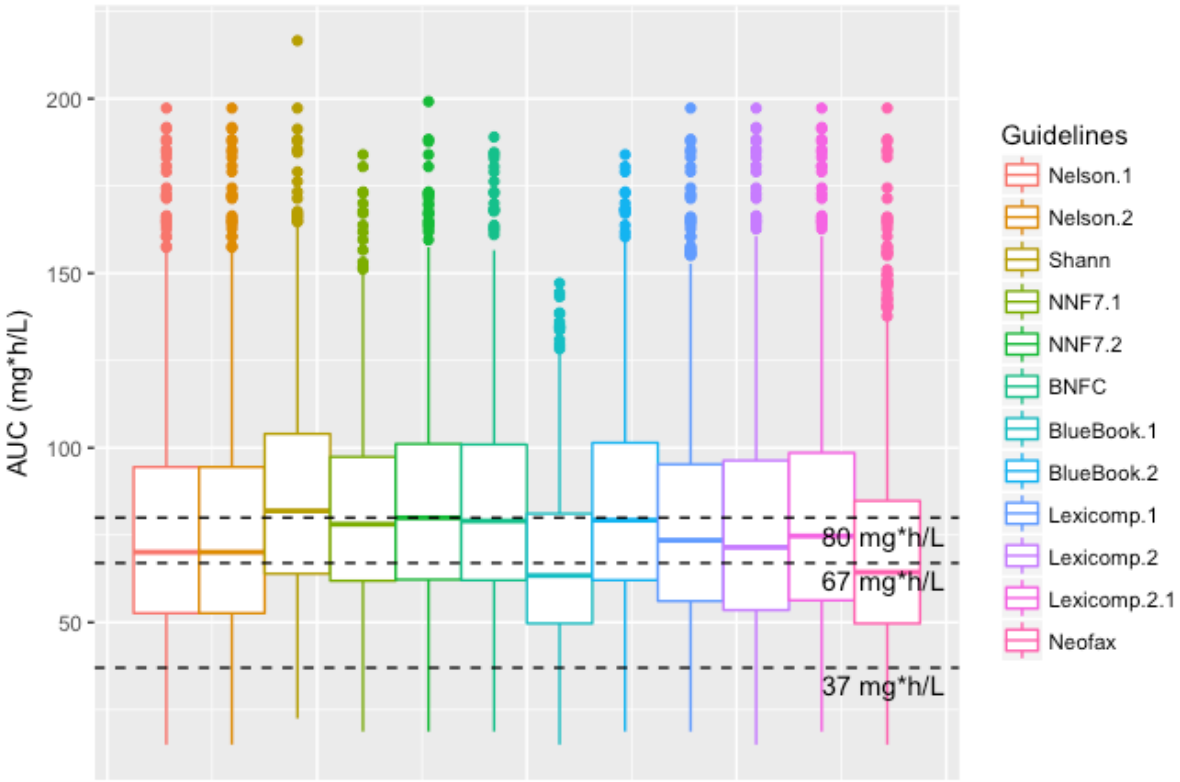

Figure S2: Distribution of area under the curve according to dosing regimen applied in international guidelines. Boxes represent the interquartile range (IQR) solid lines are the median, 25th and 75th quantile and whiskers equal 25th quantile - 1.5 IQR and 75th quantile +1.5 IQR. AUC; area under the curve, BNFc; British National Formulary for Children, Blue Book; Manual of childhood infections Blue Book, Nelson; Nelson Textbook of Pediatrics, NNF7; Neonatal Formulary 7th edition, Lexicomp; Lexicomp Pediatric & Neonatal Dosage Handbook, Red Book; Red Book report of the Committee on Infectious Diseases, Shann; Frank Shann Drug Doses.

