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Shaping the pharmacokinetic landscape for renally cleared antibiotics in obesity: Studies in adults, adolescents and children

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Dosing recommendations for vancomycin in obese children and adolescents with varying renal function based on a population pharmacokinetic study in 1892 children aged 1 – 18 years

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ABSTRACT

Objective Vancomycin is an effective but potentially nephrotoxic antibiotic commonly used for severe gram-positive infections for which guidelines for dose adjustments for obese children and adolescents with or without renal impairment are urgently needed. This study describes the pharmacokinetics of vancomycin in this clinical population, ultimately to design practical dosing guidelines.

Design A retrospective population pharmacokinetic study.

Setting Twenty-one hospitals of the Utah, USA based HMO Intermountain Healthcare organization.

Patients All patients aged 1 – 18 years who received more than 1 dose of vancomycin and had ≥1 vancomycin concentration measured between January 2006 and December 2012.

Measurements Data on vancomycin dosages, vancomycin concentrations, and covariates such as age, gender, body weight, creatinine clearance (CL_{cr}, bedside Schwartz equation), ward, race, or neutropenic status were collected. Population pharmacokinetic analysis and simulations were performed using NONMEM7.4.

Main results In total, 1892 patients (5524 samples) were included, with body weight range 6 – 188 kg (1344 normal weight, 247 overweight, and 301 obese patients) and CL_{cr} down to 8.6 mL/min/1.73m^2. In a two-compartment model, clearance (CL) was found to significantly increase with total body weight (TBW) and CL_{cr}. The central and peripheral volume of distribution and intercompartmental clearance increased with TBW. The model performed well for all age, weight, and renal function ranges, outperforming more sophisticated models separating weight for age and weight excess or incorporating maturation using a body weight-dependent exponent. Based on the model, a dosing guideline is proposed that integrates body weight and CL_{cr} and will lead to effective and safe exposures across all ages, body weight, and renal functions in the paediatric population.

Conclusions We have characterized the full pharmacokinetic profile of vancomycin in obese children and adolescents aged 1 – 18 years and propose a practical dosing guideline that integrates both body weight and renal function.

INTRODUCTION

Over the past decades, the prevalence of childhood obesity has increased at an alarming rate. Where childhood obesity practically did not exist approximately 50 years ago, 41 million children under five years of age were considered overweight or obese in 2014 [1]. In the United States of America, approximately 20% of children aged 5 – 18 year is considered obese [2]. Paediatric obesity is typically defined using growth charts with age and sex-specific values for the body mass index (BMI). The Centers for Disease Control and Prevention (CDC) define overweight and obesity as a BMI in the 85th-95th percentile or above the 95th percentile of these charts, respectively [3]. As a result, clinicians frequently must prescribe medication to children who are overweight.

It has been shown for adults that obesity can impact drug pharmacokinetics by altering different physiological processes, such as cardiac output, renal and hepatic perfusion and function of drug metabolizing or transporting enzymes [4,5]. These principles presumably also apply to obese children, although well-designed studies that explore this are scarce [5,6]. Children are generally underrepresented during drug development trials, and, if children are included, often there is no active inclusion of obese children [7]. Consequently, drug labels do not provide information on drug dosing in obese children, and specific guidelines for drug dosing in paediatric obesity are currently scant [7]. Clinical trials in obese children can be methodologically challenging since age- and obesity-related influences are both reflected in a child's body weight, i.e. body weight can increase as a result of growth and development (weight for age), and of overweight or obesity (excess weight) [8]. Pharmacokinetic trials in paediatric obesity should ideally include an in-depth analysis that allows for the study of the distinct influence of maturation versus overweight on drug pharmacokinetics [9], as has been demonstrated for busulfan, midazolam and metformin [10–12].

Vancomycin is a glycopeptide antibiotic that is widely used in serious gram-positive infections including those with beta-lactam resistant *Staphylococcus aureus* and is known for its potential nephrotoxic side effects. It has been well established that vancomycin efficacy and nephrotoxicity closely relate to the 24 h area under the curve (AUC_{24}) in relation to the minimal inhibitory concentration (MIC) [13]. An AUC_{24}/MIC threshold of 400, corresponding to an AUC_{24} of ≥400 mg*h/L assuming a MIC of 1 mg/L, has been well defined as an efficacy target, which is predominantly based on *S. aureus* infections in adults but can also be applied to children [13]. In adults, an increased risk of nephrotoxicity has been observed with exposures above 677 up to 1300 mg*h/L [14,15]. As such, a leading consensus guideline from infectious disease specialists, hospital pharmacists, and paediatricians from the US advocate an AUC_{24} target window between 400 – 700 mg*h/L to be used in children to maximize efficacy while minimizing the risk of nephrotoxicity [13].

Dosing of vancomycin in normal weight children has been investigated thoroughly [13]. However, despite its extensive use, there is to date limited data on how to tailor the dose in obese children and adolescents [13]. Some small retrospective studies have shown that with the same mg/kg dosing, higher trough concentrations are seen in obese children [16–18], although other studies contradict these results [19,20]. None of these studies have reported on the relationship between trough concentrations and AUC_{24}, which is relevant since trough concentrations are routinely measured while it is known that the relation between trough concentrations and AUC_{24} depend on age and the dosing interval [21,22]. The limited number of pharmacokinetic studies conducted have proposed different covariates for vancomycin clearance in obese children and adolescents. Among others, body size descriptors like total body weight (TBW), body surface area (BSA), or fat-free mass (FFM), parameters representing the renal function such as serum creatinine or creatinine clearance (CL_{cr}) or age have been suggested [23–26].

Hence, for obese children and adolescents, current evidence suggests that the usual paediatric vancomycin dosages should be adjusted. However, the optimal dosing strategy to ensure an AUC_{24} 400 – 700 mg*h/L in obese children and adolescents yet remains to be established, particularly when these obese children suffer from renal dysfunction. This study characterizes the population pharmacokinetics of vancomycin in a large, multi-centre clinical population of normal weight, overweight and obese children and adolescents, with varying renal function, to design practical dose recommendations for this population.

MATERIALS AND METHODS

Patients and setting

This retrospective, pharmacokinetic study was conducted using data from twenty-one hospitals of the Utah, USA based HMO Intermountain Healthcare organization. We selected all patients aged 1 – 18 years who had at least two vancomycin administrations, at least one vancomycin concentration measured, and at least one weight measurement registered between start and end of treatment with vancomycin. According to local clinical practice, vancomycin dosage and concentration measurements were left to the discretion of the treating physician. Generally, vancomycin was dosed as 15 to 20 mg/kg, administered two, three or four times per day as a 60-min infusion. Dosing adjustments were made based on therapeutic drug monitoring (TDM) blood samples which were collected as part of routine medical care. Samples could be drawn within 30 min before the dose (trough concentration), 30 min after the end of the intravenous infusion (peak concentration) or at other time points. Patients that received renal replacement therapy or extracorporeal membrane oxygenation during hospital admission were excluded from the analysis. The study was reviewed and approved by the Intermountain Healthcare and University of Utah Institutional Review Boards, and a waiver of informed consent was granted.

Data collection

Data were extracted from the electronic patient record system from 1st January 2006 to 31st December 2012. Demographics, lab values, and clinical PK data were extracted from the Intermountain Healthcare system enterprise data warehouse at the University of Utah. Data were excluded from the analysis when date and times of drug administration or drug concentrations were unavailable, where in case of missing dose amounts in less than 20% per individual, these were imputed using the last known administered amount.

Vancomycin serum drug concentrations were quantified using immunoassay via the Abbott Architect System. Assay validation was performed for clinical purposes. The linear range for the assay was 1.1 to 100 mg/L, and the limit of quantitation was 1.1 µg/mL. The intraday and interday relative standard deviations ranged from 4.7% to 7.1%.

