

# Evaluating and Improving Vancomycin Pharmacokinetic Models in Pediatric Cardiovascular Intensive Care Unit (CVICU) Patients Using Routine Clinical Care Data

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## Background

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Dose optimization of vancomycin in pediatric cardiovascular intensive care unit (CVICU) patients is inherently complex due to known alterations in vancomycin pharmacokinetics and increased risk of acute kidney injury after cardiac surgery.

InsightRX provides several CVICU-supporting vancomycin models in the Nova platform, which were developed to model the altered pharmacokinetics of vancomycin in pediatric patients after cardiac surgery.<sup>1-3</sup> However, vancomycin dose advice for most pediatric CVICU patients in

the Nova platform to-date has used the Le 2014 model, which was developed on a largely general population of pediatric patients receiving vancomycin.<sup>4</sup> InsightRX previously recommended using the Le 2014 model as the default for all patients receiving vancomycin, but changed this recommendation to the Colin 2019 model in Fall 2024. The Colin 2019 model is a meta-model that was developed to characterize vancomycin pharmacokinetics across a broad range of patient populations, including those with extreme ages and weights.<sup>5</sup>

The goal of this study was to compare the predictive performance across these five models, in order guide model selection decisions for model-informed precision dosing (MIPD) of vancomycin in pediatric CVICU patients.

## Methods

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### Data Collection

Patient data collected retrospectively or during routine clinical care of pediatric patients treated with intravenous vancomycin and entered into InsightRX Nova between January 2018 and April 2025 were de-identified and analyzed retrospectively. Patients were included if they were under the age of 20 years old, had at least one serum vancomycin level obtained as part of therapeutic drug monitoring (TDM), and were tagged as a CVICU patient by the clinician during treatment.

Patients were excluded from analysis if they received hemodialysis, continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), or a ventricular assist device (VAD), or were also tagged as neonatal ICU (NICU) or pediatric ICU (PICU) patients, as these were considered separate populations that do not describe a typical CVICU patient. Prior to analysis, we removed patients with anomalous data, such as patients flagged as potentially fake in the Nova platform, assumed inaccurate dosing records (e.g., suspected missing doses), and otherwise suspicious data (e.g., suspiciously high troughs relative to renal function, assumed typos, etc.). We also removed any treatment courses where the first dose was missing after applying other exclusion criteria, dose gaps greater than 70 hours were present, TDMs were collected during infusion, or one or more records had anomalous weights or heights for age based on CDC growth charts (< 0.1 or > 99.9th percentiles). Following model-based predictions, patients whose predictions had an absolute conditional weighted

residual (CWRES) greater than 4 for any model were removed, on account of being an extreme outlier.

A sample of non-CVICU patients who met the same inclusion and exclusion criteria was also included for analysis, as a point of comparison to contextualize our results. Propensity score matching was used to select a subset of non-CVICU patients whose baseline characteristics were similar our final sample of CVICU patients.

## **Propensity Score Matching**

Propensity scores were estimated using logistic regression of the patient group on the following baseline covariates: Sex, post-menstrual age, height, weight, and serum creatinine, as well as the total number of TDMs for each patient. The matching procedure was iterated upon until we achieved an acceptable covariate balance. We first attempted 1:1 optimal propensity score matching without replacement. This matching specification yielded an excellent balance, confirmed by graphical checks of covariate distributions between the treatment and matched groups. No improvement in balance was achieved modifying the propensity score model to include interactions between all covariates; therefore, we selected the original propensity score model as our final model for matching.

## **Pharmacokinetic Analysis**

Five population pharmacokinetic models (Colin 2019, Kamp 2024, Le 2014, Moffett 2019, Shimamoto 2023)<sup>1-5</sup> were selected for comparison from the literature using the following criteria: First, a literature search was performed to identify models suitable for describing pharmacokinetics in pediatric patients after cardiac surgery. This search identified three suitable vancomycin models, given the availability of covariates in our data set (Kamp 2024, Moffett 2019, Shimamoto 2023). Second, a small handful of general pediatric vancomycin models were selected based on their good performance and/or use in MIPD clinical routines via the InsightRX Nova precision dosing platform (Colin 2019, Le 2014). All selected models differed in the covariates used as predictors of vancomycin clearance ([Table 1](#)).

