



Bayesian Vancomycin Model Selection for Therapeutic Drug Monitoring in Neonates

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Abstract

Background and Objective Pharmacokinetic models can inform drug dosing of vancomycin in neonates to optimize therapy. However, the model selected needs to describe the intended population to provide appropriate dose recommendations. Our study aims to identify the population pharmacokinetic (PopPK) model(s) with the best performance to predict vancomycin exposure in neonates in our hospital.

Methods Relevant published PopPK models for vancomycin in neonates were selected based on demographics and vancomycin dosing strategy. The predictive performance of the models was evaluated in Tucuxi using a local cohort of 69 neonates. Mean absolute error (MAE), relative bias (rBias) and relative root mean square error (rRMSE) were used to quantify the accuracy and precision of the predictive performance of each model for three different approaches: a priori, a posteriori, and Bayesian forecasting for the next course of therapy based on the previous course predictions. A PopPK model was considered clinically acceptable if rBias was between ± 20 and 95% confidence intervals included zero.

Results A total of 25 PopPK models were identified and nine were considered suitable for further evaluation. The model of De Cock et al. 2014 was the only clinically acceptable model based on a priori [MAE 0.35 mg/L, rBias 0.8 % (95% confidence interval (CI) – 7.5, 9.1%), and rRMSE 8.9%], a posteriori [MAE 0.037 mg/L, rBias – 0.23% (95% CI – 1.3, 0.88%), and rRMSE 6.02%] and Bayesian forecasting for the next courses [MAE 0.89 mg/L, rBias 5.45% (95% CI – 8.2, 19.1%), and rRMSE 38.3%] approaches.

Conclusions The De Cock model was selected based on a comprehensive approach of model selection to individualize vancomycin dosing in our neonates.

1 Introduction

Despite the use of vancomycin in neonatal intensive care units to treat infections for more than four decades [1], a lack of consensus remains on optimal dosing. Dosing decisions

are particularly challenging in neonates, because patient characteristics such as age [gestation at birth and postnatal age (PNA)], body weight, and maturation of organ function contribute to rapid changes in vancomycin pharmacokinetics. Vancomycin is predominantly renally cleared, and its

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Key Points

A pharmacokinetic model selection based on population, disease, and treatment characteristics can help to reduce the workload for model evaluation.

A pharmacokinetic model evaluation using local population data should be used to choose the appropriate model.

A vancomycin trough concentration in neonates does not have to be higher than 15 mg/L to achieve an AUC_{24}/MIC ratio > 400 h.

renal elimination depends mainly on glomerular filtration, which increases as a function of PNA as renal function matures [2]. Although vancomycin pharmacokinetics have been extensively studied, empiric dosing based on either fixed, body weight, serum creatinine, and/or age-based dosing frequently fail to achieve the exposure targets [3]. Hence, dosing decisions should be based on vancomycin concentrations, a practice known as therapeutic drug monitoring (TDM). Trough concentrations (C_{trough}) between 10 and 20 mg/L and the ratio of the area under the 24-hour concentration–time curve to the minimum inhibitory concentration (AUC_{24}/MIC) of 400–600 h have both been considered as exposure targets in adults [4]. However, it remains unclear whether these exposure targets can be extrapolated to neonates. Previously, we have shown that vancomycin dose adjustments were required in 62% of courses of therapy of greater than 3 days [5]. Hence, better vancomycin dosing strategies and more effective TDM practices are needed to achieve vancomycin exposure targets in neonates.

Model-informed precision dosing (MIPD) software, a computational tool, has grown to use mathematical models, patients information, and observed concentrations to optimize therapy [6]. MIPD proved its benefit to predict the required dose to reach target attainment, and broad implementation is limited due to lack of understanding of its benefit and skills, costs, and regulatory issues [7]. Such software has shown benefits in reducing incidence and/or rate of adverse effects and improving clinical outcomes. Also, it proved its benefits in reducing the costs of treating infections [8].

To fully prevail these benefits, we have to select the best model to describe the local patient population, as an inaccurate prediction of drug exposure can lead to inappropriate dose recommendations [9].

Therefore, the aim of our study is to identify vancomycin PopPK models in neonates from literature and evaluate the predictive performance of the selected models using data from our local neonatal intensive care unit (NICU) population. Literature indicated that pharmacokinetics (PKs) in both preterm and full-term neonates are quite similar, and there is no real difference between term and preterm models, as vancomycin PK models consist of various combinations of significant covariates, such as postnatal age, postmenstrual age, and weight, which indicates growth and maturation [2]. Vancomycin AUC_{24}/MIC , rather than trough concentration, is the pharmacokinetic parameter used to inform dosing decisions for vancomycin in adults [10]. Recent studies have revealed that an AUC_{24}/MIC ratio 400–600 h is highly predictive of efficacy and toxicity of vancomycin in neonates [10, 11]. However, AUC_{24}/MIC calculation is practically limited in individuals due to the need of collecting more than one trough concentration. In adults, a trough concentration range between 15 and 20 mg/L is expected to reach an AUC_{24}/MIC ratio > 400 h, but in the case of neonates, lower trough concentration ranges could be sufficient to reach an AUC_{24}/MIC > 400 h [12]. As a secondary outcome, the correlation between AUC_{24}/MIC and a posteriori trough concentrations was evaluated using the best possible model.

2 Methods

2.1 Model Selection

To identify vancomycin PopPK models, a systematic literature search was performed using the PubMed database from its inception to 7 April 2022. The search terms were “vancomycin” and “neonates” and “pharmacokinetics”. Titles and abstracts were independently reviewed by two researchers (DA and RV) before full text articles were retrieved for assessment. The reference lists of included articles were manually screened to identify additional studies. PopPK models were included based on matching local demographic characteristics such as gestational age 28 (24.4–33.3) weeks, postnatal age 19 (1–91) days, postmenstrual age 31.1 (25.1–42) weeks, weight 975 (495–2142) g, and dosing regimen 15 mg/kg intermittent intravenous (IV) infusion [5]. Studies on neonates on extracorporeal membrane oxygenation were excluded. PopPK models lacking relevant details on model parameters preventing replication were also excluded. Data on model structure, population pharmacokinetic parameter values, covariate relationships, inter-individual variability, residual variability, and patient cohorts’ demographic characteristics were extracted from eligible studies. As the babies in our cohort were born as a preterm, and some of them stayed in the hospital for a long time, the median (range) of

hospital stay was 27 (7–90) days, and they received more than one vancomycin course during their hospital stay at different occasions at postmenstrual age (PMA) < 37 or > 37 weeks, we included studies with preterm and term neonates. For studies presenting more than one model with two different settings or populations we chose the model best reflecting our cohort and situation. Out of the models reflecting the same population, we choose the model with the lowest objective function value (OFV) [13]. Extracted data (DA) were independently verified by a second reviewer (TN).

