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**Title:** Development and external evaluation of a population pharmacokinetic model for continuous and intermittent administration of vancomycin in neonates and infants using prospectively collected data

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**Short running title:** Continuous and intermittent vancomycin in neonates

## **Abstract**

**Background:** Vancomycin is commonly used for nosocomial bacterial pathogens causing late-onset septicemia in preterm infants. We prospectively collected pharmacokinetic data aiming to describe PK and determine covariates contributing to the variability in neonatal vancomycin pharmacokinetics. Further, we aimed to use the model to compare  $AUC_{24h,SS}/MIC$  of several intermittent and continuous dosing regimens.

**Methods:** Newborns receiving vancomycin for suspected or confirmed late-onset sepsis were included. Peak and trough concentrations for intermittent vancomycin dosing and steady-state concentrations for continuous vancomycin dosing were measured. NONMEM 7.3 was used for population pharmacokinetic analysis. Monte Carlo simulations were performed to compare dosing schemes.

**Results:** Data from 54 infants were used for model development and from 34 infants for the model evaluation of a median (range) 29 (23.4-41.9) weeks and 28 (23.4-41.7) weeks corrected gestational age (GA), respectively. The final model was a 1-compartment model. Weight and postmenstrual age were included *a priori*; and after that no additional covariate significantly improved the model fit. Final model parameter estimates (mean (standard error)): CL 5.7 (0.3) L/h/70kg, V 39.3 (3.7) L/70kg. Visual predictive check of the evaluation dataset confirmed the model can predict external data. Simulations using MIC of 1 mg/L showed that for neonates with GA  $\leq 25$  weeks and postnatal age  $\leq 2$  weeks  $AUC_{24h,SS}/MIC$  was lower with the intermittent regimen (median 482 versus 663).

**Conclusions:** A population PK model for continuous and intermittent vancomycin administration in infants was developed. Continuous administration might be favourable for treating infections caused by resistant microorganisms in very young and immature infants.

## Introduction

The neonatal patient population have a significant morbidity and mortality associated with their susceptibility to infections.<sup>1, 2</sup> This is attributed to their immature immune function and their need for invasive devices while in the neonatal intensive care unit (NICU). Premature neonates with sepsis may have associated mortality as high as 20%<sup>3</sup> and have a higher risk of morbidities including bronchopulmonary dysplasia, necrotising enterocolitis, retinopathy of prematurity, and prolonged hospitalisation.<sup>4</sup> Bloodstream infection is associated with adverse long term neurodevelopmental outcomes including sensory and cognitive impairment.<sup>5</sup> Coagulase negative staphylococci (CoNS) and *Staphylococcus aureus* are amongst the most common nosocomial bacterial pathogens infecting neonates with the ability to induce life threatening late-onset septicaemia.<sup>6</sup>

Vancomycin is a glycopeptide antibiotic used as a first-line agent for Gram-positive bacteria exhibiting relative resistance to penicillin, methicillin and cephalosporins.<sup>7</sup> The aim of antibiotic dosing, including vancomycin, must be to promptly ensure optimal efficacy while minimising potential toxicity.<sup>8</sup> This is especially important in neonates, since the inter-individual variability in pharmacokinetics (PK) is much higher in this population, compared to adults. Neonates are different to adults, namely they have a higher distribution volume of vancomycin and lower vancomycin clearance when compared to adults.<sup>9</sup> The factors affecting vancomycin pharmacokinetics include: maturational changes in newborns, i.e. increasing glomerular filtration rates with increasing gestational age and postnatal age,<sup>10</sup> lower protein binding of vancomycin in neonates,<sup>11</sup> co-morbid pathologies like perinatal asphyxia and intra-uterine growth restriction, and co-administration of cyclo-oxygenase inhibitors.<sup>12, 13</sup> Promptly achieving optimal serum concentrations is vital for treating neonatal

sepsis. There is currently no clear consensus on optimal dosing regimen in clinical practice, and vancomycin is administered as both intermittent and continuous infusions.<sup>14</sup>

Area-under-the vancomycin concentration-time curve over 24 hours in steady state ( $AUC_{24h,SS}$ ) to the MIC for a specific pathogen ratio ( $AUC_{24h,SS}/MIC$ ) has been reported as the best indicator for favourable clinical outcome, compared to using peak and trough concentrations alone.<sup>15, 16</sup> This is due to the intermediate nature of vancomycin pharmacodynamics (PD) being both concentration-dependent and time-dependent.<sup>16</sup> A target  $AUC_{24h,SS}/MIC$  of or above 400 has been suggested.<sup>17, 18</sup>

Examining the PK and PD of a drug with the aim to develop an appropriate dosing regimen for neonates to ensure safe and effective administration is vital.<sup>12</sup> Due to the advantages over the non-compartmental approach, e.g. rich sampling schedule is not required, the population PK modelling approach is recommended when analysing PK data from neonates.<sup>19</sup>