Table 1: Covariates used as predictors of vancomycin clearance for each pharmacokinetic model included in the analysis.

Model	AGE	PMA	WT	CR	CRCL
Colin 2019	—	X	X	X	—
Kamp 2024	—	—	X	—	X
Le 2014	X	—	X	X	—
Moffett 2019	—	X	X	—	X
Shimamoto 2023	—	X	X	—	X

Abbreviation: AGE = Age (years), PMA = Post-menstrual age (weeks), HT = Height (cm), WT = Weight (kg), CR = Serum creatinine (mg/dL), CRCL = Creatinine clearance (L/hr or L/hr/1.73m<sup>2</sup>)

For each model, population PK parameters were used to predict the first serum vancomycin level of each patient treatment course. Subsequent serum vancomycin levels were predicted using individualized maximum a posteriori (MAP) Bayesian estimates of PK parameters, obtained by iteratively subsetting and fitting patients' historical data within each treatment course. In the context of clinical decision support, these *a priori* and *a posteriori* predictive values reflect the capability of a model to determine the optimal starting dose and dose adjustment strategy for a patient throughout their treatment course, respectively.

The *a priori* and *a posteriori* predictive performance of each model was evaluated for prediction precision, bias, and accuracy. Prediction precision was evaluated using root mean square error (RMSE); prediction bias was evaluated using mean percent error (MPE); and prediction accuracy was evaluated by quantifying the proportion of predicted drug concentrations that fell within an absolute error margin of 2.5 mg/L or a relative error margin of 15% of the measured concentrations. These metrics were calculated by comparing the (iteratively) predicted drug concentrations (*pred*) relative to the measured concentrations (*obs*) across  $N$  concentrations as follows:

$$\text{RMSE} = \sqrt{\frac{\sum_{i=1}^N (\text{pred}_i - \text{obs}_i)^2}{N}},$$

$$\text{MPE} = \frac{1}{N} \sum_{i=1}^N \frac{\text{pred}_i - \text{obs}_i}{\text{obs}_i}.$$

To interpret strength and uncertainty in these error metrics, point and 95% confidence interval (CI) estimates were constructed by bootstrapping samples and computing each error metric

across these samples. The resultant intervals showed the estimates most compatible with our data, given the correctness of the set of procedural and statistical assumptions used to compute each interval. For vancomycin, we considered a model as clinically acceptable if prediction precision, bias, and accuracy were within a clinically acceptable range ( $RMSE < 5$ ,  $|MPE| < 0.25$ , and  $Accuracy > 0.60$ ), and the 95% CI of bias included zero.

## Pharmacokinetic Model Refitting

The previously described pharmacokinetic analysis did not yield a clear winner in terms of a priori and a posteriori predictive performance. Therefore, we decided to repeat this analysis on refit versions of the best-performing one-compartment (Moffett 2019) and two-compartment (Shimamoto 2023) models to improve model predictions. The best-performing one-compartment and two-compartment models were selected to evaluate whether or not there is a benefit to using two-compartment models in pediatric CVICU patients dosed with vancomycin. By refitting both models, we largely removed the sample-specific biases baked into each model, allowing us to more confidently evaluate the effect of the number of compartments on describing PK.

Models were refit using NONMEM on the sample data. Any parameter that could not be estimated due to numerical instability or that converged to zero was fixed to the published value instead. The final model and covariate structures were not modified from the published models, except for estimating the allometric scaling factor on weight for clearance for the Shimamoto 2023 model.

## Software

All computational steps were done in a reproducible pipeline using the open-source programming language R (version 4.3.3, <https://www.R-project.org/>) and the targets R package. A priori and a posteriori predictions were made using NONMEM (version 7.4.4, ICON Development Solutions, Ellicott City, MD, USA) and the Perl-speaks-NONMEM (PsN; version 5.2.6, <https://uupharmacometrics.github.io/PsN/>) *execute* and *proseval* commands, respectively.

## Results

### Patient Characteristics

There were 219 patients treated across 11 sites who met the inclusion criteria ([Table 2](#)). These 11 sites were acute care hospitals or academic teaching hospitals in California, the Midwest, and the East Coast of the United States. The majority of patients came from one of three sites: 133 patients (61%) came from a single site, followed by 53 patients (24%) at a second site, and 31 patients (14%) at a third. The remaining sites had anywhere from 1 to 12 patients. Additionally, there was an excellent balance in the distribution of baseline characteristics between CVICU and propensity-score matched non-CIVU patients.

