

## Supplementary file for

### **Dosing recommendations for vancomycin in children and adolescents with varying levels of obesity and renal dysfunction: a population pharmacokinetic study in 1892 children aged 1 – 18 years**

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## 1. Methods – pharmacokinetic analysis

### *Covariates*

Available covariates were age, total body weight (TBW), length, gender, race, ICU-stay, serum creatinine, absolute neutrophil count, absolute lymphocyte count and C-reactive protein (CRP).

Body weight related to growth ( $WT_{\text{for age and length}}$ ) and excess body weight ( $WT_{\text{excess}}$ ), were calculated according to equation 1 and 2 (adapted from Van Rongen et al. (1)):

$$WT_{\text{age and length}} = BMI_{\text{for age and gender}} \times \text{length}^2 \quad (S1)$$

$$WT_{\text{excess}} = TBW - WT_{\text{age and length}} \quad (S2)$$

Where TBW is total body weight in kg, length in cm and  $BMI_{\text{for age and gender}}$  is the p50 BMI value based on the gender specific WHO or CDC BMI-for-age growth charts for 1 – 2 years and 2 – 18 years, respectively (2, 3).

If a patient's height was unknown, height was imputed using the median value of the CDC height-for-age chart (2). This was done for 18 individuals, corresponding to 0.95% of the total amount of analyzed individuals.

Body Surface Area (BSA) was calculated using the Mosteller equation (4).

FFM was estimated using the equations of Al-Sallami and Peters (5, 6).

Serum creatinine, quantified using IDMS Traceable Vitros CREA Slides and the Vitros 5.1 FS Chemistry System analyzer (Ortho Clinical Diagnostics, Inc, Rochester, New York), was included when measured within 168 h before or after a vancomycin dose. All serum creatinine values within this time-window were retained in the dataset and analyzed as time-varying covariates. Within an individual, missing creatinine values were imputed using a next-observation-carried-backward strategy where typical values were imputed using the equation from Ceriotti et al. in case no creatinine values were available for an individual (15.6% of the individuals) (7).  $CL_{Cr}$  was estimated using the bedside Schwartz equation and was studied both expressed in mL/min/1.73 m<sup>2</sup> (8) and deindexed by multiplication with BSA/1.73 ( $CL_{Cr\_di}$ ), according to equations (S3) and (S4):

$$CL_{Cr} \text{ (in ml/min/1.73 m}^2\text{)} = k * \text{length (in cm)} / \text{serum creatinine (in mg/dL)} \quad (S3)$$

$$CL_{Cr\_di} \text{ (in ml/min)} = CL_{Cr} * \text{body surface area (BSA, in m}^2\text{)} / 1.73 \quad (S4)$$

Where k is a variable fixed to 0.41 in the revised bedside Schwartz equation used in this study. In addition, we also tried to re-estimate k during covariate analysis.

We also calculated the ratio between the observed and typical creatinine value for age (creatinine-ratio).

Neutropenia was defined as an absolute neutrophil count  $<1.5 * 10^9$  cells/L blood.

## Modeling strategy

Log-transformed vancomycin serum concentrations were analyzed using non-linear mixed-effects modelling (NONMEM v7.4, Icon Development Solutions, Ellicott City, MD, USA (9)) with Perl-speaks-NONMEM (v4.9.0) and the Pirana (v2.9.9) interface (10, 11). R (v3.6.1) and Rstudio (v1.2.1335) were used for data manipulation and visualization. Vancomycin measurements reported as being below the limit of quantification (0.7% of the observations) or drawn within 1 hour after the start of the infusion (n = 218 samples, 3.7% of the observations) were excluded. Patients were analyzed as separate individuals when age increased with  $\geq 10\%$  or when there was  $\geq 14$  days between vancomycin administrations. Population pharmacokinetic modelling was conducted using first-order conditional estimation with inter-individual variability assumed to be log-normally distributed. One- two- and three-compartment models with additive, proportional, or a combined error model were evaluated. Nested models were compared using the objective function value (OFV, i.e.  $-2\log$  likelihood ( $-2LL$ )). For structural and statistical models, a drop  $\geq 3.84$ , corresponding to a p-value of  $< 0.05$  for one degree of freedom, was considered statistically significant. Models were evaluated by inspection of goodness-of-fit plots (observed versus individual or population predicted vancomycin concentrations, conditional weighted residuals versus time after dose or population predicted vancomycin concentrations), which were split for age, weight and renal function. Lastly, the precision of parameter estimates, shrinkage, and the conditional number (ratio between the highest and lowest eigenvalue) were taken into consideration.