2.2 Vancomycin Validation Dataset

We used a previously published dataset from Westmead Hospital (Sydney, Australia) NICU, which included vancomycin dosing and concentration data from 69 neonates between January–December 2019 [5]. This study was approved by the local Human Research Ethics Committee (approval number 2008-05 QA). Vancomycin dosing and TDM practices were at the discretion of the treating physician. In brief, vancomycin was administered intermittently at 15 mg/kg/dose in a frequency based on patient's corrected gestational age (CGA) and postnatal age. TDM was performed after the fourth dose in neonates age CGA > 29 weeks and before the second dose in neonates of CGA ≤ 29 weeks. The vancomycin dose was adjusted in both of under and overexposure based on the hospital's protocol. A trough concentration between 10 and 20 mg/L was considered the therapeutic target according to the hospital guidelines. All samples included this study were trough concentrations.

2.3 Model Predictive Performance Evaluation

The predictive performance of each selected model was evaluated in Tucuxi [14, 15] using the vancomycin validation dataset [5]. While Tucuxi offers a user-friendly graphical user interface, its core computing engine can also be run as a command line tool. To automate the tests and reduce the human error factor, we designed Python scripts for getting all the data from an Excel file, running the command line tool, and extracting the data. It also offered a way to detect errors in the dataset, allowing a better check of the initial data. The computations were run for all the patients in three different modes: a priori prediction, a posteriori prediction, and Bayesian forecasting for next course. Covariates considered significant in each model such as PNA, CGA, gender, birth weight, weight at initiation of the vancomycin course of therapy, and serum creatinine (Scr) were used for a priori prediction without any vancomycin concentrations. Although, each model has its own structure, whether it is 1 or 2 compartment model and various significant covariates, Tucuxi allows users to upload any model via an online drug editor and select a Bayesian prior based on the study cohort. Afterwards, using parameters and a structural

model, Tucuxi will predict concentrations, which can be compared with the observed concentrations. The observed serum vancomycin concentration for each patient was used for a posteriori estimation of individual pharmacokinetic parameters, which in turn is used to predict concentrations. For patients with more than one course of vancomycin therapy during their hospital admission, the first course of therapy was used to predict the concentrations in the next course, considering interaction between interindividual variability and residual variability for prediction of subsequent serum vancomycin concentrations (Bayesian forecasting). Mean absolute error [MAE, (Eq. 1)], relative bias [rBias, (Eq. 2)] and relative root mean squared error [rRMSE, precision (3)], were calculated to quantify the accuracy and precision of PopPK models, respectively:

$$\text{MAE} = \frac{1}{N} \sum_i^n |\text{predicted}_i - \text{observed}_i| \quad (1)$$

$$\text{rBias} = \frac{1}{N} \sum_i \frac{\text{predicted}_i - \text{observed}_i}{(\text{observed}_i + \text{predicted}_i)/2} \times 100 \quad (2)$$

$$\text{rRMSE} = \sqrt{\frac{1}{N} \sum_i \frac{(\text{predicted}_i - \text{observed}_i)^2}{((\text{observed}_i + \text{predicted}_i)/2)^2}} \times 100, \quad (3)$$

where N is the number of vancomycin concentrations.

A model was considered clinically acceptable when rBias ranged between – 20 and 20% and when the 95% confidence interval (CI) included zero [16, 17]. All models were compared based on bias and rRMSE, and we selected those models with the lowest values because there are no established thresholds for bias and rRMSE in literature; more research is needed to specify the precision acceptability threshold for vancomycin predictions in neonates [17]. The goodness of fit plots was used to assess the correlation between predicted and observed concentrations.

2.4 The Relationship Between Trough Vancomycin Concentrations and AUC_{24h}

The relationship between daily vancomycin AUC_{24h} values and predicted trough concentrations using the best performing model in an a posteriori approach was determined by the linear regression correlation constant [18].

3 Results

3.1 Model Selection

Overall, 25 vancomycin PopPK models for neonates were identified, of which 9 models were evaluated [19–27], the

overall description of the model is in Table 1. Sixteen models were excluded for the following reasons: study included mixed populations other than neonates such as older children and infants [9, 28, 29], vancomycin administration was a continuous infusion [30–32], essential details of the PopPK model description such as model structure, variability, pharmacokinetic parameters, and covariate relationships were lacking [33–37], or patients were receiving extracorporeal membrane oxygenation [38] or positive pressure ventilation [39]. Lastly, one model was excluded, as it was specifically designed to investigate the effect of amoxicillin and spironolactone coadministration on vancomycin clearance and volume of distribution [40]. In the study of De Cock et al. [19], two models were identified. One of these models was excluded, as it included ibuprofen coadministration in the covariate model and used an Amikacin covariate model to predict vancomycin clearance, which is not reflective of our cohort [41]. The flowchart in Fig. 1 summarizes the model selection criteria.

3.2 Validation Vancomycin Dataset

The validation dataset included data on 69 preterm neonates, all admitted to the NICU with a median (range) age of 28 (24.4–33.3) weeks and body weight of 975 (495–2142) g. They received an intermittent IV course of vancomycin with a median (range) daily vancomycin dosage of 18 (9–56) mg/day for 1–8 days, and 118 vancomycin concentrations were available for model validation and simulations. The demographics and baseline clinical characteristics of the population are summarized in Supplementary Table S1.