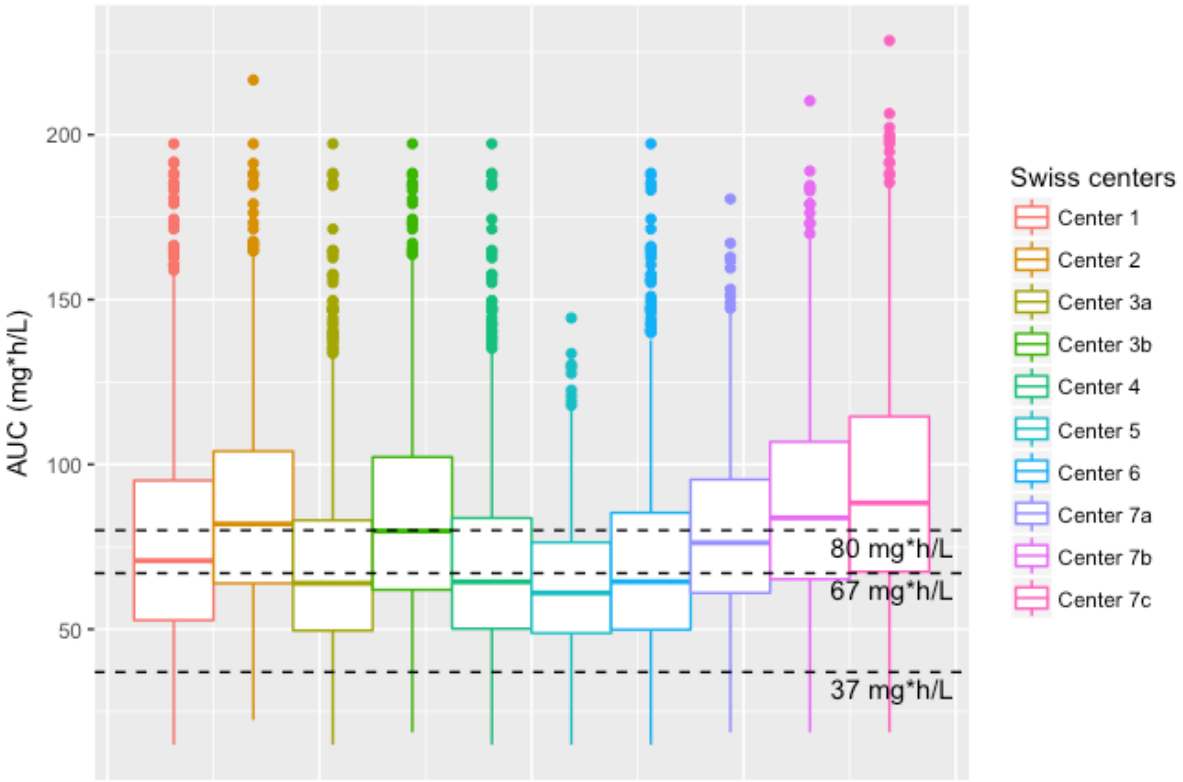

Figure S3: Distribution of area under the curve (AUC) according to dosing regimen applied in Swiss centers. Boxes represent the interquartile range (IQR) solid lines are the median, 25th and 75th quantile and whiskers equal 25th quantile - 1.5 IQR and 75th quantile +1.5 IQR.