While a number of studies using population PK modelling, for example Jacqz-Aigrain *et al.*<sup>16</sup> and Zhao *et al.*<sup>19</sup>, have suggested a dosing regimen for intermittent administration of vancomycin, there is limited data on continuous vancomycin PK and dosage in neonates.<sup>20</sup> Additionally, external validation of the model used for dosing recommendations is not often performed<sup>21</sup> (Supplementary Table 1), limiting the use of dosing recommendations only to the population studied<sup>19</sup> and furthermore, sub-therapeutic AUC concentrations of vancomycin are commonly observed with the current dosing regimens.<sup>22-24</sup>

The aim of our study was thus to develop and externally evaluate a population PK model to be able to describe vancomycin PK after continuous and intermittent administration in neonates and infants, and identify covariates contributing to the variability in this population. Furthermore, by using the model we also aimed to compare currently used vancomycin dosing regimens.

## **Methods**

### *Data collection*

Newborn infants with suspected or confirmed sepsis at Royal London Hospital receiving vancomycin were recruited into the study. Neonates with congenital malformation were excluded.

Initial recruitment for this study was between September 2014 and August 2015. The prospectively collected data from the case record forms were used for the model development. For external evaluation of the model, we prospectively collected additional data between February 2016 and June 2016.

### *Ethical approval*

The study was approved by Barts Health Clinical Effectiveness Unit. Since this study was a service evaluation using routinely collected data with no extra blood samples or interventions, the requirement for written informed parental consent was waived.

### *Dosing and sampling procedure*

For the intermittent vancomycin administration, the dosing regimen used in the study was as per British National Formulary for children (BNFc) <sup>25</sup>, i.e. vancomycin was administered via peripheral cannula over 1 hour as described in Table 1.

Continuous vancomycin infusion was administered via the central catheter. An initial loading dose of 15 mg/kg vancomycin was followed by infusion dose based on serum creatinine concentrations (SCr) as described in Table 1.

For intermittent dosing peak and trough concentrations were measured, and for continuous vancomycin, a random concentration was measured 12 hours after starting vancomycin. The

peak concentrations were measured approximately 1 hour after the administered dose and trough concentrations were measured just before the next dose was given. The volume of blood plasma samples collected for vancomycin assay was approximately 0.5 mL. The plasma vancomycin assay was performed using homogenous enzyme immunoassay technique on COBAS 702 platform (Roche Diagnostics, FDA registered). The assay is based on competition between drug in the sample and drug labelled with the enzyme glucose-6-phosphate dehydrogenase for antibody site.<sup>26</sup> The linear range for this assay was 1.7-80.0 mg/L (1.2-55.2  $\mu\text{mol/L}$ ).

#### *Assessment of nephrotoxicity*

Serum creatinine (SCr) values were collected and compared with reference ranges for this population.<sup>27, 28</sup> Acute kidney injury (AKI) while receiving vancomycin was defined as per neonatal Kidney Disease: Improving Global Outcomes (KDIGO) definition.<sup>29</sup>

#### *Population pharmacokinetic analysis*

The first order conditional estimation method with interaction in a non-linear mixed effect modelling software, NONMEM 7.3,<sup>30</sup> was used to perform the population analysis. One- and 2-compartment models were tested to determine the structural model. The between-subject variability was tested on all model parameters and assumed to be log-normally distributed. An additive, a proportional, and a combination of both residual error models were tested.

Allometric weight scaling (with a fixed exponent) and a postmenstrual age (PMA) driven maturation function (with parameters fixed to values from a previously published study<sup>31</sup>) were used *a priori*; this approach has been shown appropriate for the neonatal population.<sup>32, 33</sup>

Covariates, including, postnatal age (PNA), SCr, and inotropes were tested univariately in a stepwise procedure, i.e. they were added into the model if they produced a significant improvement in the fit of the model to the data, i.e. if the difference in the objective function value ( $\Delta OFV$ ) after their inclusion was  $>3.84$  (corresponding to  $p < 0.05$ ) and were retained in the model if after deletion the difference was  $>6.64$  (corresponding to  $p < 0.01$ ).

### *Evaluation of the model*

The model was internally evaluated using goodness-of-fit plots, showing the agreement between the observations and population (or individual) predictions; and the trends in the conditional weighted residuals. The plots were made using R version 3.5.0.<sup>34</sup> We also produced visual predictive checks (VPCs) which entailed simulating 1,000 replicates of the data, computing confidence intervals, and overlaying these over the data for comparison. PsN and Xpose4 were used to produce the VPCs.<sup>35, 36</sup>

The external evaluation was performed without any additional fitting of the model to the data (MAXEVAL=0 option in NONMEM). Model diagnostic plots and the VPCs were generated as for the internal evaluation.

Predictive performance of the model was further evaluated by computing bias and precision as specified below (Equations 1):<sup>37</sup>

$$PE = observed - predicted$$

$$MPE = \frac{1}{N} \cdot \sum_{i=1}^N \cdot PE_i \quad (\text{Equations 1})$$

$$RMSE = \sqrt{\frac{1}{N} \cdot \sum_{i=1}^N \cdot PE_i^2},$$

where PE is prediction error, MPE is mean prediction error (i.e. measure of bias), RMSE is root-mean-square error (i.e. a measure of precision).