3.3 A Priori Approach

A priori analysis for all 69 neonates using only patient's covariates showed that models by Frymoyer et al., Grimsley et al., and Mulubwa et al. [20–22] had rBias values between –20 and 20%, but they were considered biased as their 95% CI did not cross through zero (Fig. 2a). Predicted and observed concentrations for Kimura et al., Lee et al., Lo et al., Mehrotra et al., and Dao et al. [23–27] had a significant difference (> 20%), and their rBias was outside the clinically acceptable range. As such these models were not considered further. On the other hand, the De Cock model [19] had a clinically acceptable rBias. Additionally, De Cock had a precision higher than 90%, whereas all the other models had a precision < 61% (Fig. 2b).

3.4 A Priori and a Posteriori Approaches

Using the a posteriori approach for the first observed concentration and the patient's covariates, the accuracy and

precision of all models improved compared with the a priori approach (Fig. 2c, d). For example, the precision of the best fit model (De Cock) increased by 2.88% using the a posteriori approach compared with the a priori approach. A similar conclusion can be reached using the goodness of fit between predicted concentrations using a priori and a posteriori approaches (Figs. 3, 4, respectively) for all selected models. The solid line shows the ideal situation of the perfect model, where observed concentrations equal predicted concentrations. The gradient line shows the trendline of the model's prediction. Using the a priori approach, an ideal correlation factor, due to using one factor of the patient's data (patients' covariates), as such in Fig. 4 shows that the a posteriori approach enhanced the correlation results for all models as it used the recent observed concentrations as well as the patients' covariates. The goodness fit plot in Fig. 4 also suggested that the De Cock model was the best fit for the observed data using the a posteriori approach.

3.5 A Posteriori Bayesian Forecasting for the Next Course

Overall, 27 neonates had 2–5 courses of vancomycin during their hospital stay and were used to assess the Bayesian forecasting approach using the previous course's observations. In Fig. 2e, the De Cock rBias did not improve compared with the former two approaches. Furthermore, precision reduced to less than 62% for all models, as illustrated in Fig. 2f. The De Cock model was the only clinically acceptable model using all approaches. Renal changes over time in newborn were modeled using age indicator (PNA) and the ratio between observed and predicted concentrations, as in Fig. 5. It shows that predictions in neonates with age range between 15–30 days was adequate with a ratio close to 1. The trend to lower ratios in some of the models can be explained by change in renal function with PNA. Glomerular filtration maturation changes in premature babies with PMA < 37 weeks is slower than in babies with PMA > 37 weeks. This was because nephrogenesis is not accomplished before 34–35 weeks gestational age [42, 43].

3.6 Trough Concentration and AUC_{24h} Relationship

The De Cock et al. [19] model was used to compare the predicted vancomycin trough concentrations and AUC₂₄ values. In Fig. 6, the regression line shows that a trough concentration range between 10–15 mg/L correlates with an AUC₂₄/MIC ratio of 400–600 h, assuming a MIC of 1 mg/L. It showed a high correlation constant for a posteriori prediction ($r^2 = 0.9807$).

Table 1 Description of the population pharmacokinetic models for vancomycin in neonates

References	Year	Neonates (n)	Samples (n)	PNA (days) [median (mini- mum–maxi- mum)]	GeA (weeks) [median (mini- mum–maxi- mum)]	Weight (kg) [median (mini- mum–maxi- mum)]	Model struc- ture/modeling software	Pharmacokinetic parameters and covariate relation- ship	BSV (std)	RUV	Model evaluation
Lee [24]	2021	207	900	2.3 (0–16.4)	31.5 (23.3– 41.5)	1.5 (0.5–5.4)	1 CMT/NON- MEM®	CL = 2.09 * (WT/70) ^{0.75} * (PMA/31.7) * (CLcr/50.3) ^{0.741} V = 45.6 * (WT/70)	CL: 0.123 V: 0.26	Add: 2.015 mg/L Prop: 0.583	Bootstrap
Mulubwa [22]	2020	19	45	14 (3–58)	31 (23–34)	1.27 (0.63– 2.69)	1 CMT/Mono- lix 2018R2	CL = 0.102 * (wt/1.48) ^{0.75} * e ⁿ V = 0.884 * (wt/1.48) ¹ * e	CL: 0.071 V: 0.107	Exp: 0.284	GOF (IWRES) and visual pre- dictive checks (VPC).
Dao [27]	2020	405	1831	12.3 (5–14)	29 (26.7–34.9)	1.05 (0.79– 2.17)	1 CMT/NON- MEM®	CL = θ_1 * (WT/ WT _{median}) ^{0.2} * (SCR _{median} /SCR) ^{0.3} * (PMA ^{Hill} / PMA ^{Hill} + T50 ^{Hill}) V = θ_4 * WT	CL: 0.226 V: none	Add: 1.98 mg/L Prop: 0.236	GOF, bootstrap, pcVPC, and NDPE
Frymoyer [20]	2019	492	1702	19 (10–42)	34 (27–39)	2.9 (1.6–3.7)	1CMT/NON- MEM®	CL(L/h) = 0.345 (WT/2.9) ^{0.75} * 1/(1 + [PMA/34.8] ^{-4.53} * (1/SCR) ^{0.267} V(L) = 1.75 * (WT/2.9)	Exp: 0.216	Add: 1.3 mg/L Prop: 0.205	Bootstrap and NDPE
DeCock [19]	2014	273	689	14 (1–28)	29 (29–34)	1.14 (0.3–2.55)	2 CMT/NON- MEM®	CL = CL _p * (bBW/median) ^m * (1 + n * (PNA/median)) V ₁ = V _p * (cBW/ median) ^y	CL: 0.103	Prop 0.0938 mg/L	GOF and NPDE
Mehrotra [26]	2012	134	267	(26.8 ± 24.3) ^a	(32.7 ± 5.7) ^a	(2.5 ± 1.1) ^a	1CMT/NON- MEM®	CL = 0.18 * (weight/2.5) ^{0.75} * 0.42/Scr ^{0.7} * PMA/37) ^{1.4} V = 1.7 (WT/2.5) ^{1.0}	CL: 0.249 V: 0.215	Add: 1.5 mg/L Prop: 0.16	Predictive check

Table 1 (continued)