Other data included age, total body weight (TBW), length, gender, race, ICU-stay, serum creatinine, absolute neutrophil count, absolute lymphocyte count and C-reactive protein (CRP). Overweight and obesity were defined as >85th percentile or >95th percentile of the BMI (corrected for age and sex) growth charts of the WHO for age 1 – 2 years, and CDC for 2 – 18 years [3,27,28]. To be able to distinguish between the influence of growth-related changes in weight and obesity-related changes in weight, for each patient body weight related to growth ($WT_{for\ age\ and\ length}$) and excess body weight (WT_{excess}), was calculated according to equation 1 and 2 (adapted from Van Rongen et al. [10]):

$$WT_{age\ and\ length} = BMI_{for\ age\ and\ gender} \times length^2 \quad (1)$$

$$WT_{excess} = TBW - WT_{age\ and\ length} \quad (2)$$

Where TBW is total body weight in kg, length in cm and $BMI_{for\ age\ and\ gender}$ 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 [27,28].

If a patient's height was unknown, height was imputed using the median value of the CDC height-for-age chart [27]. Body Surface Area (BSA) was calculated using the Mosteller equation [29]. FFM was estimated using the equations of Al-Sallami and Peters [30,31]. 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. 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 [32]. CL_{Cr} was estimated using the bedside Schwartz equation and was studied both

expressed in mL/min/1.73 m^2 [33] and deindexed by multiplication with BSA/1.73 (CL_{cr_di}). 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.

Population pharmacokinetic analysis

Log-transformed vancomycin serum concentrations were analysed using non-linear mixed-effects modelling (NONMEM v7.4, Icon Development Solutions, Ellicott City, MD, USA [34]) with Perl-speaks-NONMEM (v4.9.0) and the Pirana (v2.9.9) interface [35,36]. 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 analysed as separate individuals when age increased with ≥10% or when there was ≥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. -2log likelihood [-2LL]). For structural and statistical models, a drop ≥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 (3) for exponential relations and (4) for linear relations:

$$P_i = P_p \times \left(\frac{COV}{COV_{standard}}\right)^X \quad (3)$$

$$P_i = P_p \times \left(1 + Y \times \left(COV - COV_{median}\right)\right) \quad (4)$$

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 [37], for X also a body weight-dependent exponent (BDE) according to equation (5) was tested [38,39]:

$$X = F \times TBW_i^Z \quad (5)$$

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 (6), as described earlier [10,11]:

$$P_i = P_p \times \left(\frac{WT_{age\ and\ length}}{TBW_{median}}\right)^U + (V \times WT_{excess}) \quad (6)$$

where P_i and P_p are the individual and population parameter estimates, $WT_{age\ and\ length}$ is the body weight related to growth (equation 1), WT_{excess} the excess body weight (equation 2), TBW_{median} is the median total body weight, U is the scaling exponent for $WT_{age\ and\ length}$ (either fixed to 0.75 or estimated), V represents the linear influence of WT_{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 (≥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^2) 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^2) and weight group (normal weight, overweight and obese) [40]. Parameter precision of the structural and final model was analysed by the sampling importance resampling (SIR) procedure [41].

Dose simulations

To evaluate existing dosing guidelines and, if necessary, design a new guideline concentration-time profiles were simulated for several typical individuals from the dataset with different ages, body weight and renal functions using the ranges found across the dataset. Dosing guidelines from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists (abbreviated to IDSA) [13], the Dutch Paediatric Formulary [42] and the

British National Formulary for Children (BNFc) [43] were evaluated (see supplementary file). Based on the final model, a dosing guideline aiming for an AUC_{24} of 400 – 700 mg*h/L at day 3 after the start of treatment (AUC_{day3}) as primary target was developed. Secondary target was an AUC_{24} in the first 24 h (AUC_{day1}) within 400 – 700 mg*h/L. Lastly, trough (C_{min}) concentrations corresponding to the primary target were explored.

RESULTS

Data was obtained for 1924 individuals, after which patients on renal replacement therapy or extracorporeal membrane oxygenation (n = 26) or without a recorded body weight (n = 6) were excluded. This resulted in 1892 patients in which 5524 vancomycin concentrations were available for analysis (Figure 1). Of these patients, 247 (13%) and 301 (16%) individuals fulfilled the criteria for overweight and obesity, respectively, resulting in a broad range of body weights from 6 – 188 kg. Figure 1 shows the wide scatter in sampling time after dose for the three groups. Most characteristics, including age and renal function, were similarly distributed across the three weight groups (Table 1). There was a broad range in CL_{cr} (bedside Schwartz equation) with values as low as 8.6 mL/min/1.73 m^2. In total, 12 patients had a CL_{cr} under 30 mL/min/1.73 m^2, of which 5 patients were overweight or obese. All relevant baseline characteristics are shown in Table 1.

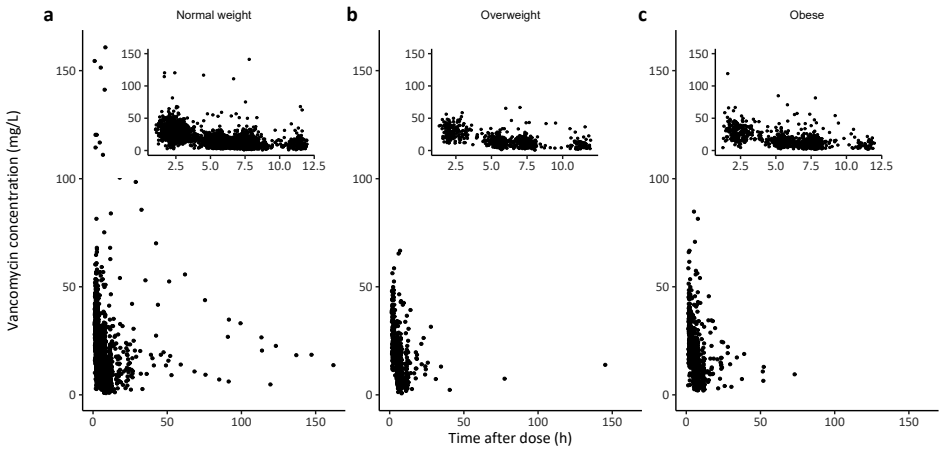

Figure 1. Observed vancomycin concentrations in mg/L versus time after dose in hours for (a) non-obese, (b) overweight, and (c) obese individuals. Inserts show the same data for the time frame 0 – 12 hours after the last dose.

Population 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. The pharmacokinetic parameters of the structural model without covariates are shown in Table 2.

In the covariate analysis, we found an important influence of both renal function expressed using bedside 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^2 and a power equation for TBW (ΔOFV -2356.1 compared to the structural model without covariates [p <0.001]). The specific influence of TBW and CL_{cr} on vancomycin CL is visualized in Figure 2. This combined covariate model outperformed models with the separate implementation of TBW or CL_{CR}, i.e. TBW on CL with a power function (ΔOFV -1125.7 [p <0.001] compared with the structural model without covariates), TBW on CL with a body weight-dependent exponent (ΔOFV -1180.9 [p <0.001] compared with the structural model without covariates) and CL_{cr_di} on CL using a power function (ΔOFV -2230.3 [p <0.001] compared with the structural model without covariates). 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 (ΔOFV -1129.2 versus ΔOFV -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, ΔOFV -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 (ΔOFV +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 (ΔOFV -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, ΔOFV -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 (ΔOFV -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.

Table 1. Baseline characteristics.