### *Simulations to compare dosing regimens*

For the simulated dataset, a uniform distribution was used for GA, and log-normal for PNA, with ranges and standard deviations as in the original dataset. PMA was obtained by summing GA and PNA. Previously published equations, based on the PMA, were used to determine weight,<sup>38</sup> and serum creatinine.<sup>32</sup> MIC was set to 1 mg/L. Monte Carlo simulations (n=1,000 for each regimen) and parameter estimates from the final model were used to compare  $AUC_{24h,SS}/MIC$  achieved with different reference dosing regimens, presented in Table 1, with more detail on the continuous dosing regimens given in Supplementary table S1. Due to the lack of agreement on the dosing regimen, the list presented in the table is not exhaustive and more dosing regimens for vancomycin in neonates are being used in NICUs. However, we decided to test the most commonly recommended intermittent dosing regimens, and (since they are fewer) all continuous regimens that we were able to find in the literature.

## Results

### *Data*

For the model development, 54 newborns and older neonates/infants were studied, 31 of whom received continuous vancomycin infusion and provided 102 vancomycin concentration measurements (Figure 1); and 23 infants on intermittent vancomycin, providing 81 vancomycin samples (Table 2). The model evaluation dataset included a total of 34 infants; 9 infants from the intermittent, and 25 from the continuous group, providing 23 and 84 vancomycin concentration measurements (Figure 1), respectively (Table 2). Infants in both datasets had similar postnatal and gestational ages (Table 2).

Three vancomycin concentrations were below the limit of quantification (2 in the model development dataset, and 1 in the evaluation dataset), and since this represented only 1% of all data, half of the lower limit of quantification was used in these cases. Vancomycin concentrations (n=18 from the model development, and n=5 from the evaluation dataset) with unknown time of sampling and/or unknown time (and amount) of the administered dose were excluded. An additional vancomycin concentration, reported as >50 mg/L was also excluded, as we assumed this was probably a laboratory error (the upper limit of quantification was reported as 80 mg/L). For subjects with missing weight information, weight was obtained using a previously published formula using postmenstrual age.<sup>38</sup>

SCr creatinine values results were available for 77 out of 88 infants (87.5%) in the whole cohort. Seventy six (98.7%) of infants had initial creatinine values within the reference ranges and only one infant had pre-existing high creatinine value above the reference range. Four infants (5.2%) met the criteria for development of acute kidney injury in neonates while on vancomycin. Three of these infants had Stage 1 injury (SCr rise  $\geq 1.5$  to 1.9 times baseline

levels) and one had a Stage 3 injury (SCr rise  $\geq 2.0$  to 2.9 times baseline levels) based on neonatal KDIGO classification.

#### *Population pharmacokinetic modelling*

A 2-compartment model provided no improvement (judged by  $\Delta$ OFV and visual diagnostics); therefore the final structural model was a 1-compartment model. Weight and postmenstrual age were included *a priori*; after that no additional covariate (PNA, SCr or inotropes) significantly improved the model fit thus it was not retained in the final model. Only 2 infants had concomitant administration of non-steroidal anti-inflammatory agents and this was not included as a covariate.

Internal evaluation showed the model was able to adequately describe the data (Figure 2, and Supplementary figures S1 and S3). Final model parameter estimates are shown in Table 3. External evaluation confirmed that the model can predict prospectively collected external data that were not used in the model fitting (Figure 2, Supplementary figure S2). Median (95% CI prediction error was -0.09 (-20.9, 10.8) mg/L in the intermittent administration group, and 0.146 (-13.8, 6.8) mg/L in the continuous group. Bias was -1.99 mg/L for the intermittent and -1.23 mg/L for the continuous administration; and precision 8.48 mg/L for the intermittent and 5.97 mg/L for the continuous administration.

#### *Simulations to compare dosing regimens: continuous might be beneficial over intermittent vancomycin administration in young and immature neonates*

Simulations of the tested dosing regimens (Table 1) showed that when vancomycin was given as either continuous or intermittent infusion and MIC of 1 mg/L was assumed, the majority of

simulated subjects of all age groups reached the pharmacodynamic target ( $AUC_{24h,SS}/MIC$  of 400) (Table 4, Figure 3). The difference between continuous and intermittent regimens was most apparent for the youngest and most immature group of infants (i.e. GA  $\leq$  25 weeks and PNA  $\leq$  2 weeks), where both  $AUC_{24h,SS}/MIC$  and  $AUC_{0-24}/MIC$  were higher with the continuous administration, for example, median (95% CI)  $AUC_{24h,SS}/MIC$  was 663 (246, 1401) with the continuous, and 482 (322, 783) with the intermittent regimens (Table 4). If vancomycin was administered as a continuous infusion and a loading dose was not given<sup>39</sup> or if a loading dose  $<15$  mg/kg was used,<sup>40</sup> the exposure was lower, compared to a loading dose of  $\geq 15$  mg/kg, which was especially obvious in the first 24 hours of therapy where  $AUC_{0-24}/MIC$  was even below 400 (Table 4, Supplementary figure S4). Similar results were observed when age of the younger group was increased to PMA  $<29$  weeks (Table 4).