For the covariate analysis, potential covariates were identified based on inter-individual variability versus covariate plots. Continuous covariates were entered into the model using equation (S5) for exponential relations and (S6) for linear relations:

$$P_i = P_p \times \left( \frac{COV}{COV_{standard}} \right)^X \quad (S5)$$

$$P_i = P_p \times (1 + Y \times (COV - COV_{median})) \quad (S6)$$

where  $P_i$  and  $P_p$  are the individual and population parameter estimates,  $COV$  is the covariate value,  $COV_{median}$  is the median value for the covariate.  $X$  represents the exponent for a power function, and  $Y$  is the slope parameter for the linear covariate relationship. Linear covariate relations could also be entered into the model by using equation 3 with  $X$  fixed to 1. As it has been shown that with body weight as a covariate the scaling factor  $X$  may decrease with age for clearance in children (12), for  $X$  also a body weight-dependent exponent (BDE) according to equation (S7) was tested (13, 14):

$$X = F \times TBW_i^Z \quad (S7)$$

where  $TBW_i$  is the individual's total body weight,  $F$  is the intercept of the scaling exponent, and  $Z$  is the exponent that allows the scaling exponent to change with body weight.

A  $WT_{excess}$  covariate model was tested using equation (S8), as described earlier (1, 15):

$$P_i = P_p \times \left( \frac{WT_{age \text{ and length}}}{TBW_{median}} \right)^U + (V \times WT_{excess}) \quad (S8)$$

where  $P_i$  and  $P_p$  are the individual and population parameter estimates,  $WT_{\text{age and length}}$  is the body weight related to growth (equation 1),  $WT_{\text{excess}}$  the excess body weight (equation 2),  $TBW_{\text{median}}$  is the median total body weight,  $U$  is the scaling exponent for  $WT_{\text{age and length}}$  (either fixed to 0.75 or estimated),  $V$  represents the linear influence of  $WT_{\text{excess}}$  on the parameter value. Categorical covariates were entered into the model by calculating a separate pharmacokinetic parameter for each category of the covariate.

Inclusion of a covariate was justified upon assessing the OFV drop ( $\geq 10.8$  points, corresponding with  $p < 0.001$ ) between models with or without this covariate. Also, goodness-of-fit plots were reviewed as described earlier with specific emphasis on the plots split for age (1 – 2, 2 – 12 and 12 – 18 years), estimated  $Cl_{cr}$  ( $< 30$ , 30 – 60, 60 – 90 and  $> 90$  mL/min/1.73 m<sup>2</sup>) and weight group (normal weight, overweight and obese). Lastly, it was assessed whether the inter-individual variability decreased, and if trends in the inter-individual variability versus covariate plot disappeared.

The resulting final model was internally validated by assessment of normalized prediction distribution errors (NPDE) ( $n = 10,000$  datasets) and prediction and variability corrected visual predictive check (pvcVPC) ( $n = 500$  datasets). These diagnostics were split for age group (1 – 2, 2 – 12 and 12 – 18 years), estimated renal function ( $< 30$ , 30 – 60, 60 – 90 and  $> 90$  mL/min/1.73 m<sup>2</sup>) and weight group (normal weight, overweight and obese) (16). Parameter precision of the structural and final model was analyzed by the sampling importance resampling (SIR) procedure (17).

## 2. Results – pharmacokinetic analysis

A two-compartment model with inter-individual variability on clearance (CL) and peripheral volume of distribution (V2) with a proportional residual error model best described the data.