Characteristic	Normal weight (n = 1344)
Age (years)	6.9 [2.9 – 13.2] (1.0 – 18.0)
Age group (N, (% of the total of age group))	1 – 2 year: 214 (66)
	2 – 12 year: 727 (72)
	12 – 18 year: 403 (71)
Gender (% male)	57.3
Race (N, (% of the total of the group)	Caucasian: 1198 (72)
	Asian: 11 (85)
	Hispanic: 17 (65)
	African American: 27 (62)
	Other: 91 (62)
TBW (kg)	20.6 [13.0 – 38.8] (5.8 – 82.6)
Height (cm)	119 [92 – 150] (62 – 203)
BMI (kg/m^2)	16.1 [14.6 – 17.7] (8.6 – 25.6)
BSA (m^2)	0.83 [0.58 – 1.28] (0.32 – 2.10)
Serum creatinine (mg/dL)	0.40 [0.30 – 0.54] (0.06 – 8.20)
Bedside Schwartz creatinine clearance (ml/min/1.73 m^2)	121.2 [101.2 – 144.6] (8.6 – 963.5)
Bedside Schwartz group[a] (N, (% of the total of the group))	>90: 1100 (73)
	60 – 90: 200 (63)
	30 – 60: 37 (64)
	<30: 7 (58)
Patients admitted to ICU (%)	466 (35)
Patients with neutropenia (N, (% of total))	223 (17)
No. of samples (N, (% of total))	3968 (72)
No. of samples per individual	4 [2 – 7] (1 – 37)
Sampling time after dose (h)	5.8 [4.3 – 7.5] (1.0 – 162.0)

Values are shown as median [interquartile range] (range) unless specified otherwise

[a] Schwartz group is shown in mL/min/1.73 m^2

BMI Body Mass Index, *BSA* Body Surface Area.

Overweight (n = 247)	Obese (n = 301)
7.2 [3.0 – 12.6] (1 – 17.6)	6.9 [2.5 – 13.2] (1.0 – 18.0)
1 – 2 year: 41 (13)	1 – 2 year: 68 (21)
2 – 12 year: 137 (14)	2 – 12 year: 135 (14)
12 – 18 year: 69 (12)	12 – 18 year: 98 (17)
53.4	54.1
Caucasian: 217 (13)	Caucasian: 248 (15)
Asian: 2 (15)	Asian: 0 (0)
Hispanic: 1 (4)	Hispanic: 8 (31)
African American: 8 (19)	African American: 8 (19)
Other: 19 (13)	Other: 37 (25)
25.0 [13.8 – 51.4] (7.3 – 99.3)	30.0 [14.0 – 78.1] (7.5 – 188.0)
115 [87 – 149] (63 – 193)	116 [85 – 159] (54 – 196)
18.9 [17.9 – 23.2] (16.9 – 23.2)	23.2 [19.7 – 29.8] (18.1 – 60.1)
0.89 [0.58 – 1.45] (0.36 – 2.31)	1.00 [0.57 – 1.86] (0.35 – 3.04)
0.40 [0.30 – 0.57] (0.10 – 3.53)	0.44 [0.30 – 0.61] (0.12 – 3.16)
114.7 [91.0 – 142.3] (14.8 – 291.1)	111.7 [91.3 – 134.5] (21.3 – 323.9)
>90: 186 (12)	>90: 220 (15)
60 – 90: 48 (15)	60 – 90: 68 (22)
30 – 60: 9 (16)	30 – 60: 12 (21)
<30: 4 (33)	<30: 1 (8)
91 (37)	113 (38)
53 (22)	40 (13.3)
698 (13)	858 (16)
4 [2 – 6] (1 – 34)	4 [2 – 7] (1 – 34)
5.9 [4.5 – 7.6] (1.3 – 145.3)	6.4 [4.8 – 7.7] (1.3 – 73.0)

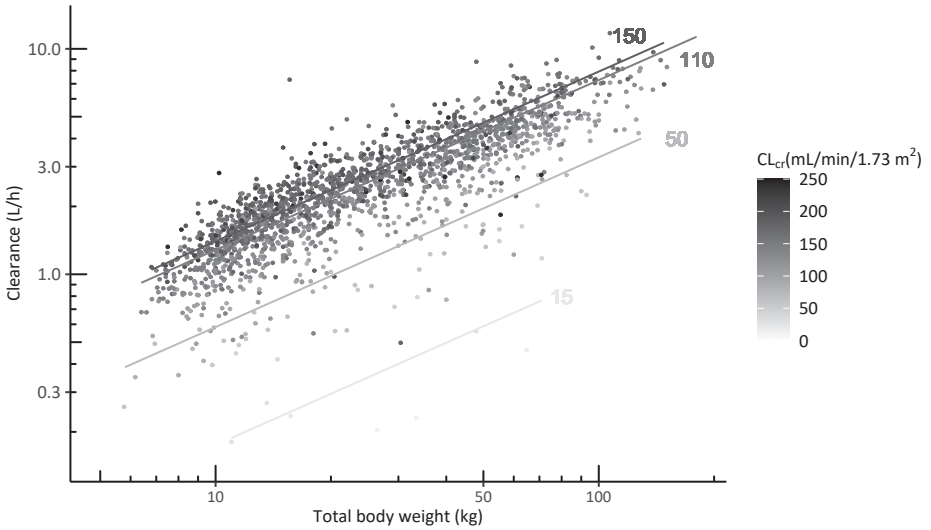

Figure 2. Vancomycin clearance (in L/h) versus total body weight (in kg) for varying creatinine clearance values (CL_{cr}). Each dot represents one individual, with darker colour representing a higher CL_{cr}. The lines show how clearance changes with body weight over the available weight range according to the final model for four typical values of CL_{cr} (i.e., 15, 50, 110 and 150 mL/min/1.73 m²), with corresponding CL_{cr} value shown in the figure for each line (mL/min/1.73 m²). *CL_{cr}* creatinine clearance based on the bedside Schwartz equation (in mL/min/1.73 m²).

As a result of introducing these covariates, inter-individual variability on CL reduced from 52.8% in the structural model without covariates to 28.7% in the final model, at a slight increase in inter-individual variability on V2 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 (ΔOFV +457.2 [p <0.001]), we decided to retain it in the final PK model. Figure 3 shows that each covariate gave a distinct improvement in goodness-of-fit plot across the different subpopulations and that all subpopulations are well described. For the group with the lowest renal function (<30 mL/min/1.73 m²), some over-prediction is seen, which may result from the small number of individuals (n = 12). The validity of our model across all subgroups was confirmed by NPDE (Figure S1, supplementary file) and pvcVPC (Figure 4 and S2-3 in the supplementary file) across different subpopulations. The final pharmacokinetic model parameters are shown in Table 2.

Table 2. Population pharmacokinetic model parameters of the structural base model (without covariates) and the final model (with covariates) for vancomycin in normal weight, overweight and obese children and adolescents aged 1 – 18 years old with and without renal impairment.