## Discussion

We developed a pharmacokinetic model for vancomycin in neonates and young infants, using prospectively collected data. Externally evaluation of the model proved it could be used for predictions outside of the studied population. Monte Carlo simulations using the model showed that continuous vancomycin administration might be advantageous over the intermittent administration for the very young and premature neonates when treating infections caused by microorganisms with higher MICs. The continuous dosing regimens (with loading dose  $\geq 15$  mg/kg and MIC of 1 mg/L) also achieved  $AUC_{24h}/MIC \geq 400$  in the first 24 hours of the treatment, which was not possible with the intermittent regimen for most infants.

Our results are in agreement with previously published work, where it was also identified that continuous vancomycin infusions outperform intermittent dosing since they consistently achieve target AUC more often compared to intermittent vancomycin infusions.<sup>6,41</sup> However, whilst our simulations revealed that a loading dose (given as a bolus or 1h infusion) is necessary to achieve  $AUC_{24h}/MIC \geq 400$  as early as possible; some researchers did not find that.<sup>39, 40</sup> When comparing different regimens for continuous vancomycin administration, we also found that although having an advantage of avoiding setting arbitrary cut-offs for when a certain dose should be used, a more complex dosing regimen (as suggested by Zhao *et al.*<sup>19</sup>), did not provide much advantage over a very simple one-fits-all regimen suggested by e.g. Oudin *et al.*<sup>21</sup> (Figure 3). In general, all tested continuous regimens (with a loading dose  $\geq 15$  mg/kg) performed similarly, perhaps showing that a simple one described above could be selected.

While the consensus on vancomycin efficacy target of  $AUC_{24h,SS}/MIC$  in neonates is lacking, most researchers, e.g. Pauwels *et al.*<sup>13</sup> suggest  $AUC_{24h,SS}/MIC \geq 400$ , and some, e.g. Padari *et*

*al.*<sup>42</sup> suggest a lower target might already be effective perhaps due to lower protein binding<sup>11</sup> and therefore higher unbound (i.e. active) vancomycin concentrations in neonates, compared to adults. Since more work is needed to determine whether the target should be lower in neonates, we used a generally accepted target of  $AUC_{24h,SS}/MIC \geq 400$ <sup>16, 43</sup> when performing simulations of several different dosing regimens.. Although it has been recently shown by Zasowski *et al* that vancomycin AUC of 700 mg h/L increases the risk of nephrotoxicity in hospitalised adults,<sup>44</sup> the exposure causing nephrotoxicity is still to be defined in neonates and infants.

Vancomycin pharmacokinetics have been shown to be highly variable, especially in the neonatal population,<sup>43</sup> which was confirmed by our study (between-subject variability in clearance and volume of distribution was estimated as approximately 30% in both cases (Table 2)). A one compartment model described our data best, which has also been found previously in the literature.<sup>21, 45, 46</sup>

Although factors that can affect the PK of vancomycin reported in the literature include weight, gestational age and postmenstrual age, as well as mechanical ventilation, creatinine concentration and use of medications (non-steroidal anti-inflammatory drugs and vasoactive drugs),<sup>13, 21</sup> only weight and PMA were included as covariates in the final model. Serum creatinine, standardised for postmenstrual age,<sup>32</sup> was significant at  $p=0.05$  but not at  $p=0.01$ , therefore it was not retained in the model. The lack of statistically significant covariates might be due to a small size of our dataset, and perhaps not big enough ranges of the tested covariates. However, our study concurred that in terms of vancomycin clearance, weight and age were significant covariates.<sup>7</sup>

Median prediction error in the intermittent and continuous administration group was close to zero (i.e. -0.09 and 0.15 mg/L, respectively), showing our model gives unbiased predictions

of the external data; however, the 95% confidence interval was wider, meaning that there were some outliers that the model did not capture. This is also shown by the calculated bias and the precision metrics. Although the numbers might seem high (i.e. precision was 8.48 mg/L for the intermittent and 5.97 mg/L for the continuous administration), one should keep in mind that some measured vancomycin concentrations were as high as 40 mg/L meaning that relatively to the vancomycin concentration, precision is perhaps not that unacceptable.

While we collected data from 88 preterm and term infants of varying gestational ages and weights (Table 1), and so representing the neonatal intensive care population well, our dataset could be considered small. But, we managed to collect a mean of 3.5 and 3.3 samples per patient from the intermittent and continuous regimen of the model development dataset, and similarly for the model evaluation dataset (Table 1). Smaller dataset is not just a limitation of our study; PK studies often have few subjects included and subsequent limited number of samples for analysis.<sup>47</sup>

Another possible disadvantage could be that this was a single centre study. The local population at the centre was approximately 30-40% Bangladeshi in ethnic origin therefore likely to be different to the rest of Europe. Song *et al.* found that median values for clearance and volume of distribution were higher in Chinese neonates compared to Caucasian neonates.<sup>48</sup> However, to our knowledge, there are no reports of differing pharmacokinetics in Bangladeshi neonates so we believe the results would also represent neonates in other parts of Europe.