In the covariate analysis, we found an important influence of both renal function expressed using Schwartz formula ( $CL_{cr}$ ) and total body weight (TBW) on CL. Vancomycin CL was best described by linear implementation of  $CL_{cr}$  which was maximized at 120 mL/min/1.73 m<sup>2</sup> and a power equation for TBW ( $\Delta OFV$  -2356.1 compared to the structural model without covariates [ $p < 0.001$ ]). Higher cut-off values or no capping of  $CL_{cr}$  lead to a significantly worse fit ( $\Delta OFV$  +413.1, +15.6, +91.6, for models without capping or capping at 140 or 160 mL/min/1.73 m<sup>2</sup>, respectively [all  $p < 0.001$ ], compared to a model where  $CL_{cr}$  was capped at 120 mL/min/1.73 m<sup>2</sup>). This combined covariate model outperformed models with the separate implementation of TBW or  $CL_{cr}$ , i.e. TBW on CL with a power function ( $\Delta OFV$  -1125.7 [ $p < 0.001$ ] compared with the structural model without covariates), TBW on CL with a body weight-dependent exponent ( $\Delta OFV$  -1180.9 [ $p < 0.001$ ] compared with the structural model without covariates) and  $CL_{cr\_di}$  on CL using a power function ( $\Delta OFV$  -2230.3 [ $p < 0.001$ ] compared with the structural model without covariates). The model with  $CL_{cr}$  and TBW on CL was also superior over a model where TBW was combined with creatinine or creatinine-ratio as a covariate on CL, all with a power equation ( $\Delta OFV$  -2126.9 or -2083.5, respectively, [both  $p < 0.001$ ] compared with the structural model without covariates). Re-estimating the value  $k$  in the Schwartz-equation did not significantly improve the model compared to using the standard value of 0.413 in the original bedside Schwartz-equation ( $\Delta OFV$  of -4.5 [ $p > 0.01$ ] compared to using a fixed value of 0.413).

A covariate model that uses  $WT_{age\ and\ length}$  and  $WT_{excess}$  (equation 6) instead of TBW resulted in a similar OFV and goodness-of-fit as the model with only TBW as covariate ( $\Delta OFV$  -1129.2 versus  $\Delta OFV$  -1125.7 compared with the structural model without covariates, respectively [ $p > 0.01$ ]). For the implementation of  $CL_{cr}$ , a model with an estimated exponent compared to a linear model led to similar results regarding the goodness-of-fit and OFV (estimated exponent 0.94,  $\Delta OFV$  -6.1 compared to the model with a linear function with one additional degrees of freedom [ $p > 0.01$ ]). These results indicate that regarding the influence of body weight on vancomycin clearance, the influence of weight from growth is similar to the influence of excess weight. Inclusion of neutropenia as a binary covariate on CL did not improve the model ( $\Delta OFV$  +0.8 compared to the model with TBW and  $CL_{cr}$  on CL [ $p > 0.05$ ]). No other covariates for CL could be identified.

Both V1 and V2 were significantly influenced by TBW in a linear function ( $\Delta OFV$  -830.4 [ $p < 0.001$ ] compared to the model without covariates on V1 or V2). There was no significant difference between a linear or a power function with an estimated exponent for TBW (estimated exponent 1.05,  $\Delta OFV$  -2.3 points compared to the model with TBW on V1 and V2 linearly,  $p > 0.05$ ). The model with TBW linearly on V1 and V2 provided a slightly better fit compared to a  $WT_{excess}$  model for V1 and V2 using equation (6), which resulted in an OFV reduction of -813.5 points ( $p > 0.01$ ). The addition of TBW exponentially on Q gave a further improvement in OFV ( $\Delta OFV$  -113.4 [ $p < 0.001$ ]). Lastly, the covariance between CL and V2 was included in the model using an OMEGABLOCK, decreasing OFV with 36 points.

After implementing covariates, inter-individual variability on CL reduced from 52.8% in the structural model without covariates to 28.7% in the final model, and inter-individual variability on V2 slightly increased from 89.4% to 109.5% (shrinkage 57%). As the goodness-of-fit and OFV substantially deteriorated when inter-individual variability for V2 was removed from the model ( $\Delta\text{OFV} +457.2$  [ $p < 0.001$ ]), we decided to retain it in the final PK model.

### 3. Pediatric dosing guidelines used for simulations

*Infectious Diseases Society of America, the American Society of Health-System Pharmacists, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists (IDSA) (18):*

15 mg/kg every 6 hours (max 3600 mg / day). Obese: loading dose 20 mg/kg

*Dutch Paediatric Formulary (19):*

15 mg/kg every 6 hours + GFR 50 – 80: every 24h, GFR 10 – 50 every 48 hours. Maximum 4 gram/day.

*British National Formulary for Children (BNFc) (20):*

< 12y: 10 – 15 mg/kg every 6h (no maximum dose).

12 years and older: 15 mg/kg every 8 hours (maximum 2 g).