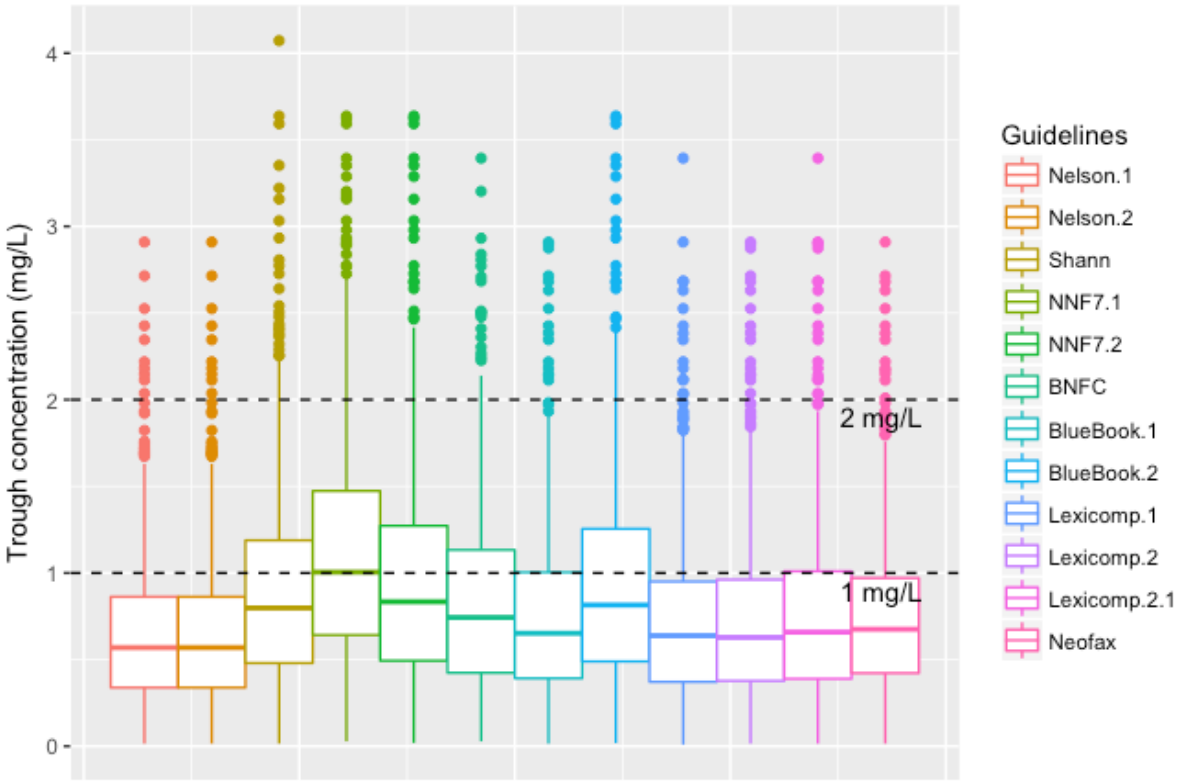

Figure S4: Distribution of simulated trough concentrations according to dosing regimen applied in international guidelines. Boxes represent the interquartile range (IQR) solid lines are the median, 25th and 75th quantile and whiskers equal 25th quantile - 1.5 IQR and 75th quantile +1.5 IQR. BNFc; British National Formulary for Children, Blue Book; Manual of childhood infections Blue Book, Nelson; Nelson Textbook of Pediatrics, NNF7; Neonatal Formulary 7th edition, Lexicomp; Lexicomp Pediatric & Neonatal Dosage Handbook, Red Book; Red Book report of the Committee on Infectious Diseases, Shann; Frank Shann Drug Doses.