Unlike most studies we also performed an external evaluation of the model with a new set of data, collected prospectively especially for this purpose. Given the fact that there have not been many prospective studies of vancomycin in neonates published and since the data are usually collected with greater accuracy in prospective studies compared to retrospective

studies, our study is especially valuable. Our results showed the model was able to predict data similar to the observed (Figure 2) and could therefore be used for simulation of dosing schemes for vancomycin in newborns and older neonates/infants.

### *Conclusion*

A population pharmacokinetic model for intermittent and continuous vancomycin administration in neonates and infants on a neonatal unit was developed. External evaluation showed that the model could predict external prospectively collected data, confirming the model's possible application for Bayesian prediction and simulations. Monte Carlo simulations showed that in regards to achieving  $AUC_{24h,SS}/MIC \geq 400$  target continuous vancomycin administration (with a loading dose  $\geq 15$  mg/kg) could be advantageous over the intermittent administration for the very young and premature neonates, especially for infections with more resistant microorganisms or to help reach higher (therapeutic) exposures faster. More research is warranted to determine what vancomycin exposure could increase risk of nephrotoxicity in neonates and infants.

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## **Transparency declarations**

None to declare.

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## Tables and Figures

Table 1: Dosing regimens used in the study and/or compared in the Monte Carlo simulations

Intermittent administration		Continuous administration	
Patient characteristics	Dosing regimen	Patient characteristics	Dosing regimen
<b>BNFc</b> <sup>25 a</sup>		<b>Our study</b> <sup>a</sup>	
PMA (weeks)	15 mg/kg every:	SCr (μmol/L)	L: 15 mg/kg
<29	24 h	<64	30 mg/kg per 24 h
29-35	12 h	64-100	25 mg/kg per 24 h
>35	8 h	>100-150	15 mg/kg per 24 h
<b>Neonatal formulary</b> <sup>49</sup>		<b>Patel 2013</b> <sup>41</sup>	
PMA (weeks)	15 mg/kg every:	SCr (μmol/L)	L: 15 mg/kg
<29, 1 <sup>st</sup> week of life	24 h	<40 & PMA<40 wks	40 mg/kg per 24 h
<29, older than 1 week	12 h	<40 & PMA≥40 wks	50 mg/kg per 24 h
29-35	12 h	40-60	30 mg/kg per 24 h
36-44	8 h	>60	20 mg/kg per 24 h
>44	6 h		
<b>Blue book</b> <sup>50</sup>		<b>Zhao 2013</b> <sup>19</sup>	
GA (weeks)	15 mg/kg every:	/	L: TC * 0.791 * (WTg/1416) <sup>0.898</sup>
<29	24 h		M <sup>c</sup> : TC * 0.0571 * (WTg/1416) <sup>0.531</sup> * (birthWTg/1010) <sup>0.5</sup>
29-35	12 h		<sup>99</sup> *
>35	8 h		(1+0.282*(PNAd/ 17)) * (SCr/42) <sup>-</sup> 0.525 * 24h
<b>Red book</b> <sup>51</sup>		<b>Oudin 2010</b> <sup>21</sup>	
SCr (μmol/L) <sup>b</sup>		/	L: 20 mg/kg (bolus)
<61.9	15 mg/kg every 12 h		30 mg/kg per 24 h
61.9-79.6	20 mg/kg every 24 h		
>79.6-106.1	15 mg/kg every 24 h		
>106.1-141.4	10 mg/kg every 24 h		

>141.4	15 mg/kg every 48 h		
/	/	<b>Plan 2008</b> <sup>39</sup> SCr (μmol/L) ≤90 >90	L: / 30 mg/kg per 24 h 20 mg/kg per 24 h
/	/	<b>Pawlotsky 1998</b> <sup>40</sup> PMA (weeks) 25-26 <sup>d</sup> 27-28 29-30 31-32 33-34 35-36 37-38 39-40 41-42 43-44 >44	L: 7 mg/kg 10 mg/kg per 24 h 12 mg/kg per 24 h 15 mg/kg per 24 h 18 mg/kg per 24 h 20 mg/kg per 24 h 23 mg/kg per 24 h 26 mg/kg per 24 h 29 mg/kg per 24 h 31 mg/kg per 24 h 34 mg/kg per 24 h 40 mg/kg per 24 h

BNFc British National Formulary for Children, PMA postmenstrual age, PNA postnatal age, GA gestational age, SCr serum creatinine, WTg weight in grams, PNAd is postnatal age in days, L loading dose (administered over 1h, except when specified), M maintenance dose, TC target concentration (20 mg/L was suggested in their study)<sup>19</sup>, <sup>a</sup> dosing regimen used in our study, <sup>b</sup> the following conversion was used 1 mg/dL = 88.4 μmol/L, <sup>c</sup> in simulations, WTg was used as birth WTg was not available, <sup>d</sup> ≤26 weeks was used instead since some virtual subjects had PMA below 25 weeks