#### 4. Supplementary Table

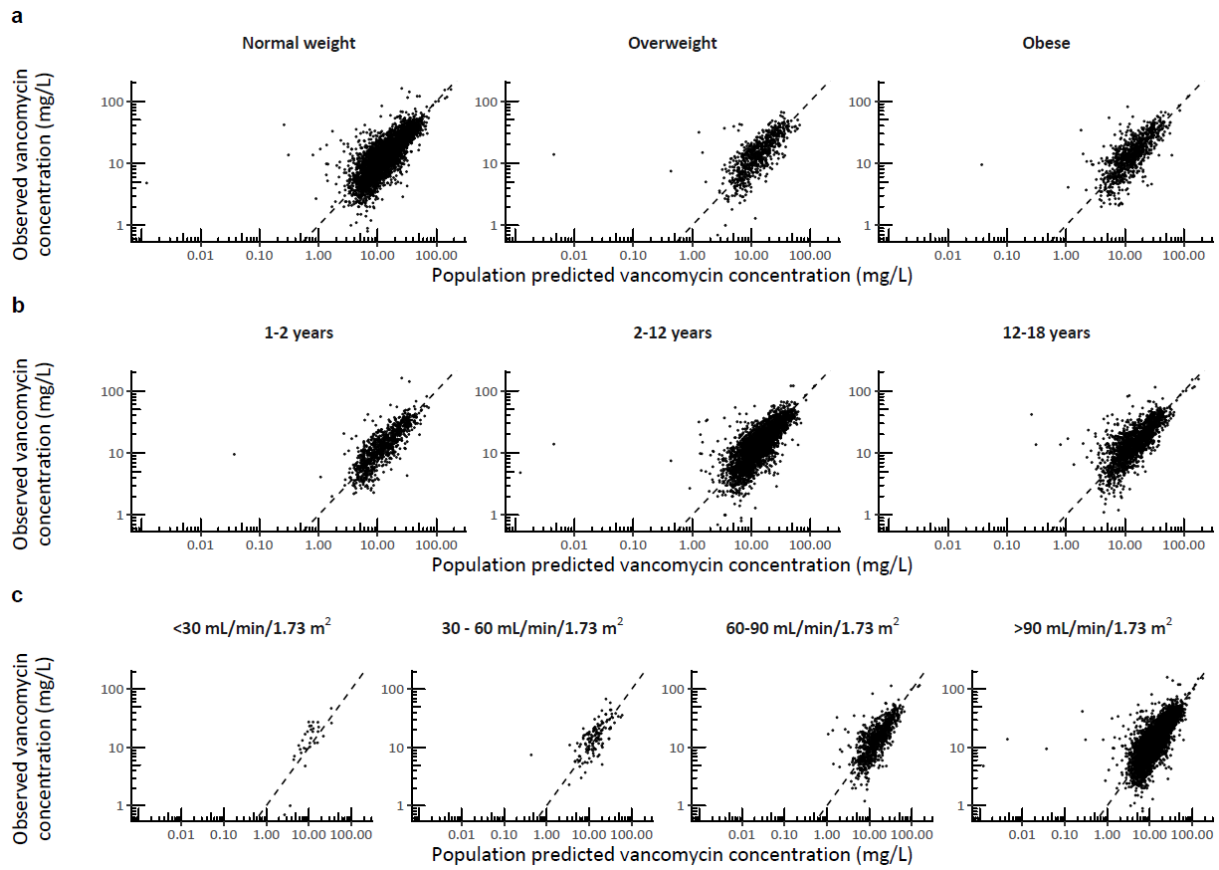
**Table S1.** Dosing guideline for continuous infusion of vancomycin in children and adolescents aged 1 – 18-years based on total body weight and renal function according to bedside Schwartz.

| Schwartz<br>creatinine<br>clearance<br>(mL/min/1.73 m <sup>2</sup> ) | Total body weight (kg)          |                                 |                                 | Relative<br>daily<br>dose (%) |
|----------------------------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|-------------------------------|
|                                                                      | <30                             | 30 -70                          | >70                             |                               |
| >90                                                                  | 60 mg/kg over 24 h <sup>a</sup> | 45 mg/kg over 24 h <sup>a</sup> | 36 mg/kg over 24 h <sup>a</sup> | 100%                          |
| 50 – 90                                                              | 44 mg/kg over 24 h <sup>a</sup> | 33 mg/kg over 24 h <sup>a</sup> | 24 mg/kg over 24 h <sup>a</sup> | 70%                           |
| 30 – 50                                                              | 20 mg/kg over 24 h <sup>a</sup> | 15 mg/kg over 24 h <sup>a</sup> | 12 mg/kg over 24 h <sup>a</sup> | 35%                           |
| 10 – 30                                                              | 10 mg/kg over 24 h <sup>a</sup> | 6 mg/kg over 24 h <sup>a</sup>  | 6 mg/kg over 24 h <sup>a</sup>  | 15%                           |