References	Year	Neonates (n)	Samples (n)	PNA (days) [median (mini- mum–maxi- mum)]	GeA (weeks) [median (mini- mum–maxi- mum)]	Weight (kg) [median (mini- mum–maxi- mum)]	Model struc- ture/modeling software	Pharmacokinetic parameters and covariate relation- ship	BSV (std)	RUV	Model evaluation
Lo [25]	2010	116	835	6.6 ± 1.6	27.5 ± 1.1	0.97 ± 0.09	1 CMT/ NONMEM®	CL = 1.0 * (WT/70) ^{0.75} * (PMA/30) ^{3.16} * [0.83 * SGA 1 1.03 * (1-SGA)] V = 36.6 * (WT/70)	CL: 0.202 V: 0.125	Add: 1.5 mg/L Prop: 0.229	VPC and Boot- strap
Kimura [23]	2004	19	(3–71) ^b	(24.1–41.3) ^b	710–5200	1 CMT/NON- MEM®	CL = 0.0323 * WT/SCr; if PCA ≥ 34 CL = 0.025 * WT/ SCr; if PCA < 34 V = 39.4 * (WT/70) * 1.19 (L/70 kg)	CL: 0.226 V: 0.205	Add: 3.22 mg/L	Bootstrap	
Grimsley and Thomson [21]	1999	59	347	19 (2–76)	29 (25–41)	1.52 (0.57– 4.23)	1 CMT/NON- MEM®	CL = 3.56 * WT/ SCr ^c V = 0.669 * WT (L/kg) Q = r * CL V ₂ = V ₁	CL: 0.217 V: 0.178	Add: 4.53 mg/L	Diagnostic plots

Add RRE additive residual random error, BSV between-subject variability, BW birth weight (kg), CL clearance (L/h), CMT compartment, CL_{Cr} creatinine clearance (mL/min) calculated with Schwartz equation, GA gestational age (weeks), GOF goodness of fit, NPDE normalised prediction distribution errors, pcVPC prediction-corrected visual predictive check, PCA postconceptional age, PNA post-natal age (days), Prop RRE proportional residual random error, Q inter-compartmental clearance (L/h), RUV residual unexplained variability, SCr serum creatinine (µmol/L), SGA small for gestational age, V volume of distribution (L), V₁ central volume of distribution (L), V₂ peripheral volume of distribution (L), VPC visual predictive check, IWRES individual weighted residuals

^aMean ± SD

^bRange

^cSerum creatinine in mmol/L

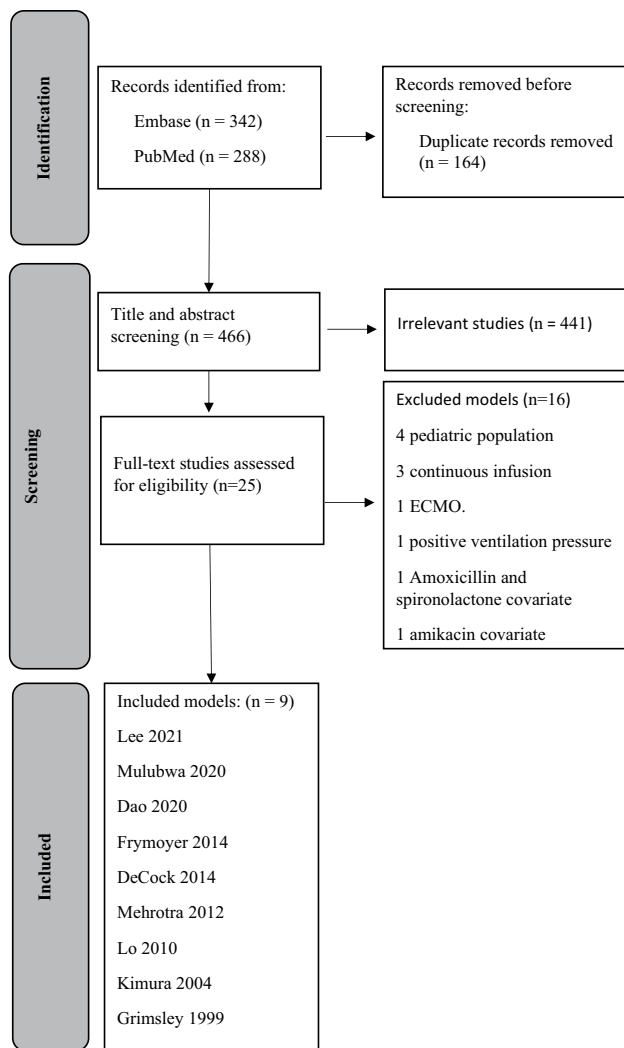


Fig. 1 Flowchart of the model selection

4 Discussion

The predictive performance of nine PopPK models for vancomycin in neonates were evaluated in a cohort of 69 preterm neonates (Table 2). In our study, we informed on the most appropriate model to be used in dosing software to calculate vancomycin dosing in NICU. All the models used the trough concentration (one reading) to predict concentration, but no peak concentration was collected in our cohort; this was one of our study limitations. For neonates < 29 weeks gestational age, blood sampling was done before the second dose, which could not be extrapolated to steady state concentration. The De Cock model was the best performing

model based on the lowest rBias, bias, and rRMSE using all approaches, and it shows minimal data spread around the linear regression between predicted and observed concentration. As shown in Fig. 2, RMSE values were low for the De Cock model in the first two approaches, and a priori and a posteriori approaches 8.9 and 6.02%, respectively; on the other hand, the RMSE value was not low in case of the third approach (38.3%). This can be explained by the fact that the maturation of renal function in neonates, which is highly related to PNA, is expected to affect volume status and clearance and, therefore, change vancomycin pharmacokinetic in the next course.

In Fig. 4, using a Bayesian method and trough only concentrations, observed concentrations are very close to predicted concentrations. Unfortunately, no peak concentration was collected in our cohort, and this was one of our study limitations. For neonates < 29 weeks gestational age, blood sampling was done before the second dose, which could not be extrapolated to steady state concentration. There were cases with more than one trough concentration in our cohort, ten babies had two trough samples, and three babies had three samples during their treatment course. For patients with multiple courses of vancomycin, the accuracy and precision of all the model's predictions did not improve when using vancomycin concentrations from a previous course of therapy. This highlights the importance of obtaining vancomycin concentration during the current course of therapy in preterm neonates and the use of it to guide dosing. This may in part reflect the rapid organ maturation in neonates [44] and/or dynamic changes in physiology related to their critical/unstable conditions [45]. Hence, timely collection of a new vancomycin concentration in the ongoing course will provide the most accurate and precise information on drug exposure and is best suited to guide the dose.