Table 2: Summary statistics of infants in the model development and evaluation datasets

	Model development dataset (n=54)	Model evaluation dataset (n=34)
Infants on intermittent/continuous regimen (n/n)	23/31	9/25
Vancomycin samples from infants on intermittent/continuous regiment (n/n)	81/102	23/84
Corrected gestational age (weeks) <sup>a</sup>	29 (23.7-41.9)	28 (23.4-41.7)
Postnatal age <sup>b</sup> at inclusion in the study (days) <sup>a</sup>	30 (1-156)	19 (2-219)
Serum creatinine at the start of therapy ( $\mu\text{mol/L}$ ) <sup>a,c</sup>	31.0 (18-98)	34.0 (15-77)
Peak serum creatinine during therapy ( $\mu\text{mol/L}$ ) <sup>a,c</sup>	27.0 (18-83)	29.0 (18-162)
C-reactive protein (mg/L) <sup>a</sup>	20.0 (5-237)	17.5 (5-205)
Infants with positive blood cultures (n, %)	4 <sup>d</sup> (7.4)	2 <sup>e</sup> (5.8)

<sup>a</sup> median (range), <sup>b</sup> day 0 indicates date of birth, <sup>c</sup> Compensated Jaffe method was used to measure serum creatinine, <sup>d</sup> CoNS (n=4), <sup>e</sup> Methicillin-resistant *Staphylococcus aureus* (MRSA) (n=2)

Table 3: Final parameter estimates with uncertainty

	Mean	Standard error <sup>a</sup>
CL (L/h/70kg)	5.7	0.26
V (L/70kg)	39.3	3.7
BSV in CL <sup>b</sup>	0.10	0.03
BSV in V <sup>b</sup>	0.10	0.05
Covariance between BSV in CL and BSV in V	0.04	0.04
Proportional RUV	0.09	0.02

CL is clearance, V is volume of distribution, BSV is between-subject variability, RUV is residual unexplained variability; <sup>a</sup> from NONMEM covariance step, <sup>b</sup>  $\eta$ -shrinkage was 12.5% for CL, and 40.1% for V.



Table 4: Summary of areas under the curve at steady state (SS), and in the first 24 hours of therapy

	AUC <sub>24h,SS</sub> /MIC <sup>a</sup>		AUC <sub>0-24</sub> /MIC <sup>a</sup>	
	Intermittent	Continuous	Intermittent	Continuous
All	531 (214-1186)	467 (210-1084)	423 (197-847)	443 (202-967)
GA >25 weeks and PNA >2 weeks	532 (214-1188)	475 (210-1124); 466 (209-1066) <sup>b</sup>	425 (197-848)	511 (260-1030); 443 (202-961) <sup>b</sup>
GA ≤25 weeks and PNA ≤2 weeks	482 (322-783)	791 (379-1445); 663 (246-1401) <sup>b</sup>	349 (236-486)	613 (400-1202); 493 (206-1165) <sup>b</sup>
PMA <29 weeks	467 (225-1212)	674 (312-1444)	346 (181-751)	624 (310-1262)

<sup>a</sup> Median (95% confidence interval), <sup>b</sup> continuous regimens including those regimens without a loading dose<sup>39</sup> or with a lower loading dose<sup>40</sup> (Table 1). GA is gestational age, PNA is postnatal age, PMA is postmenstrual age