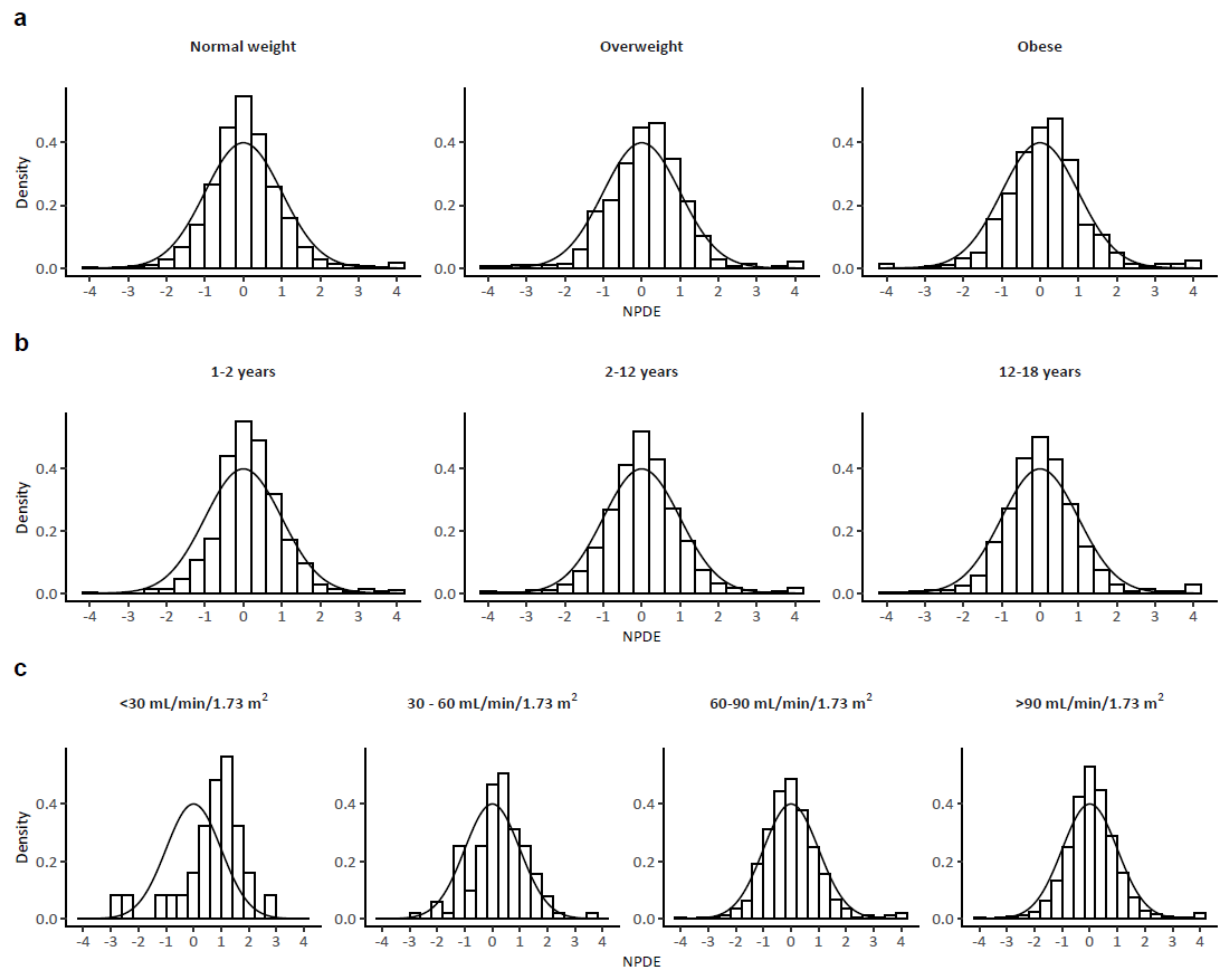
<sup>a</sup>Loading dose is 15 mg/kg, followed after 3 hours with proposed maintenance dose.