Parameter	Structural model (RSE %)	Final model (RSE %) [95% CI]
Fixed effects		
CL (L/h) $TVCL \times \left(\frac{TBW}{22.1}\right)^{\theta_1} \times \left(\frac{SCHW^{a}}{100}\right)$	2.17 (2)	-
TVCL (L/h)	-	2.12 (1) [2.07 – 2.17]
θ_1	-	0.745 (2) [0.720 – 0.768]
V1 (L) $TVV1 \times \left(\frac{TBW}{22.1}\right)$	5.27 (8)	-
TVV1 (L)	-	8.90 (3) [8.50 – 9.33]
Q (L/h) $TVQ \times \left(\frac{TBW}{22.1}\right)^{\theta_2}$	2.24 (4)	-
TVQ (L)	-	1.55 (5) [1.44 – 1.65]
θ_2	-	0.599 (9) 0.517 – 0.685]
V2 (L) $TVV2 \times \left(\frac{TBW}{22.1}\right)$	11.9 (8)	-
TVV2 (L)	-	12.3 (6) [11.2 – 13.6]
Inter-individual variability (IIV, %) [b,c]		
CL	52.8 (3)	28.7 (5) [27.1 – 30.7]
Covariance IIV $_{CL\text{-}V2}$	-	-0.085 [-0.11 - -0.062]
V2	89.4 (7)	110 (7) [95.9 – 130]
Residual variability		
Proportional error[d,e]	0.107 (7)	0.0789 (6) [0.0746 – 0.0836]
OFV	-1886.4	-5222.5

[a] Schwartz value is maximized to 120 mL/min/1.73 m²

[b] Shrinkage of inter-individual variability in the final model is 24% for CL, 57 % for V2

[c] Coefficient of variation, calculated by $\sqrt{(e^{\omega^2} - 1)}$

[d] Proportional error is shown as σ

[e] Epsilon shrinkage for the final model is 16%

CI confidence interval obtained from sampling importance resampling (SIR) procedure, *CL* clearance, *OFV* objective function value, *Q* inter-compartmental clearance between V1 and V2, *RSE* relative standard error based on the covariance step in NONMEM, SCHW creatinine clearance according to bedside Schwartz equation, *TBW* total body weight, *TVCL* typical value of CL for an individual weighing 22.1 kg and with creatinine clearance of 100 ml/min/1.73 m², *TVQ* typical value of Q for an individual weighing 22.1 kg, *TVV1* typical value of V1 for an individual weighing 22.1 kg, *TVV2* typical value of V2 for an individual weighing 22.1 kg, *V1* volume of distribution of central compartment, *V2* volume of distribution of the peripheral compartment.

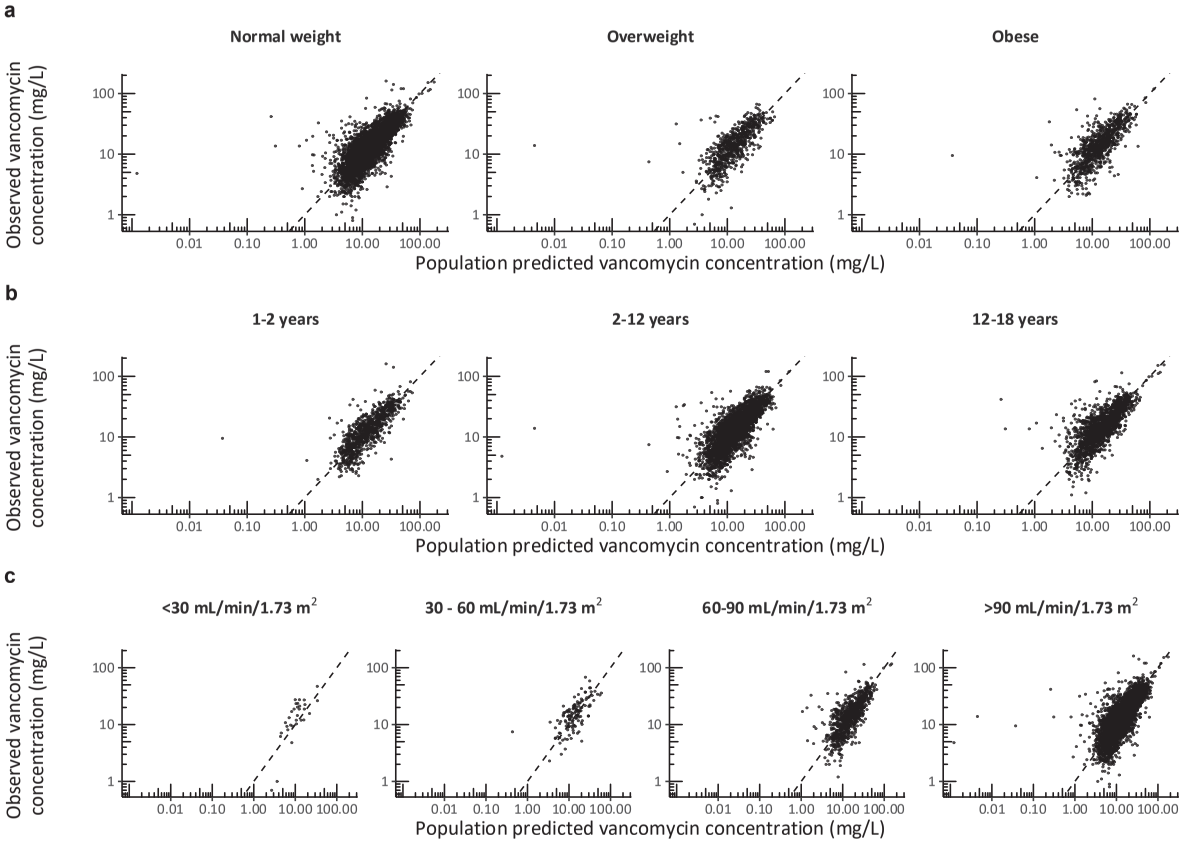

Figure 3. Observed versus population predicted vancomycin concentrations for the final model, split for (a) weight group, (b) age group or (c) renal function group (creatinine clearance based on the bedside Schwartz equation).

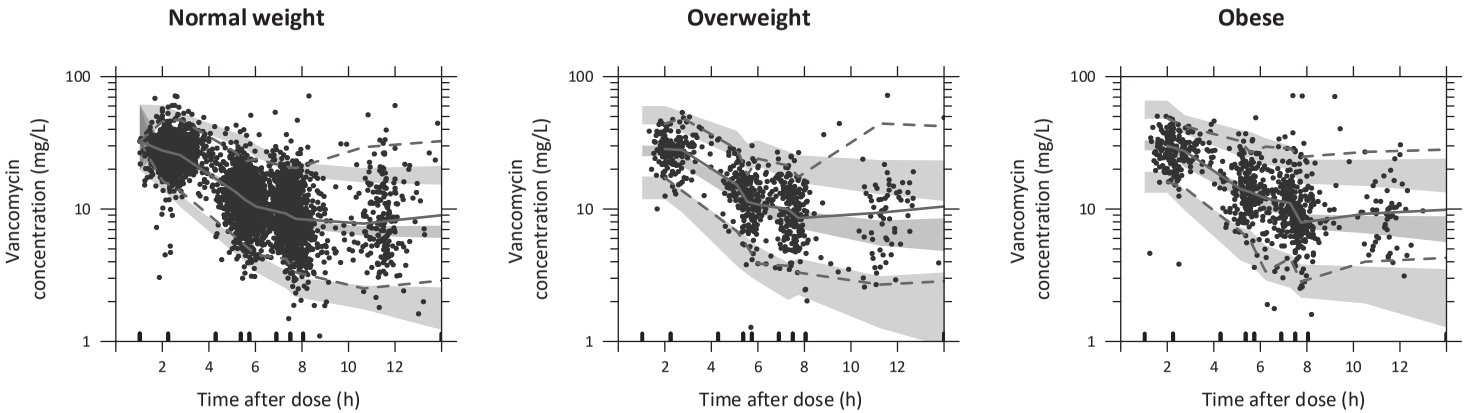

Figure 4. Prediction and variability corrected visual predictive check (pvcVPC), split for weight. Prediction corrected observations are shown as dots, with the median, 2.5th and 97.5th percentiles shown as solid, lower, and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of predicted concentrations (n = 500) based on the pharmacokinetic model. Intervals of the bins are shown by the vertical ticks on the bottom of the plot.