Neonates are a diverse group, ranging from extremely premature infants to full-term newborns, and factors such as gestational age, birth weight, ethnicity, and postnatal age can significantly affect the pharmacokinetics and pharmacodynamics of vancomycin. Herein, many factors could affect the process of model building and evaluation, such as study settings, population characteristics, sample size used to build the model, and analytical model. Race and ethnicity can affect drug response and metabolism, because it contributes pharmacokinetic of drugs such as renal secretion (clearance), hepatic metabolism, protein binding, and volume of distribution [46]. A study in adult patients showed that a race-based based estimated glomerular filtration rate (eGFR) equation performed better to predict vancomycin clearance in Thai population [47]. This has not yet been confirmed in

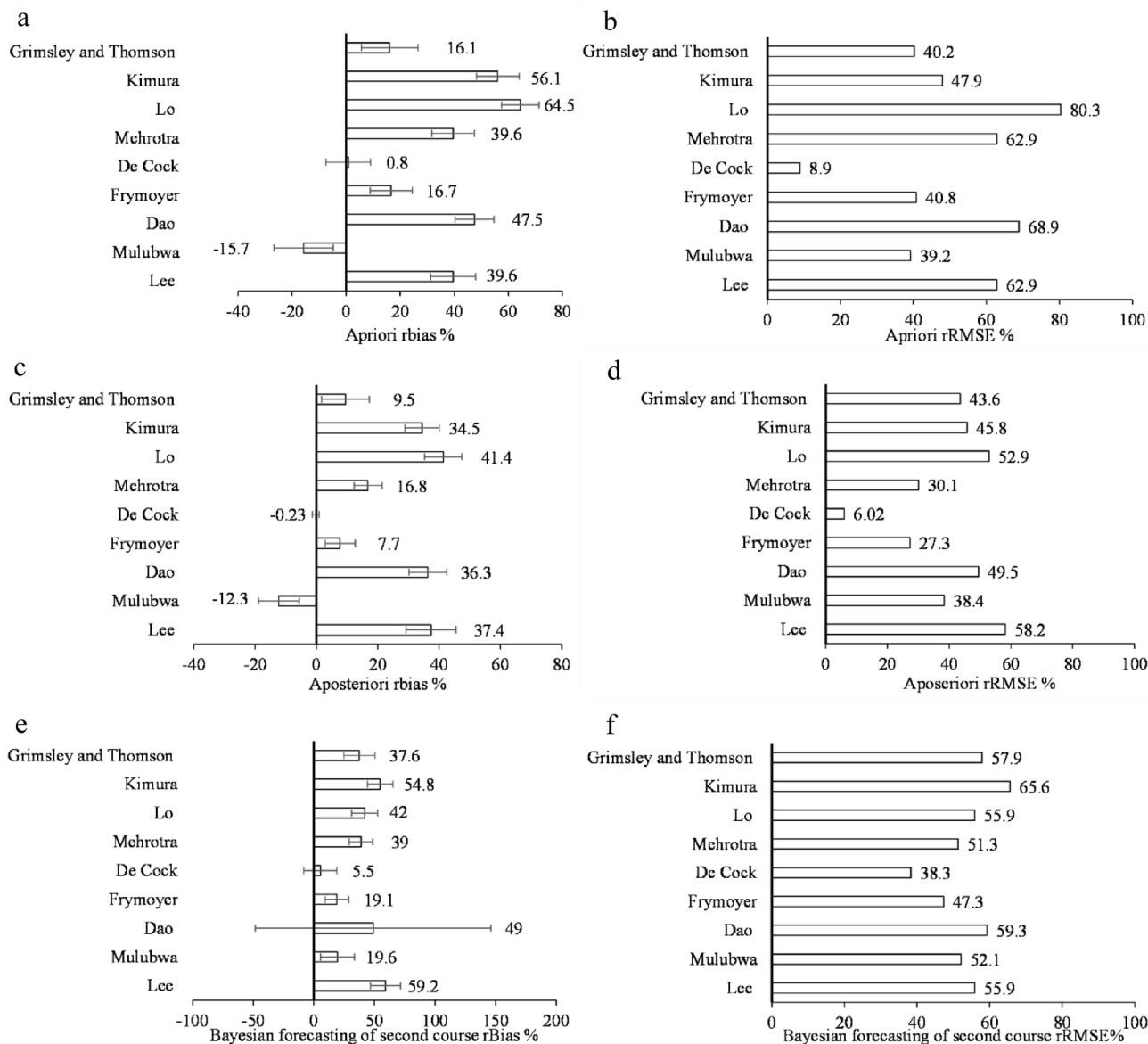


Fig. 2 Models rBias (a) and rRMSE (b) for apriori prediction, models rBias (c) and rRMSE (d) for a posteriori prediction, and models rBias (e) and rRMSE (f) for Bayesian forecasting of second course predictions. Data labels adjacent to each bar are shown for rBias and

rRMSE. Error bars; 95% CI of rBias%. For the clinically acceptable model, the rBias was between -20 and 20%, and 95% CI passed through zero. *rBias* relative bias (accuracy), *rRMSE* relative root mean square error (precision)

neonates likely due to underpowered studies [48]. Therefore, model built using a wide range of neonatal populations may exhibit a great variability and could be generalized, as it is not restricted to one category of population. For example, our dataset had a diverse ethnicity, as the catchment area of our hospital has the largest ethnic diversity in Australia [49]. As such, models built based on a specific ethnic group

of population may not be adequate to predict PK parameters in a more general population, such as the model by Lo et al., which was built using data from Malaysian preterm neonates. Moreover, differences in study design could affect model building and evaluation process, such as retrospective versus prospective studies. Retrospective studies rely on medical records and may have limited control over data