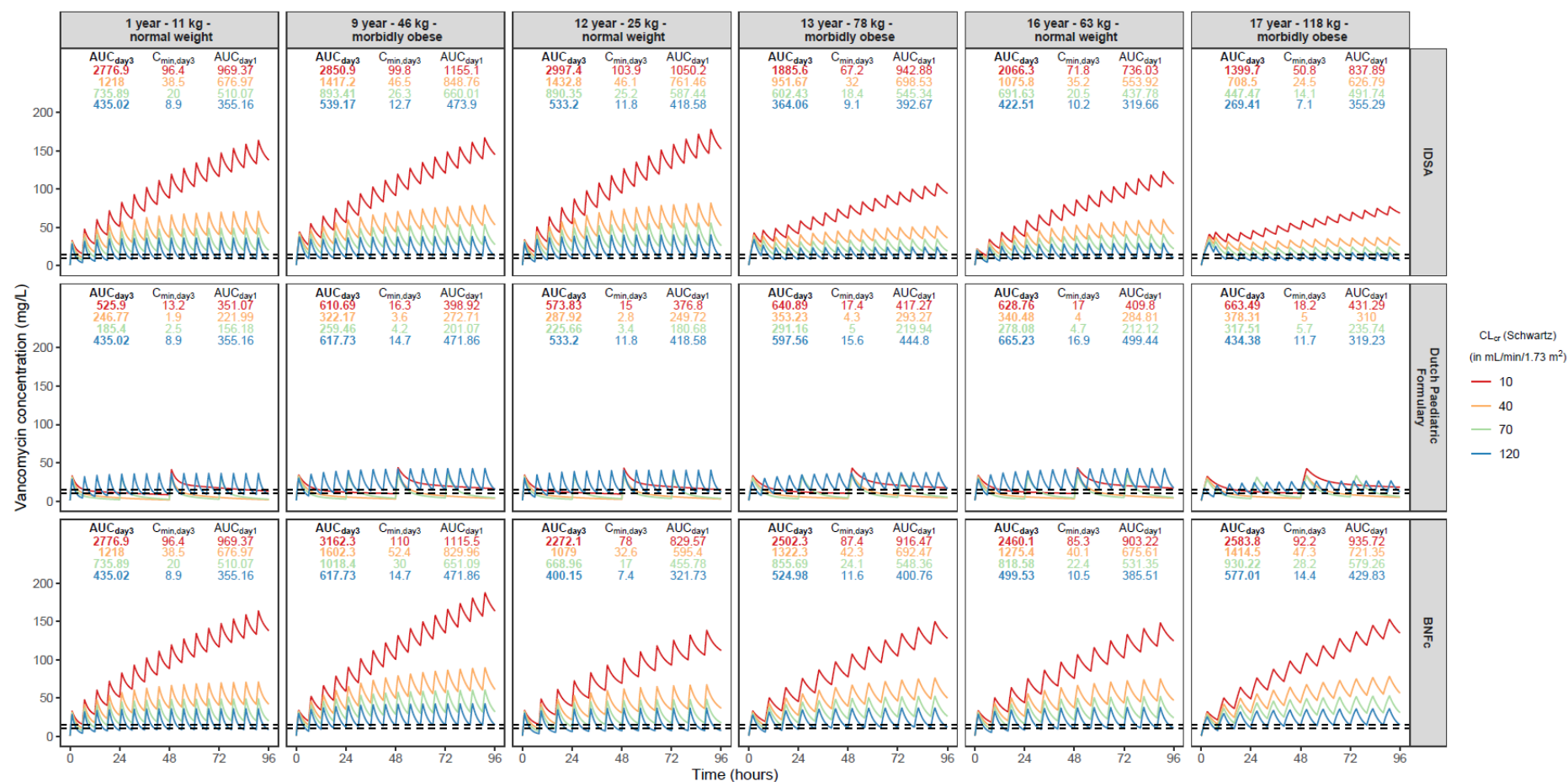
## 5. Supplementary Figures



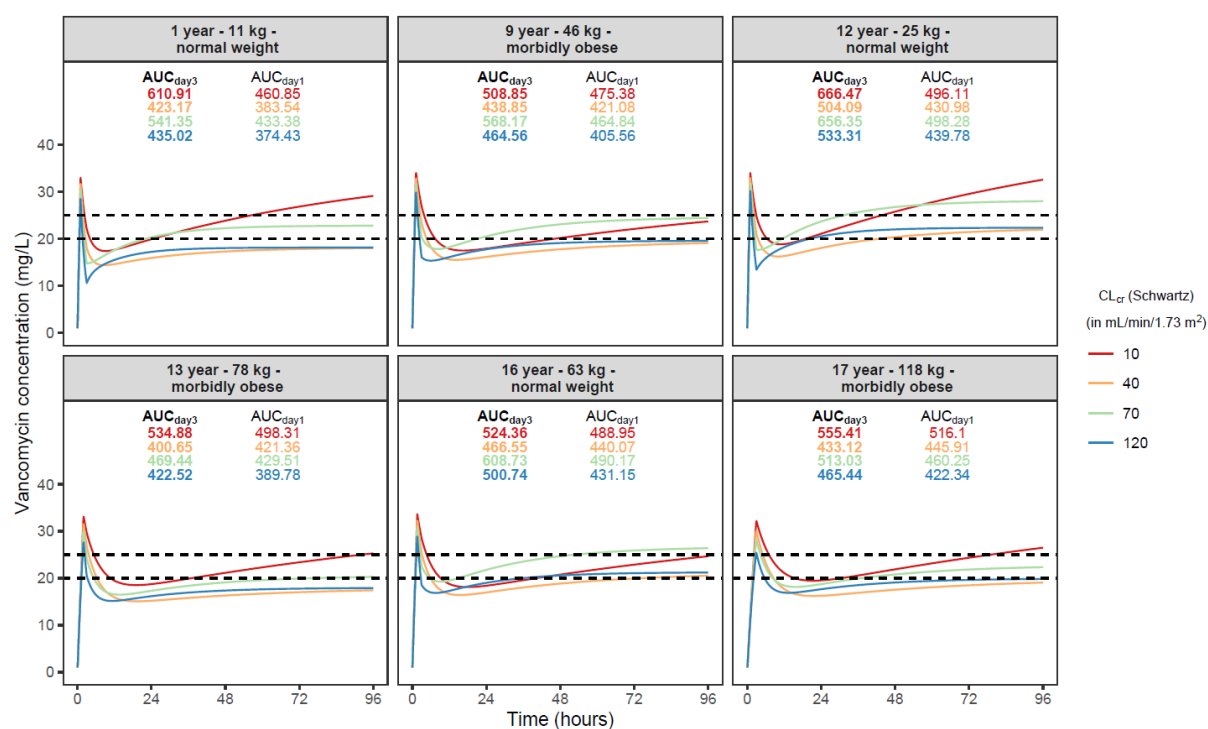
**Figure S1.** Observed versus population predicted vancomycin concentrations for the final model, split for (a) weight group, (b) age group or (c) renal function group (creatinine clearance based on the bedside Schwartz equation).



**Figure S2.** Distribution of the normalized prediction distribution errors (NPDE) for the final model, split for (a) weight group, (b) age group or (c) renal function group (based on the bedside Schwartz equation). The solid line depicts a normal distribution.



**Figure S3.** Vancomycin concentrations (mg/L) versus time (hours) in several typical individuals with bodyweight ranging 10 – 120 kg and renal function ranging 10 – 120 mL/min/1.73 m<sup>2</sup> where vancomycin is dosed according to three existing dosing guidelines: Infectious Diseases Society of America (IDSA, upper panel), Dutch Paediatric Formulary (middle panel) and British National Formulary for Children (BNFC, lower panel). For each individual, AUC (in bold), C<sub>min</sub>, at day 3, as well as AUC at day 1 is shown in the graph (where colour corresponds to the individual's renal function). Dashed lines represent the target concentrations for the trough concentrations (10 – 15 mg/L). AUC area under the curve, C<sub>min</sub> minimum (trough) concentration.



**Figure S4.** Vancomycin concentrations (mg/L) versus time (hours) in different typical individuals with body weight ranging 10 – 120 kg and renal function ranging 10 – 120 mL/min/1.73 m<sup>2</sup> where vancomycin is dosed as continuous infusion according to the proposed dose nomogram (Table 3). Here, the first dose of 15 mg/kg was given as a loading dose, after 3 hours followed by the proposed daily maintenance dose given as a 24 h infusion. For each individual, AUC at day 3 (in bold), as well as AUC at day 1 is shown in the graph (where colour corresponds to the individual's renal function). Dashed lines represent the target concentrations for continuous infusion (20 – 25 mg/L). AUC area under the curve.