Dose simulations and proposed dosing guideline

Based on the influence of both renal function and body weight on vancomycin clearance, we developed dosing recommendations for the paediatric population (Table 3). As shown in Table 3, the first dose is 15 mg/kg for all groups followed by doses adjusted to body weight and renal function. The obtained concentration-time profiles using this dosing guideline for six representative individuals from the dataset (normal weight and morbidly obese individuals ranging from 1 – 17 years and 11 – 118 kg) are shown in Figure 5. For each individual, four curves with different renal functions (Schwartz 10 – 120 mL/min/1.73 m^2) are shown. For reference, the profiles for the same individuals using the currently leading paediatric dosing guidelines are shown in Figure S4 in the supplementary file. When the proposed dose nomogram is used, the obtained AUC_{day3} (defined as the AUC from 48 to 72 hours after the first dose) was within the target of 400 – 700 mg*h/L for all individuals, regardless of body weight, weight group (obese or normal weight), renal function or age. Additionally, already in the first 24 h target AUC's were reached in all individuals, except for the individuals with renal function >120 mL/min/1.73 m^2 (Figure 5). Similar results are obtained when the dosing guideline is adapted to a continuous infusion dosing regimen (Figure S5 in the supplementary file). Here, 15 mg/kg is given as a loading dose, followed after 3 hours by the proposed daily dose given as a 24 h infusion. For the reader's convenience, we have provided this continuous infusion dosing guideline in the supplementary file (Table S1). The results obtained using the dosing guideline as shown in Table 3 and Figure 5 contrast with what was obtained using the currently leading dosing guidelines (IDSA, Dutch Paediatric Formulary, BNFc), as shown in Figure S4, where the current guidelines result in high, potentially toxic exposures (AUC_{day3} >700 mg*h/L) especially in children with renal impairment or who are considered obese. This particularly applies to BNFc and IDSA guidelines, which do not recommend dose adjustments for patients with reduced renal function. Figure 5 shows that for the typical individuals trough concentrations corresponding to an AUC_{day3} 400 – 700 mg*h/L vary between 7.2 and 23 mg/L, when dosed according to the proposed dosing guideline in Table 3.

Table 3. Dosing guideline for intermittent dosing of vancomycin in children and adolescents aged 1 – 18-years based on total body weight and renal function according to bedside Schwartz.

Schwartz creatinine clearance (mL/min/1.73 m^2)	Total body weight (kg)			Relative daily dose (%)
	<30	30 – 70	>70	
>90	15 mg/kg every 6 h	15 mg/kg every 8 h	18 mg/kg every 12 h	100%
50 – 90	11 mg/kg every 6 h[a]	11 mg/kg every 8 h[a]	12 mg/kg every 12 h[a]	70%
30 – 50	5 mg/kg every 6 h[a]	5 mg/kg every 8 h[a]	6 mg/kg every 12 h[a]	35%
10 – 30	5 mg/kg every 12 h[a]	3 mg/kg every 12 h[a]	3 mg/kg every 12 h[a]	15%

[a] First dose is 15 mg/kg.

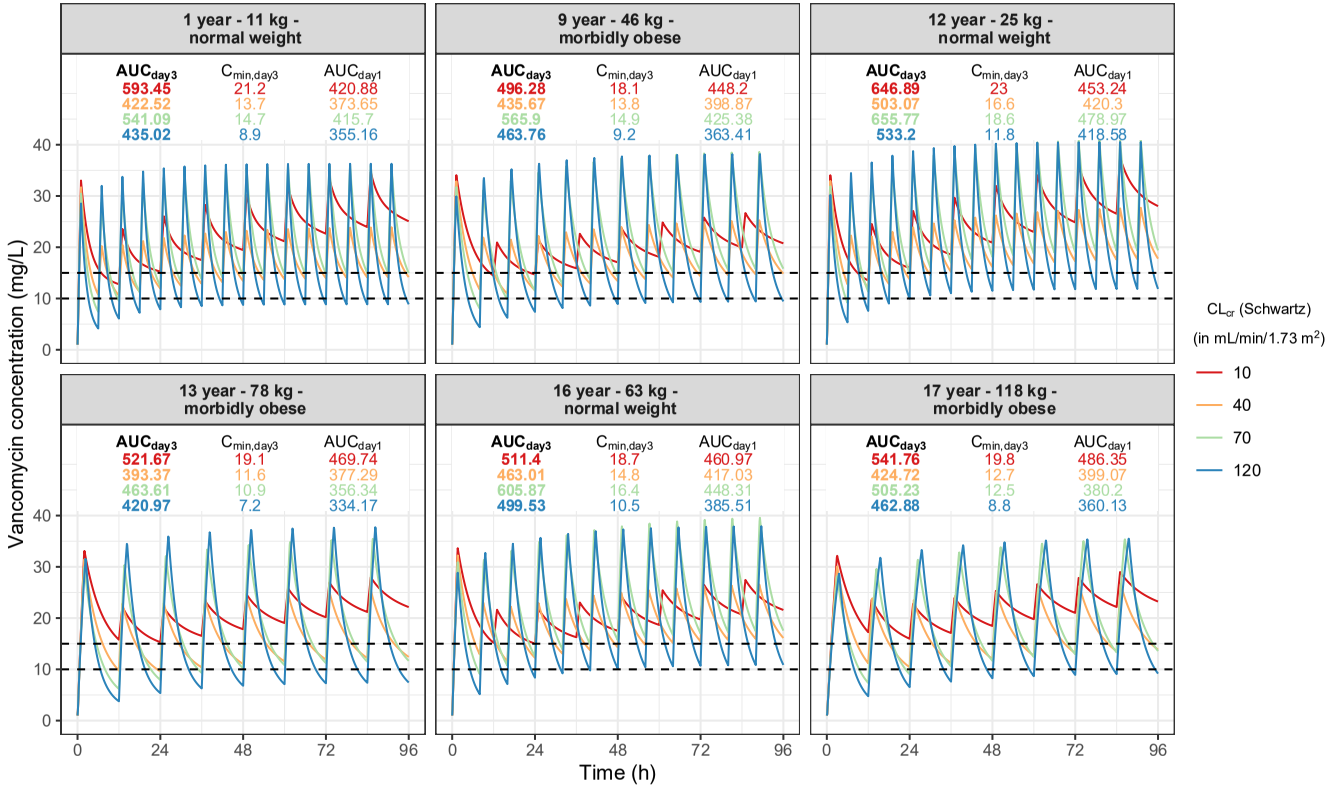

Figure 5. Vancomycin concentrations (mg/L) versus time (hours) in different typical individuals with body weight ranging 10 – 120 kg and renal function ranging 10 – 120 mL/min/1.73 m² where vancomycin is dosed according to the proposed dosing guideline (Table 3). For each individual, AUC (in bold), $C_{min,}$ at day 3, as well as AUC at day 1 are 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_{min} minimum (trough) concentration.