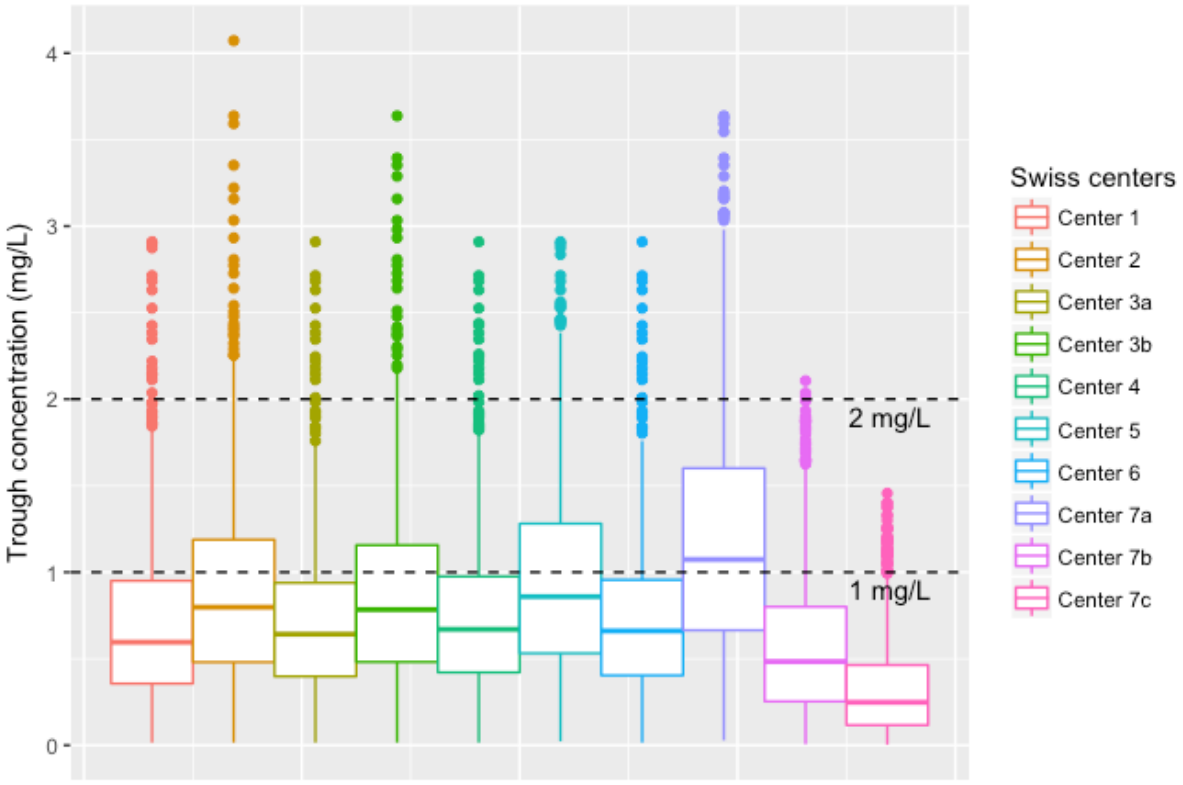

Figure S5: Distribution of simulated trough concentrations according to dosing regimen applied in Swiss centers. Boxes represent the interquartile range (IQR) solid lines are the median, 25th and 75th quantile and whiskers equal 25th quantile - 1.5 IQR and 75th quantile +1.5 IQR.

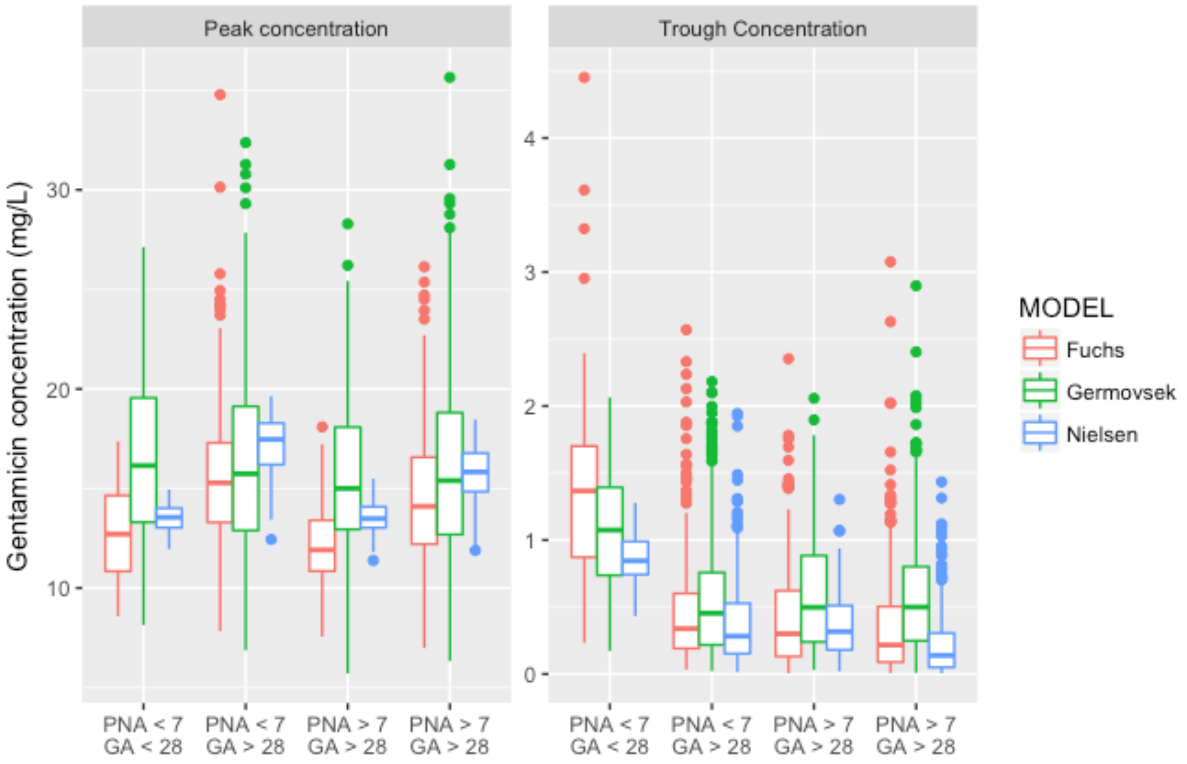

Figure S6: Distribution of peak and trough concentration after single 7.5 mg/kg gentamicin dose over 48h interval (PNA < 7 days or PNA ≥ 7 days & GA ≤ 28 weeks) or 36h interval (PNA ≥ 7 days & GA > 28 weeks) for three different gentamicin PK models. PNA; post-natal age, GA; gestational age. Boxes represent the interquartile range (IQR), solid lines are the median, 25th and 75th quantile and whiskers equal 25th quantile -1.5 IQR and 75th quantile + 1.5 IQR.