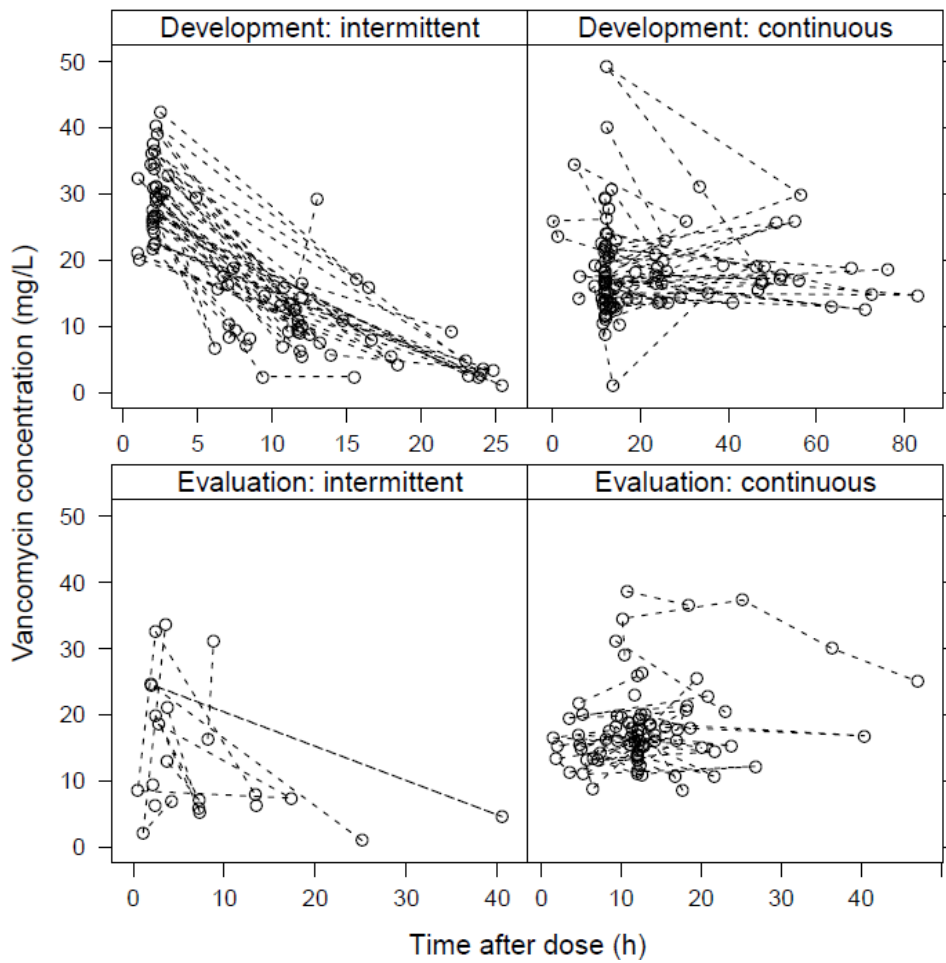


Figure 1: Vancomycin concentration-time profiles used in the model development (above) and evaluation (below) plotted against time after start of an infusion, for both intermittent (left) and continuous (right) vancomycin administration. Data points from the same individual are connected with a dashed line (although not always taken from the same dosing interval).