DISCUSSION

In this study, we provide a practical paediatric dosing guideline based on a thorough characterization of the vancomycin pharmacokinetics in a large paediatric and adolescent population aged 1 – 18 years that consists of normal weight, overweight and obese individuals with a wide range of renal functions. We have demonstrated that vancomycin clearance can be well predicted using a combination of renal function calculated by the bedside Schwartz formula and total body weight. To our best knowledge, the paediatric pharmacokinetics of vancomycin has not been described before in such a large and rich dataset, with a broad range and overlay of multiple relevant covariates such as age, body weight and renal function and where the vancomycin samples showed a good distribution in time after dose, especially over the first 12 h. This straightforward dosing guideline is in line with the IDSA vancomycin dose recommendation for non-obese children (15 mg/kg four times daily) [13] and our recently proposed dose recommendations for vancomycin in obese adults (35 mg/kg per day) [44]. However, it adds dose adaptations for paediatric obesity and renal impairment, the latter in both normal weight and overweight/obese children. We demonstrate that by following our proposed dosing guideline (Table 3), effective exposures with minimal risk of toxicity (AUC_{day3} between 400 and 700 mg*h/L) can be expected throughout the population. Besides, by starting with a first (loading) dose of 15 mg/kg in all groups, target exposures can be reached in the first 24 h after the start of treatment for most individuals, both in intermittent or continuous infusion regimens. Finally, we show that trough concentrations may vary vastly, with values ranging from 7.2 – 23 mg/L in our typical individuals, even though the exposure is within the target for these individuals (Figure 5). The variability in trough concentrations related to target exposure as a result of dosing frequency, age or weight has been described before for several populations, including obese adults and normal-weight children [21,22,44]. Therefore, clinicians should not base dose adjustments on trough concentrations alone, but preferably use Bayesian forecasting to relate TDM samples to predict exposure, as is also recommended in the recently revised vancomycin therapeutic drug monitoring guideline [13]. For Bayesian forecasting, the current PK model can be used as a basis.

There is currently a limited number of vancomycin pharmacokinetic studies that have been performed in obese children or adolescents [18,23–26,45]. In contrast to our study, the majority of these publications lack specific dose recommendations, in particular regarding the combination of renal impairment and obesity. Several studies found that when vancomycin was dosed on a similar mg/kg basis in obese and non-obese children, higher trough concentrations were obtained in obese children [18,23,45]. This finding is in agreement with our observations, showing that the IDSA and BNFc guidelines lead to increasing exposure and trough concentrations with increasing body weight to the point where the dose is being capped. Most pharmacokinetic studies found that clearance increases with body weight, but varying

covariate relationships have been described. An analysis by Lanke et al. in 463 adolescents aged 12 – 18 years found that vancomycin clearance increased with TBW and creatinine clearance based on the bedside Schwartz equation, similar to our results [24]. Another study in 196 mostly adolescent overweight and obese children found that besides serum creatinine, fat-free mass best predicted vancomycin clearance [25]. In their dataset, total body weight could not be identified as a predictor of clearance. It is unclear what explains these results, but it cannot be excluded that these findings are explained by the absence of adolescents with normal weight unlike the data of our study. Lastly, Le et al. have also found that in 87 pairs of obese and non-obese children, aged 2 – 18 years, vancomycin clearance can best be predicted by a combination of total body weight (using an allometric function with exponent 0.75), serum creatinine and age [26], which is roughly in line with our results. However, the authors state that the differences between obese and non-obese individuals are small and do not necessitate any dose adjustments. Our study clearly show that dose adjustments are however necessary to prevent subtherapeutic or toxic exposures.

Some limitations of our study should be addressed. Children under one year of age were excluded in this study. Therefore, readers should not use our results in children below one year of age for which we refer to other dosing guidelines [21]. In addition, although we included patients with renal function ranging down to 8.6 mL/min/1.73 m^2, there were relatively few patients with an estimated renal function <30 mL/min/1.73 m^2 (n = 12). The diagnostics of our final model show some underprediction of vancomycin concentrations in this group (Figure 3C), while the dose recommendations show that due to an increased elimination half-life, steady-state concentration has not been reached on day 3 in this patient group. Consequently, our dose recommendations must be used with extra caution for this subgroup. Also, vancomycin was given exclusively as intermittent infusions in the population included in our dataset. With this study design we can adequately estimate clearance, which mainly drives the maintenance dose for both intermittent and continuous regimens. However, some caution should be applied when extrapolating our results to continuous infusion regimens. Lastly, there is considerable variability in the PK model. This stresses the need to apply TDM still to guide dose adjustments further, as is currently widespread practice for vancomycin in the paediatric population [13].

In the covariate analysis, we have investigated several approaches for the inclusion of weight as a covariate for vancomycin clearance. First, we found that for predicting clearance, there was no benefit of a sophisticated model that separately characterizes the influence of weight for age-and-length and weight excess (equations 1, 2 and 6) over a simple covariate model using only total body weight. This implies that for vancomycin clearance in children, there seems to be no difference in the influence of weight resulting from growth and development and excess weight resulting from obesity. Our results are in line with studies with similar

populations for metformin and midazolam, where for metformin clearance and midazolam volume of distribution a $WT_{for\ age\ and\ length}/WT_{excess}$ model performed similar as compared to a model with TBW as a covariate [10,11]. For busulfan clearance, a large study in children and adolescents including many with underweight and overweight showed that estimating an additional factor that accounts for under- or overweight (using the Z-score) did not give a better description of the data than a model with only TBW [12]. Second, we could not identify a maturation model for clearance with a body weight-dependent exponent in the power function to capture the decrease in exponent with age (equation 5). This is not unexpected, since it is well-known that the maturation of renal excretion processes such as glomerular filtration rate (GFR) is nearly complete around one year of postnatal age [46]. As such, in our population of children over one-year-old, such a maturation function was not of added value. This is substantiated by another pharmacokinetic analysis of vancomycin, which was done in non-obese children without renal dysfunction where almost 80% of the included patients were younger than one year [39]. This study found a body weight-dependent exponent to be superior over a model with a power function for TBW. Third, we estimated an exponent of 0.745 for the effect of TBW on vancomycin clearance. This value is close to 0.75 which is often used for weight-based allometric scaling of paediatric drug clearance from adult values. Although the principles of allometric scaling have been well established in predicting drug clearance in normal-weight children over five years of age, this is not the case for obese children or children aged below five years [47]. For this reason, we decided to keep the estimated value of 0.745 in the final model, keeping in mind that we cannot rule out coincidence as the cause for finding a similar value as the allometric exponent of 0.75 in this particular population.

CONCLUSIONS

We have successfully characterized the population pharmacokinetics of vancomycin in children and adolescents aged one year and above, with varying degrees of obesity and renal functions. Vancomycin clearance can be well predicted using a combination of CL_{cr} (using the bedside Schwartz equation) and total body weight. Using this model, we have designed a dosing guideline that provides quantitative detail on the IDSA recommendation of 15 mg/kg four times daily by specifying the dose reductions required for renal impairment in both obese and non-obese individuals. With this dosing guideline, effective and safe exposures at day 3 (AUC_{day3} of 400 – 700 mg*h/L), but also in the first 24 h of treatment are expected throughout the paediatric population aged 1 – 18 years.

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SUPPLEMENTARY FILE

Paediatric 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) [13]:
15 mg/kg every 6 hours (max 3600 mg / day). Obese: loading dose 20 mg/kg.

Dutch Paediatric Formulary [42]:
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) [43]:
< 12y: 10 – 15 mg/kg every 6h (no maximum dose).
12 years and older: 15 mg/kg every 8 hours (maximum 2 g).

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 creatinine clearance (mL/min/1.73 m²)	Total body weight (kg)			Relative daily dose (%)
	<30	30 -70	>70	
>90	60 mg/kg over 24 h[a]	45 mg/kg over 24 h[a]	36 mg/kg over 24 h[a]	100%
50 – 90	44 mg/kg over 24 h[a]	33 mg/kg over 24 h[a]	24 mg/kg over 24 h[a]	70%
30 – 50	20 mg/kg over 24 h[a]	15 mg/kg over 24 h[a]	12 mg/kg over 24 h[a]	35%
10 – 30	10 mg/kg over 24 h[a]	6 mg/kg over 24 h[a]	6 mg/kg over 24 h[a]	15%

[a] Loading dose is 15 mg/kg, followed after 3 hours with proposed maintenance dose.