## 6. NONMEM control stream for the final model

\$PROBLEM VANCO 1-18

```
$INPUT ID      TIME  AMT  RATE  DV=DROP      LNDV=DV      MDV  LLOQ  BLQ  OCC
      EVID  HT    WT   LBW_AS      LBW_P BSA    WTAGE      WTEXSBMI  GRP
      AGED  AGEG  SEX   RACE  RRT    ICU    HOSP  TIM0  TAD    CREAT CREAT_TV
      CREAT_FIRST CREAT_BL    SCHW SCHW_FIRST SCHW_di    SCHW_di_FIRST
      SCHW_BL    SCHW_BL_di  SCHW_SL    SCHW_di_SL  CREAT_IMP  NEUT  NPEN
      RIFLE  NEPHROTOX  NPENE CRP    LYMPH SCHW_GRP
```

\$DATA nonmem\_1\_18J\_NOCB\_SCHW\_GRP.prn IGNORE=# IGNORE=(RRT.EQ.1) IGNORE=(BLQ.EQ.1)  
IGNORE=(WT.LT.0)

\$SUBROUTINE ADVAN3 TRANS4

\$PK

SCHW\_MAX=SCHW

IF(SCHW.GT.120) SCHW\_MAX=120

CREAT\_RATIO=CREAT/CREAT\_TV

;

IF (WT.GT.0) THEN

TVCL\_WT = THETA(1) \* ((WT/22.1)\*\*THETA(6)); TVCL\_WT

TVV1 = THETA(2)\*((WT/22.1)\*\*THETA(7))

TVQ = THETA(3)\*((WT/22.1)\*\*THETA(8))

TVV2 = THETA(4)\*((WT/22.1)\*\*THETA(7))

ELSE

TVCL\_WT = THETA(1)

TVV1 = THETA(2)

TVQ = THETA(3)

TVV2 = THETA(4)

ENDIF

;

TVCL = TVCL\_WT\*((SCHW\_MAX/100)\*\*THETA(5))

;

CL = TVCL\*EXP(ETA(1))

V2 = TVV2\*EXP(ETA(2))

;

V1 = TVV1\*EXP(ETA(3))

Q = TVQ\*EXP(ETA(4))

;

S1 = V1 ;

;

ET1=ETA(1)

ET2=ETA(2)

ET3=ETA(3)

ET4=ETA(4)

\$THETA

(0, 2.12) ; TVCL\_WT

(0, 8.87) ; TVV

(0, 1.54) ; Q

(0, 12) ; V2

(1) FIX ; CL\_SCHW EXP

(0.753) ; CL\_WT\_EXP

(1) FIX ; EXP V1\_V2\_WT

(0,0.75) ; Q\_WT\_EXP

\$OMEGA BLOCK(2)

0.0822 ; CL ETA 1

-0.0313 ; COVAR ET1-ET2,

0.67 ; V2 ETA 2

\$OMEGA

0 FIX ;V1 ETA 3

0 FIX ;Q ETA 4

\$ERROR

IPRED=0

IF(F.GT.0) IPRED = LOG(F)

IRES = DV - IPRED

W = F

IF(W.EQ.0) W = 1

IWRES = IRES/W

Y = IPRED+ERR(1);

\$SIGMA

0.0788 ; PROP ERR IN LOGDOMAIN

\$ESTIMATION METHOD=1 INTER MAXEVAL=9999 POSTHOC ;

\$COVARIANCE PRINT=E ;

\$TABLE ESAMPLE=10000 ID TIME IPRED IWRES CWRES AMT TVCL CL TVV1 V1 TVQ Q TVV2 V2  
ET1 ET2 ET3 ET4 NPDE MDV BLQ LLOQ CREAT\_RATIO HT WT LBW\_AS LBW\_P BSA WTAGE WTEXS  
BMI GRP AGED AGEG SEX RACE RRT ICU HOSP TIM0 TAD CREAT CREAT\_FIRST CREAT\_BL SCHW  
SCHW\_GRP SCHW\_FIRST SCHW\_di SCHW\_di\_FIRST SCHW\_BL SCHW\_BL\_di SCHW\_SL SCHW\_di\_SL  
CREAT\_IMP NEUT NPEN RIFLE NEPHROTOX NPENE CRP LYMPH NOPRINT ONEHEADER

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