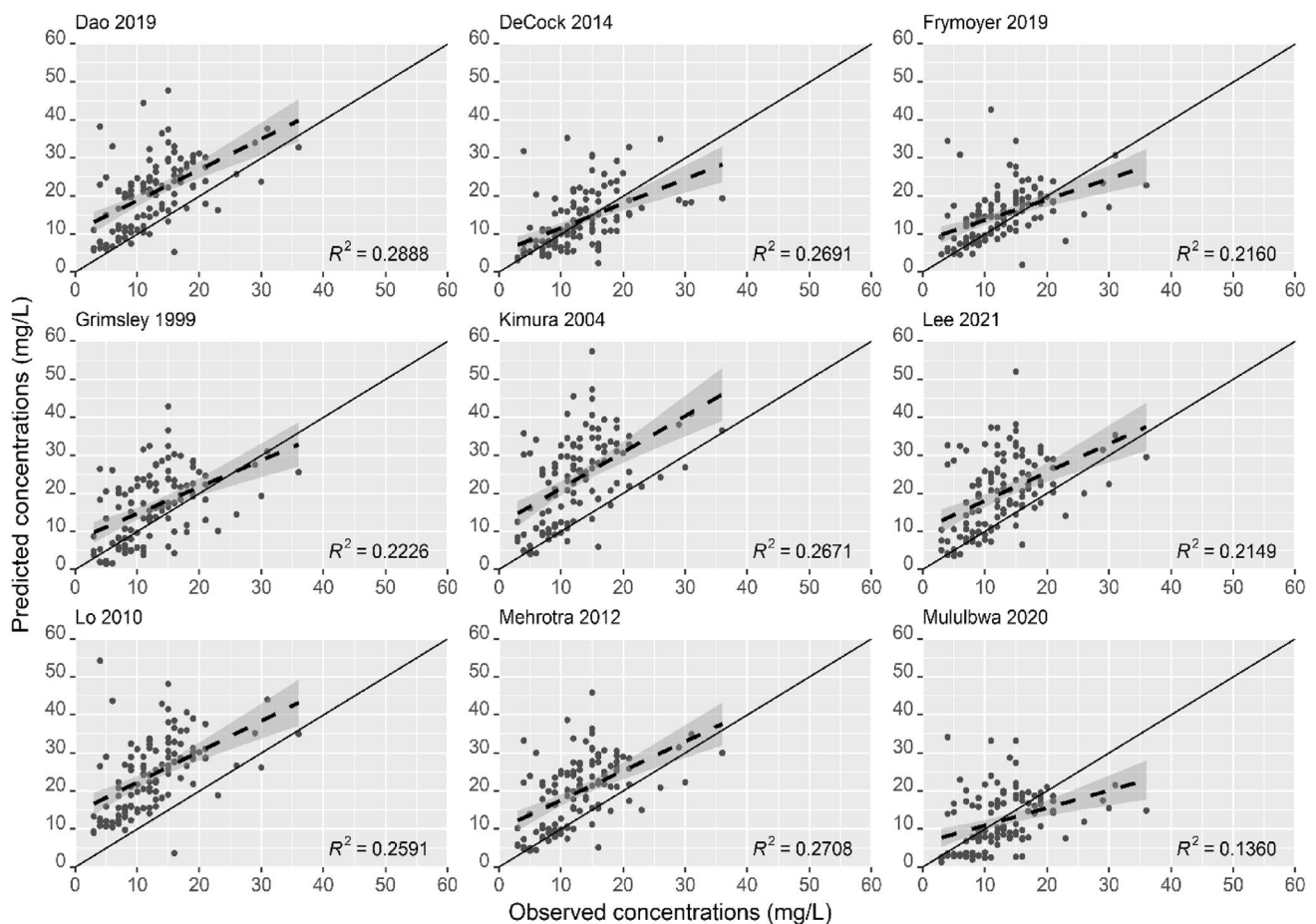


Fig. 3 Goodness of fit plot, portraying the predicted concentrations using a priori approach for all selected models. The solid line shows the ideal situation of the perfect model, where observations equal predictions. The gradient shows the trendline of the model's prediction

collection and patient management. Prospective studies, on the other hand, allow for standardized data collection, more rigorous monitoring, and controlled dosing regimens, reducing some sources of variability. Furthermore, models built using a smaller population size may not give a complete description of patient's population pharmacokinetics of vancomycin. This may result in biased or imprecise Bayesian estimation of vancomycin exposure, such as what we noticed in the Mulubwa and Kimura models, which were built using only 19 neonates, which might be the reason that those two models did not perform well in our dataset. Variations in laboratory techniques, calibration standards, and quality control procedures can introduce variability in measured drug concentrations across studies, as such, affecting model building and evaluation.

There are multiple possible reasons why the De Cock model performed well with our data. First, vancomycin exposure after IV infusion is generally described by a two-compartment model [9]. The original model by De Cock et al. is a two-compartment model, and it was based on a large dataset of 689 neonates, where all neonates were preterm with a birth weight range between 385 and 2550 g and a PNA of 1–28 days. In our cohort, all neonates were born prematurely (< 28 weeks gestation) and started a vancomycin course within a median (range) of 20 (1–91) days of their life. Comparable neonatal populations (i.e., gestational age and birth body weight) between the model building dataset of De Cock and our validation dataset might explain the good performance of the De Cock model compared with other models.