Table 2: Summary of baseline CVICU and propensity-score matched non-CIVU patient characteristics.

Characteristic	CVICU	Non-CVICU
Sites, N	11	25
Patients, N	219	219
Treatment courses, N	391	403
Doses, N	4,152	4,421
TDMs, N	1,136	1,151
Sex, n (%)		
Female	101 (46%)	104 (47%)
Male	118 (54%)	115 (53%)
Age (years), median (IQR) [range]	1.1 (0.4–5.2) [0.1–17.8]	1.2 (0.4–5.2) [0.0–17.8]
Post-menstrual age (weeks), median (IQR) [range]	99 (61–310) [46–970]	102 (60–309) [41–970]
Height (cm), median (IQR) [range]	73 (61–110) [51–187]	74 (61–109) [50–187]
Weight (kg), median (IQR) [range]	9 (6–19) [3–91]	9 (6–19) [3–100]
Serum creatinine (mg/dL), median (IQR) [range]	0.31 (0.21–0.48) [0.06–2.44]	0.31 (0.22–0.48) [0.06–2.44]

The distribution of patient characteristics in our sample was similar to that of the Kamp 2024, Moffett 2019, and Shimamoto 2023 models developed on pediatric cardiac surgery patients ([Table 3](#)). The development population for the Colin 2019 meta-model included older adult

patients, and the development population for the generic Le 2014 model skewed towards older children, leading to higher physical measurements and postnatal ages relative to our sample.

Table 3: Sample size and patient characteristics of the pharmacokinetic models included in the analysis. Values are median (IQR) [range].

Model	N	AGE	PMA	HT	WT	CR
Colin 2019	2554	[0.00–101.00]	[23.5–5266.43]	[26–202]	[0.42–160.0]	[0.15–9.75]
Kamp 2024	133	0.24 (0.08–0.55) [0.00–17.18]	51 (43–69) [35–933]	57 (52–68) [43–175]	4.5 (3.5–7.0) [2–70]	0.32 (0.23–0.50) [0.11–2.00]
Le 2014	138	6.10 (2.20–12.20)	–	–	22.2 (13.2–37.9)	0.37 (0.30–0.50)
Moffett 2019	261	0.31 (0.07–0.77)	54.6 (42.6–76.9)	58 (51.5–67.1)	4.8 (3.4–7.4)	0.32 (0.25–0.41)
Shimamoto 2023	152	0.33 (0.09–1.31) [0.01–13.53]	55.2 (43.5–107.1) [37.9–744.7]	57.5 (48.5–72.3) [41.0–153.0]	4.6 (3.1–7.9) [1.8–38.7]	0.32 (0.25–0.39) [0.11–1.06]

Abbreviation: AGE = Age (years), PMA = Post-menstrual age (weeks), HT = Height (cm), WT = Weight (kg), CR = Serum creatinine (mg/dL)

## Model Re-Estimation

The re-estimated model parameters are shown in Tables 4 and 5 for the Moffett 2019 and Shimamoto 2023 models, respectively. For the Moffett 2019 model, re-estimated parameters for the volume of distribution and inter-individual variability (IIV) on clearance and in the volume of distribution were all higher in our sample compared to the published values; and the effect of post-menstrual age and creatinine clearance on vancomycin clearance were all lower. For the Shimamoto 2023 model, re-estimated parameters for the effect of creatinine clearance on vancomycin clearance and inter-individual variability (IIV) on clearance and in the peripheral volume of distribution were all higher in our sample compared to the published values; clearance, the central volume of distribution, the effect of weight on vancomycin clearance, and additive error were all lower. For both models, the remaining re-estimated parameters parameters were similar to the published values.

Table 4: Model parameters from the published and refit Moffett 2019 models.