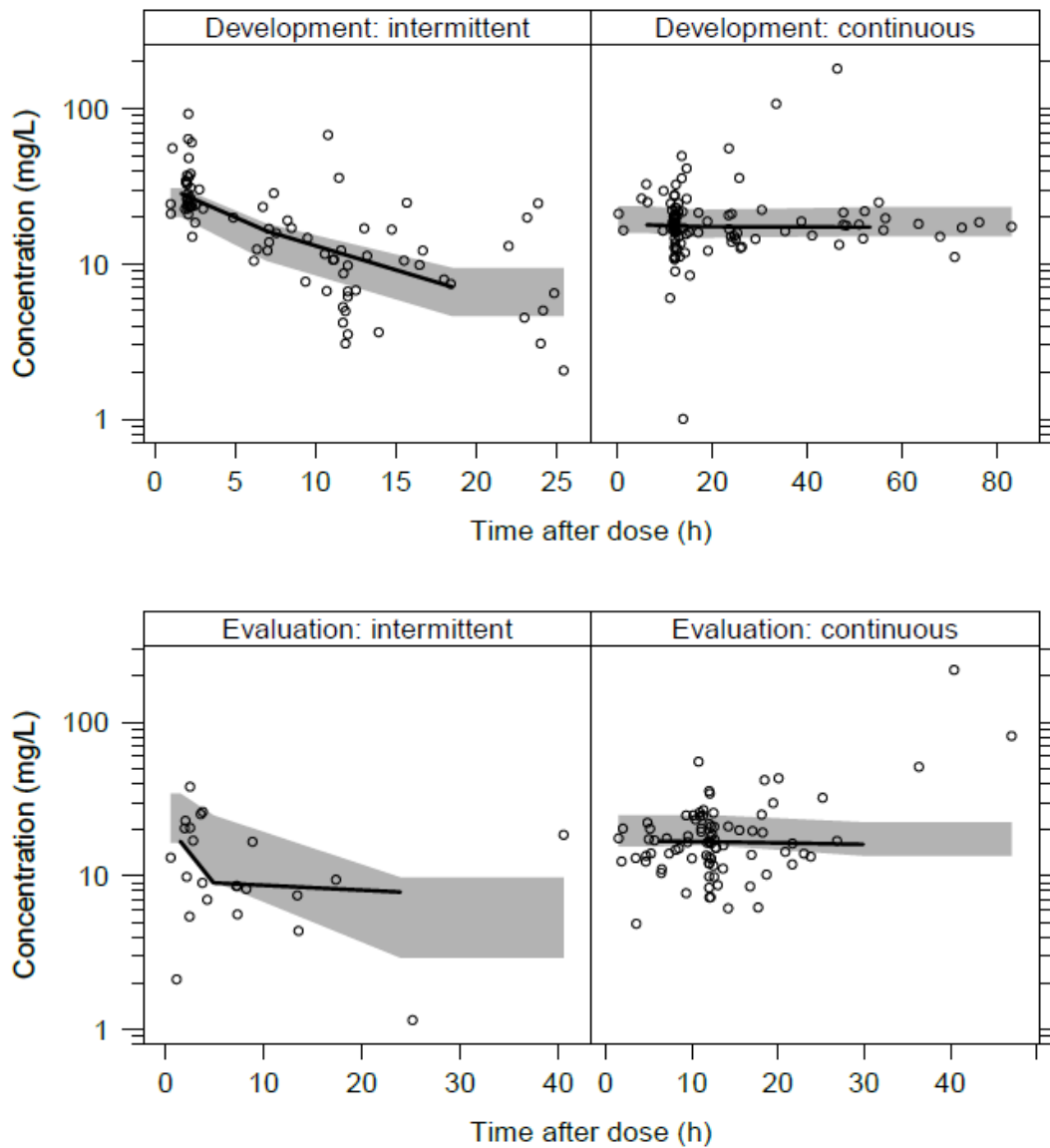


Figure 2: Prediction-corrected visual predictive checks with vancomycin concentrations binned according to time after the start of an infusion. The shaded areas represent 95% confidence interval from 1,000 simulations around the median percentiles (lines) of the model development data (above) and external evaluation data (below).

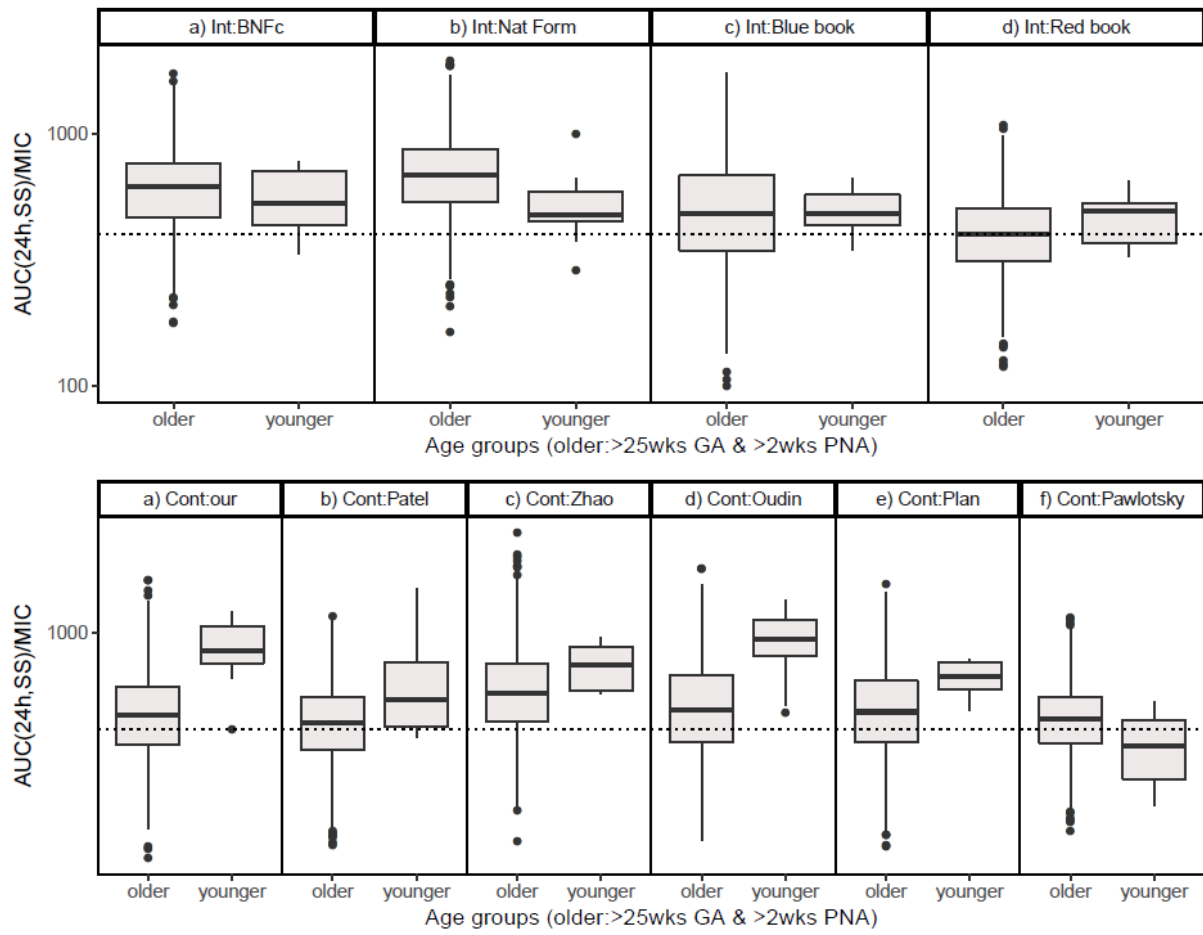


Figure 3: Simulated area under the curve from several intermittent and continuous dosing regimens for vancomycin in neonates/young infants. Distribution of 24h AUC in steady state for very young and immature infants against the rest for intermittent (above) and continuous (below) dosing regimens. GA is gestational age. PNA is postnatal age. Dotted line represents  $AUC_{24h,ss}/MIC$  of 400.