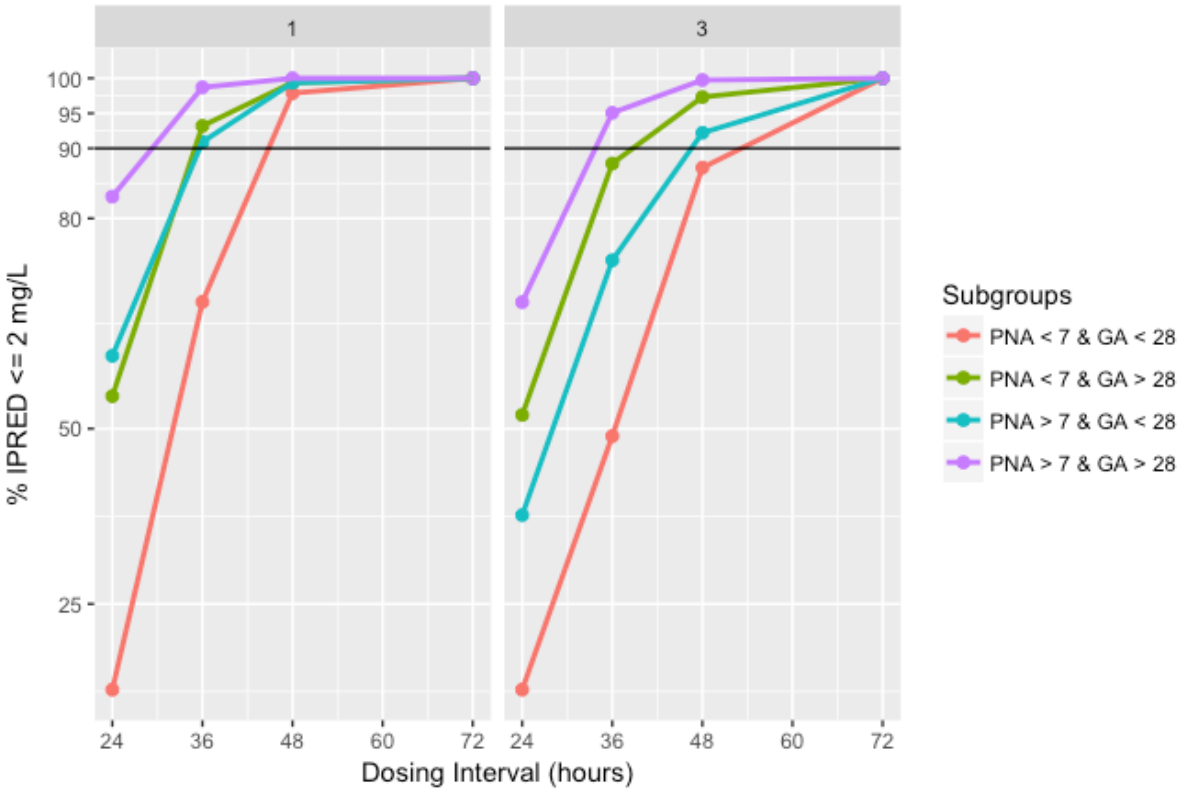

Figure S7: Percentage of patients achieving trough levels above 2 mg/L after first dose (1) or one week of treatment (3). Different colors represent subgroups after single 7.5 mg/kg gentamicin dose over 48h interval (PNA < 7 days or PNA ≥ 7 days & GA ≤ 28 weeks) or 36h interval (PNA ≥ 7 days & GA > 28 weeks). IPRED; Individual concentration predictions, PNA; post-natal age, GA; gestational age.

1. **Nielsen EI, Cars O, Friberg LE.** 2011. Pharmacokinetic/pharmacodynamic (PK/PD) indices of antibiotics predicted by a semimechanistic PKPD model: a step toward model-based dose optimization. Antimicrobial agents and chemotherapy **55:**4619-4630.
2. **Turnidge J.** 2003. Pharmacodynamics and dosing of aminoglycosides. Infectious disease clinics of North America **17:**503-528.