Parameter	Moffett 2019		Moffett 2019 (refit)	
	Estimate	SE	Estimate	SE
$\theta_{CL}$	7.86	0.16	7.50	0.03
$\theta_{VD}$	63.60	3.23	70.44	0.08
$\theta_{PMA}$	-0.28	0.09	-0.17	0.37
$\theta_{CRCL}$	0.90	0.05	0.77	0.08
$\theta_{PROP}$	0.20	0.02	0.24	0.03
$\omega_{CL}$ (IIV)	0.17	0.03	0.32	0.06
$\omega_{VD}$ (IIV)	0.26	0.09	0.35	0.12

Abbreviation: CL = Clearance (L/hr), VD = Volume of distribution (L), PMA = Post-menstrual age (weeks), CRCL = Creatinine clearance (mL/min/1.73m<sup>2</sup>), PROP = Proportional error (%), IIV = Interindividual variability (%)

Table 5: Model parameters from the published and refit Shimamoto 2023 models. Blank estimates were fixed to the value of the published estimates.

Parameter	Shimamoto 2023		Shimamoto 2023 (refit)	
	Estimate	SE	Estimate	SE
$\theta_{CL}$	4.88	0.38	3.56	0.10
$\theta_{V1}$	21.60	2.05	12.72	0.31
$\theta_Q$	2.95	0.46	—	—
$\theta_{V2}$	21.70	1.74	26.72	0.08
$\theta_{WT}$	0.75	—	0.56	0.05
$\theta_{CRCL}$	0.55	0.04	0.63	0.07
$\theta_{HILL}$	1.73	0.52	—	—
$\theta_{T50}$	36.90	3.43	—	—
$\theta_{PROP}$	0.24	0.01	0.21	0.06
$\theta_{ADD}$	0.97	0.24	0.89	0.23
$\omega_{CL}$ (IIV)	0.23	0.05	0.26	0.05
$\omega_{V2}$ (IIV)	0.41	0.10	0.47	0.15

Abbreviation: CL = Clearance (L/h), V = Volume of distribution (L), Q = Intercompartmental clearance (L/h), WT = Weight (kg), CRCL = Creatinine clearance (mL/min/1.73m<sup>2</sup>), HILL = Hill coefficient, T50 = Postmenstrual age at which 50% of adult clearance is reached (weeks), PROP = Proportional error (%), IIV = Interindividual variability (%)

## Comparison of Model Predictive Performance

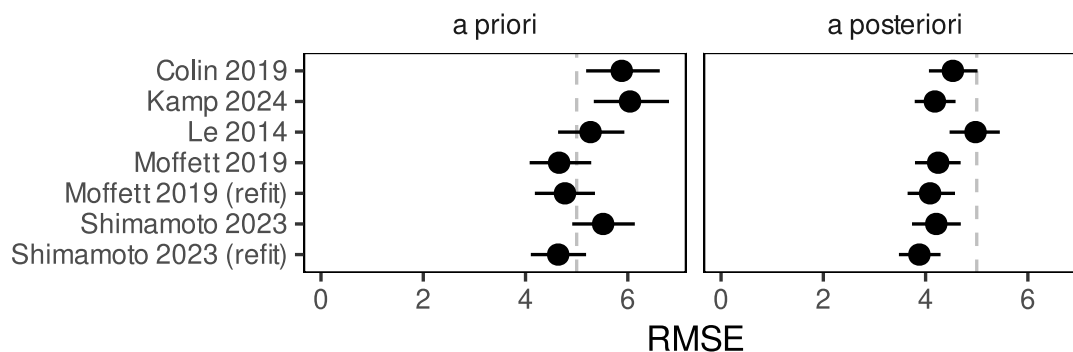
Model prediction precision ([Figure 1A](#)) was best for pediatric CVICU patients using the refit Shimamoto 2023 model a priori and a posteriori. However, there was substantial overlap in the RMSE estimates most compatible with our data between the refit Shimamoto 2023 model and the (refit) Moffett 2019 models for a priori predictions; and the Kamp 2024, (refit) Moffett 2019, and published Shimamoto 2023 models for a posteriori predictions. Additionally, for a priori predictions, all models but Colin 2019 and Kamp 2024 had RMSE estimates that fell inside our chosen clinically acceptable range ( $RMSE < 5$ )—although no model fell exclusively inside this range. For a posteriori predictions, all models but Colin 2019 and Le 2014 models had RMSE estimates that fell exclusively inside our chosen clinically acceptable range.