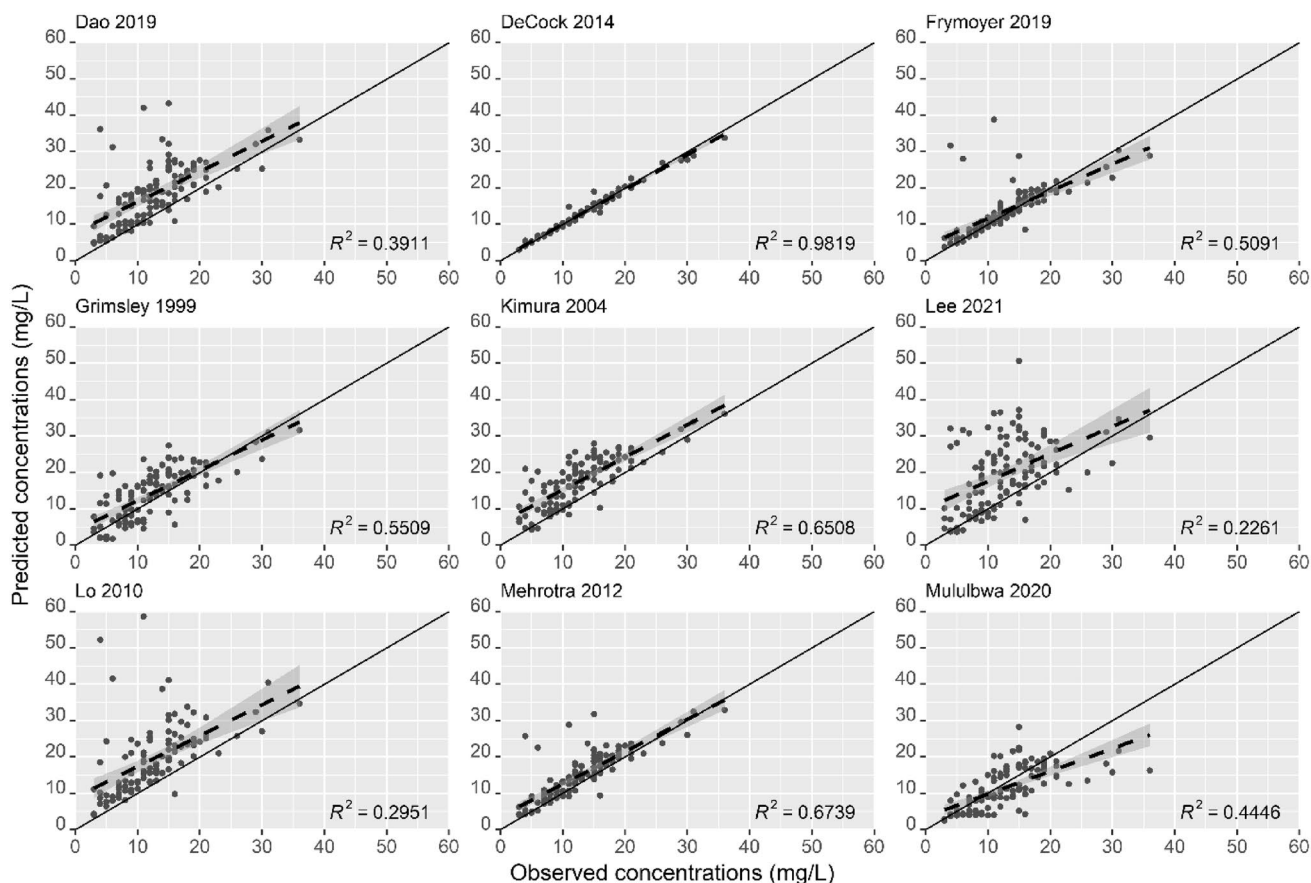


Fig. 4 Goodness of fit plot, portraying the predicted concentrations using a posteriori prediction approach for all selected models. The solid line shows where observations equal predictions. The dashed line shows the trendline of the model's prediction

AUC_{24}/MIC is an important pharmacokinetic parameter used to evaluate the efficacy of vancomycin therapy in adults. For most infection caused by susceptible Gram-positive bacteria, a target AUC_{24}/MIC ratio of 400–600 h is considered optimal [50]. In this study, an AUC_{24}/MIC ratio of 400–600 h correlated well with a trough concentration of 10–15 mg/L, with a high correlation coefficient close to one that is consistent with the high correlation factor found by other studies, which used a large number of neonates, such as Tseng et al. [51]. It was found that the trough concentration does not have to be higher than 15 mg/L in neonates to achieve AUC_{24}/MIC ratio > 400 h [52]. Also a recent study revealed a significant correlation between trough concentration and AUC_{24}/MIC at

different dosing and dosing intervals [11]. The PMA of our cohort ranged from 25 to 42 weeks, with a weight of 495–2142 g, which can be considered heterogeneous. The vancomycin dosing regimen of our hospital [3] includes dosing according to PMA and PNA, bodyweight, and renal function, which likely corrected for this heterogeneity, as shown in Fig. 6.

Our study also has some limitations. We applied a predefined criterion developed with the aim to select a model suitable for clinical practice in our patient population. Use of this criterion may have resulted in the exclusion of models that could have performed well. This was seen earlier in a study by Colin et al. [53], which included a greater age range than considered appropriate for our intended population. In our