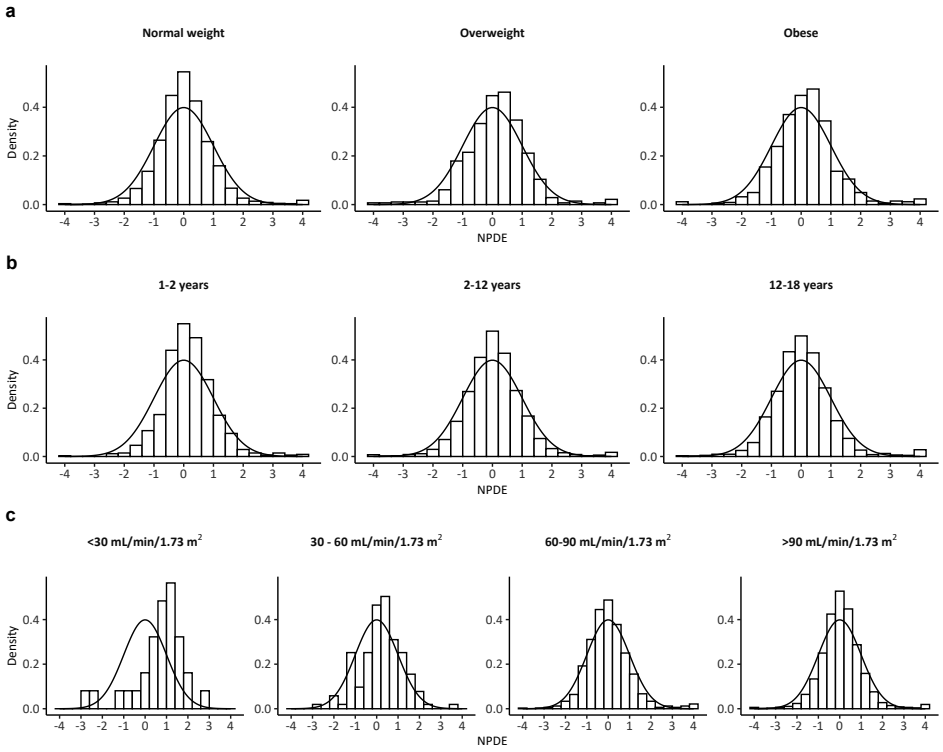

Figure S1. Distribution of the normalized prediction distribution errors (NPDE) for the final model, split for (a) weight group, (b) age group or (c) renal function group (based on the bedside Schwartz equation). The solid line depicts a normal distribution.

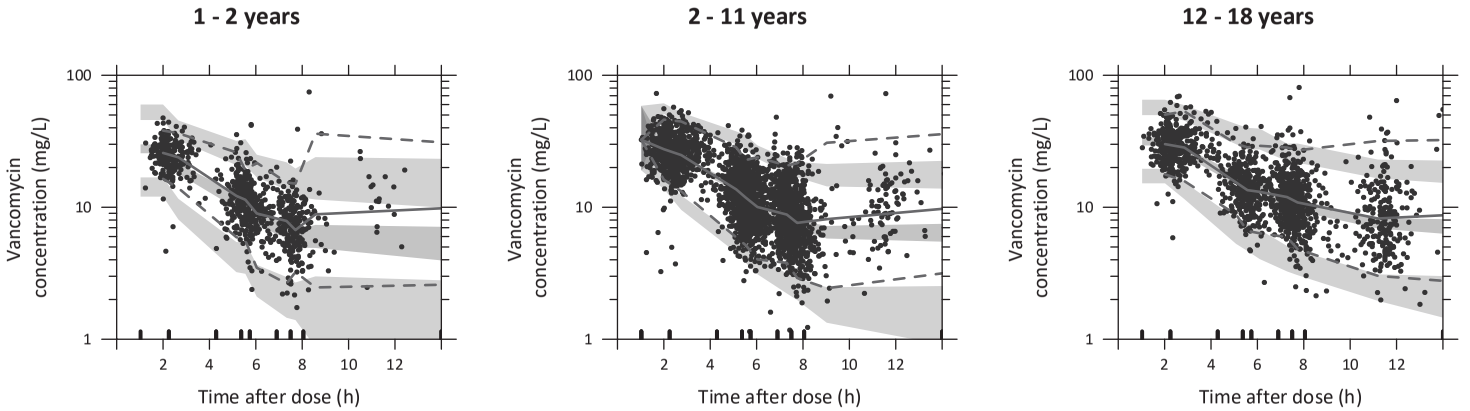

Figure S2. Prediction and variability corrected visual predictive check (pvcVPC), split for the age. Prediction corrected observations are shown as dots, with the median, 2.5th and 97.5th percentiles shown as solid, lower, and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of predicted concentrations (n = 500) based on the pharmacokinetic model. Intervals of the bins are shown by the vertical ticks on the bottom of the plot.

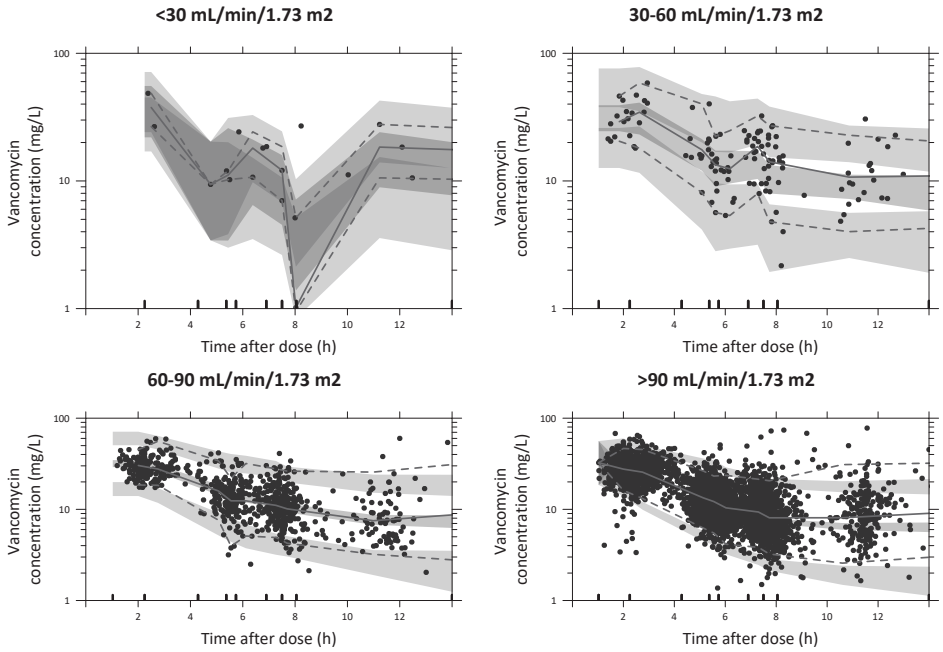

Figure S3. Prediction and variability corrected visual predictive check (pvcVPC), split for renal function group based on bedside Schwartz. Prediction corrected observations are shown as dots, with the median, 2.5th and 97.5th percentiles shown as solid, lower, and upper dashed lines. Grey shaded areas represent the 95% confidence intervals of the median (dark grey) and 2.5th and 97.5th percentiles (light grey) of predicted concentrations (n = 500) based on the pharmacokinetic model. Intervals of the bins are shown by the vertical ticks on the bottom of the plot.