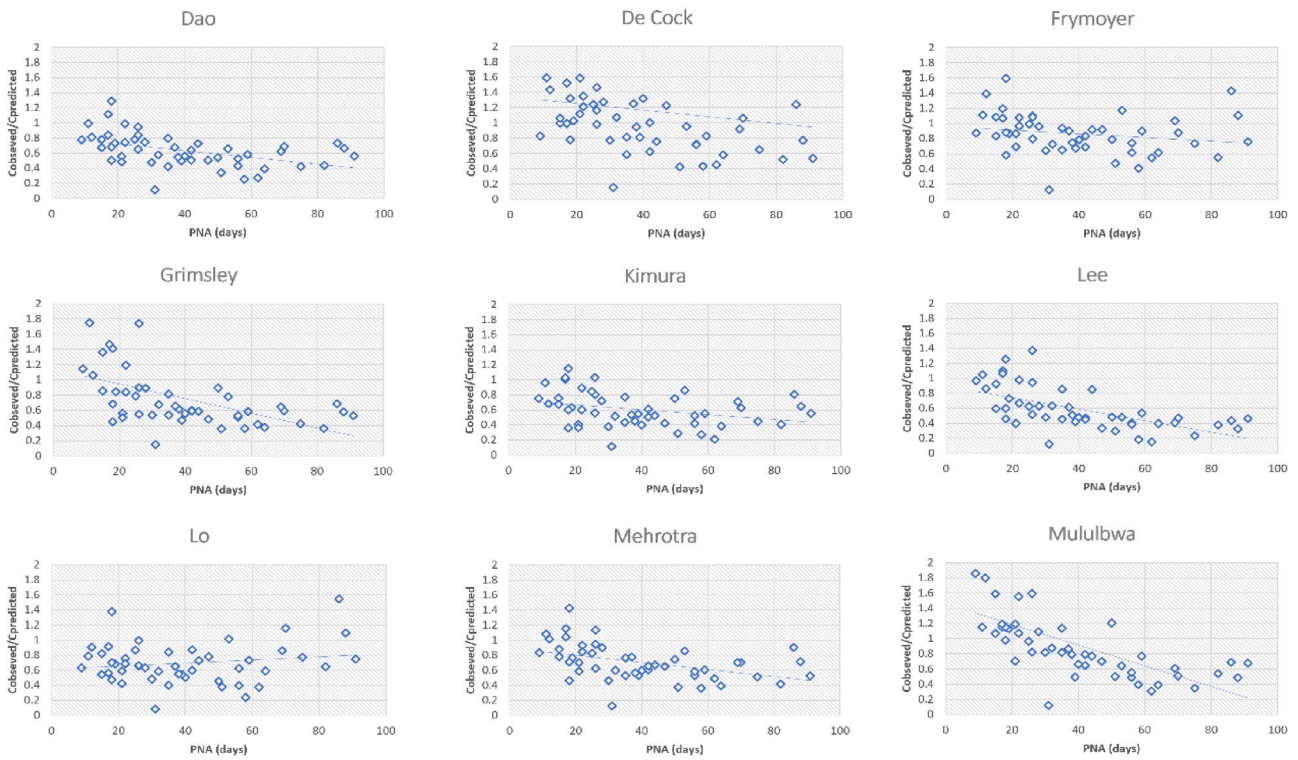


Fig 5 Overall performance of concentration prediction for vancomycin using the prediction of a next course approach using postnatal age (PNA) and ratio between observed and predicted concentrations in all models

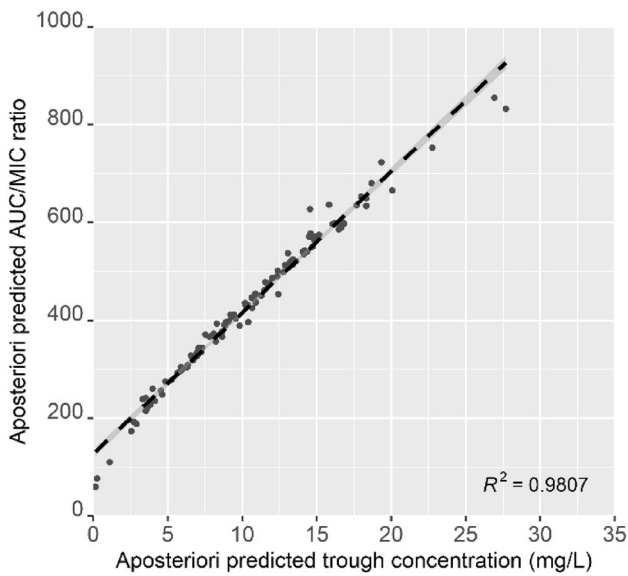


Fig. 6 AUC/MIC and trough concentration correlation using De Cock model in a posteriori approach

study, we did not exclude outliers, as bias due to outliers may have impacted model performance. However, in our opinion, the current number of patients in the validation dataset was fit for the purpose in selecting the best model for the local patient population suitable for clinical implementation. Models used for extracorporeal membrane oxygenation (ECMO) patients and positive ventilation pressure were excluded, as it was not representative of our cohort.

5 Conclusions

The De Cock model was the most precise and accurate in predicting vancomycin exposure (with and without including a vancomycin concentration) in neonates. Using a recent vancomycin concentration improved the predictive performance of all models evaluated. Also, a trough concentration 10–15 mg/L is adequate to reach $AUC_{24}/MIC > 400$ h in neonates.

Table 2 The overall model bias and precision for Bayesian predicted vancomycin concentrations

Model	A priori			A posteriori Bayesian forecasting			A posteriori Bayesian forecasting for the next course		
	MAE	rBias mean (95% CI)	rRMSE	MAE	rBias mean (95% CI)	rRMSE	MAE	rBias mean (95% CI)	rRMSE
Lee [24]	0.848	39.6 (31.3, 47.9)	62.9	0.804	37.4 (29.2, 45.6)	58.2	0.557	59.2 (46.8, 71.6)	55.9
Mulubwa [22]	0.566	- 15.7 (-26.6, - 4.8)	39.2	0.284	- 12.3 (- 18.9, - 5.6)	38.4	0.290	19.6 (5.6, 33.6)	52.1
Dao [27]	0.896	47.5 (40.3, 54.7)	68.9	0.638	36.3 (30.2, 42.5)	49.5	0.382	49 (- 48.2, 146.2)	59.3
Frymoyer [20]	0.494	16.7 (8.9, 24.5)	40.8	0.240	7.7 (2.9, 12.6)	27.3	0.199	19.1 (9.5, 28.8)	47.3
De Cock [19]	0.426	0.8 (- 7.5, 9.1)	8.9	0.035	- 0.23 (- 1.3, 0.88)	6.02	0.172	5.5 (- 8.2, 19.1)	38.3
Mehrotra [26]	0.796	39.6 (31.7, 47.4)	62.9	0.289	16.8 (12.3, 21.4)	30.1	0.299	39 (29.3, 48.7)	51.3
Lo [25]	1.285	64.5 (57.6, 71.4)	80.3	0.762	41.4 (35.3, 47.4)	52.9	0.358	42 (31.3, 52.7)	55.9
Kimura [23]	1.135	56.1 (48.2, 64.0)	47.9	0.544	34.5 (28.9, 40.1)	45.8	0.456	54.8 (44.3, 65.3)	65.6
Grimsley and Thomson [21]	0.681	16.1 (5.7, 26.6)	40.2	0.414	9.5 (1.7, 17.3)	43.6	0.373	37.6 (24.8, 50.4)	57.9

These values represent the Bayesian predictive performance of the tested models for a priori, aposteriori, and Bayesian forecasting for the next course. A model had a clinically acceptable bias if rBias was between - 20 and 20%, and the 95% confidence interval passed through 0. The model with the lowest rRMSE has a high predictive precision

MAE mean absolute error, rBias relative bias, rRMSE relative root mean square error

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Declarations

Conflict of interest All authors have no conflict of interest.

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