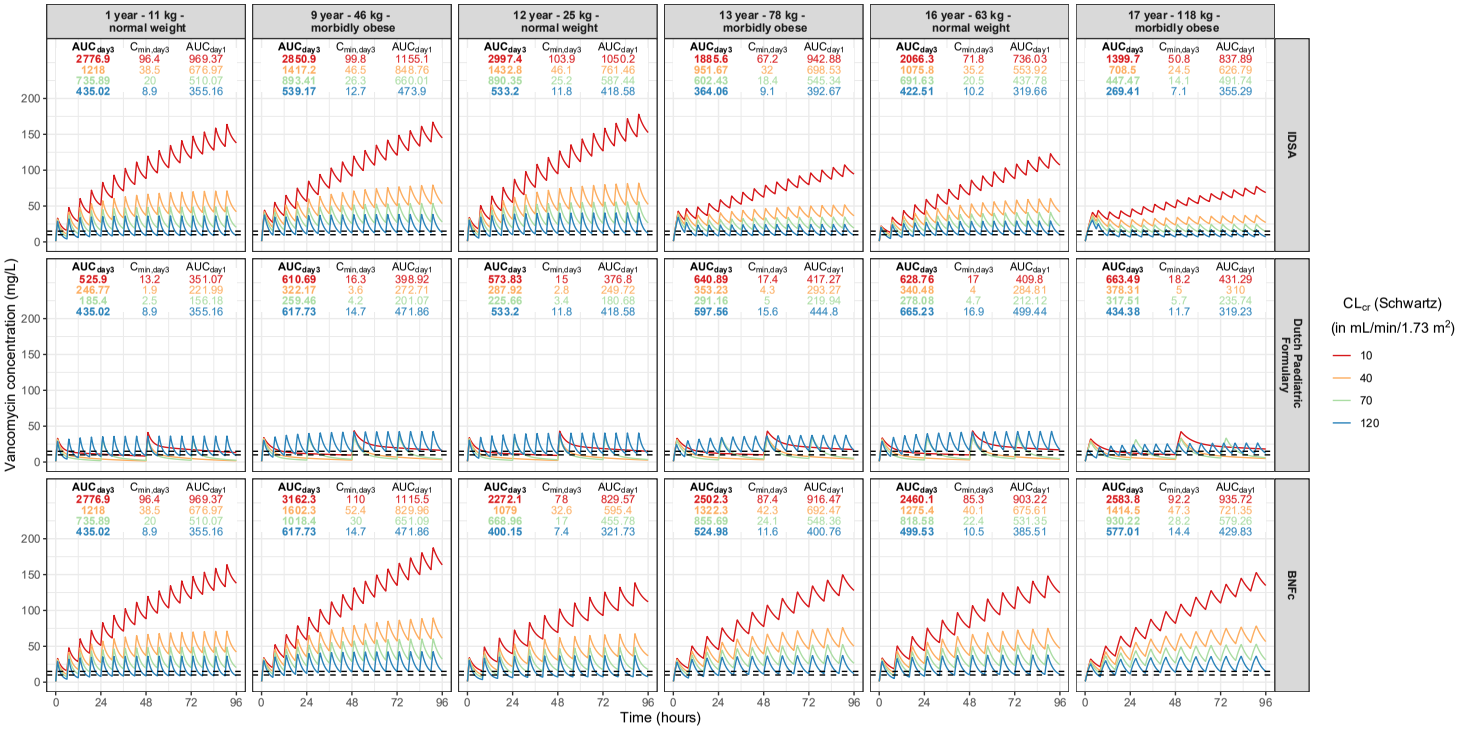

Figure S4. Vancomycin concentrations (mg/L) versus time (hours) in several typical individuals with bodyweight ranging 10 – 120 kg and renal function ranging 10 – 120 ml/min/1.73 m² where vancomycin is dosed according to three existing dosing guidelines: Infectious Diseases Society of America (IDSA, upper panel), Dutch Paediatric Formulary (middle panel) and British National Formulary for Children (BNFc, lower panel). For each individual, AUC (in bold), $C_{min,}$ at day 3, as well as AUC at day 1 is shown in the graph (where colour correspondents 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_{min} minimum (trough) concentration.

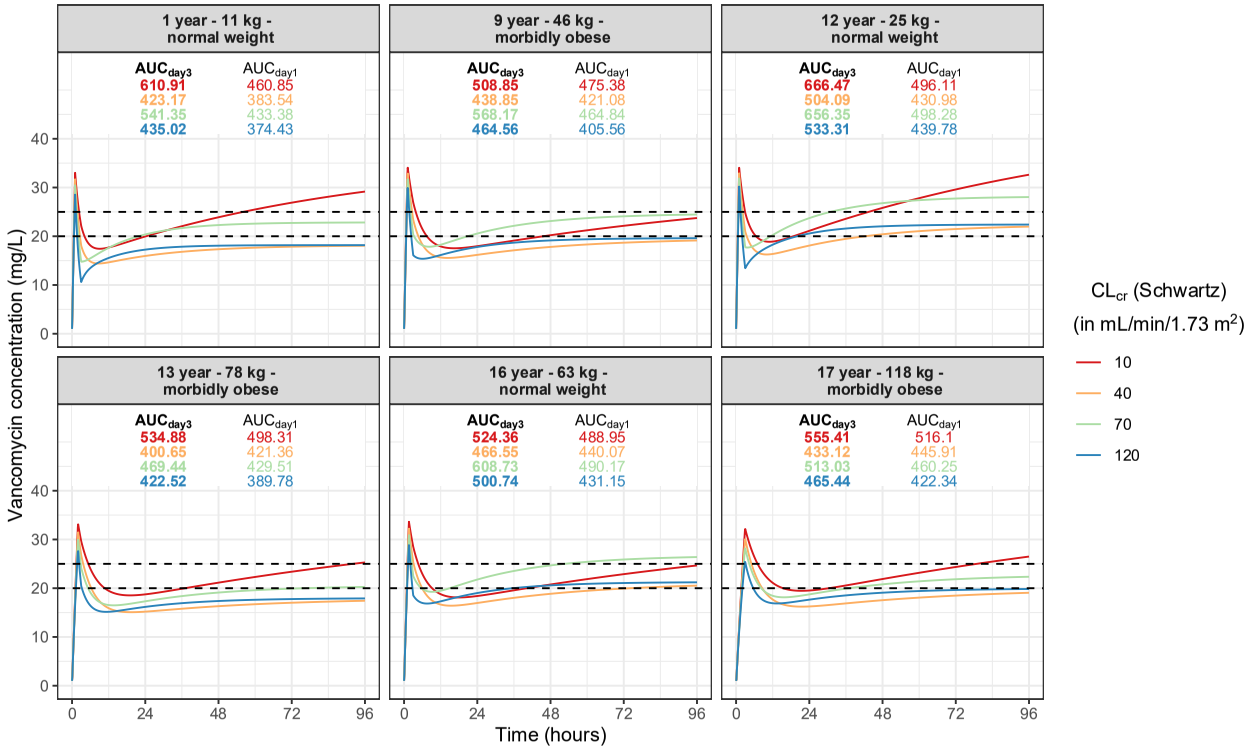

Figure S5. Vancomycin concentrations (mg/L) versus time (hours) in different typical individuals with body weight ranging 10 – 120 kg and renal function ranging 10 – 120 ml/min/1.73 m² where vancomycin is dosed as continuous infusion according to the proposed dose nomogram (Table 3). Here, the first 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.

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
WTEXS BMI GRP AGED AGEG SEX RACE RRT ICU HOSP
TIMo TAD CREAT CREAT_TV CREAT_FIRST CREAT_BL SCHW
SCHW_FIRST SCHW_di SCHW_di_FIRST SCHW_BL S C H W _ B L _
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
```