The Moffett 2019 model produced the least biased predictions a priori, and the Colin 2019 and refit Shimamoto 2023 models—which had similar absolute values—produced the least biased predictions a posteriori ([Figure 1B](#)). In both cases, these were the only models whose MPE estimates most compatible with our data included zero, with the addition of the refit Moffett 2019 model for a posteriori predictions. However, for a priori predictions, the Le 2014 and refit Shimamoto 2023 models did fall exclusively within our chosen clinically acceptable range ( $|MPE| < 0.25$ ); and for a posteriori predictions, all models fell exclusively in this range.

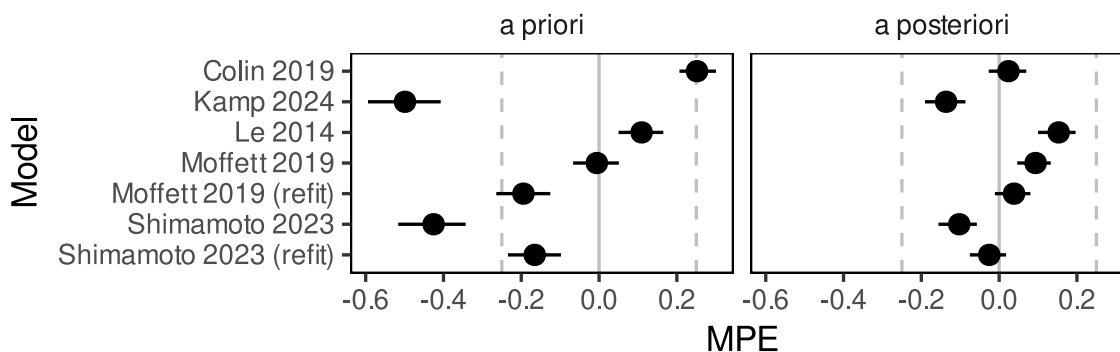
Model prediction accuracy ([Figure 1C](#)) was best for pediatric CVICU patients using the published Moffett 2019 model a priori, and the refit Moffett 2019 and refit Shimamoto 2023 models a posteriori, which had near-identical estimates (within 1 percentage point). In the latter case, these were the only models whose point estimate for accuracy fell inside our chosen clinically acceptable range ( $Accuracy > 0.60$ ). In addition, for a posteriori predictions, all other models—with the exception of Le 2014—had accuracy estimates that were also compatible with our chosen clinically acceptable range. For a priori predictions, accuracy estimates for all models fell exclusively outside this range.

On balance, the refit Shimamoto 2023 model had the best performance across a priori and a posteriori predictions, and was the only model aside from the refit Moffett 2019 model close to satisfying all our criteria for clinical acceptability a posteriori. However, its a priori performance came short of satisfying these criteria—additionally losing out to the published Moffett 2019 model, which had similar prediction precision and accuracy but lesser bias.

(A)



(B)



(C)

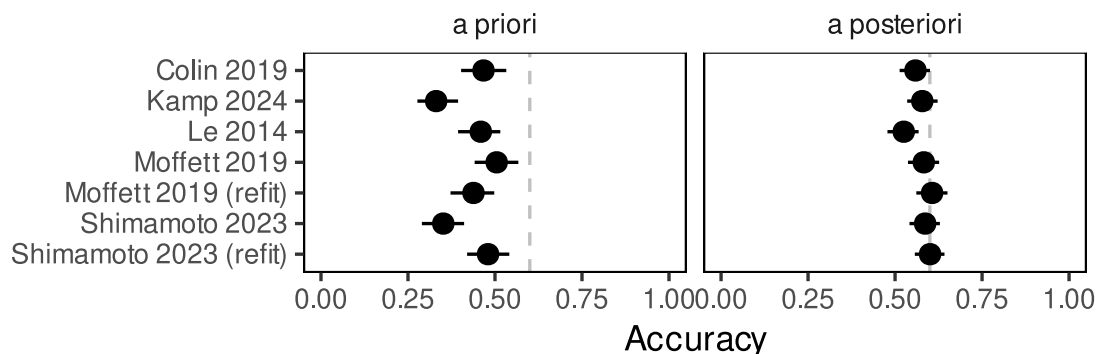
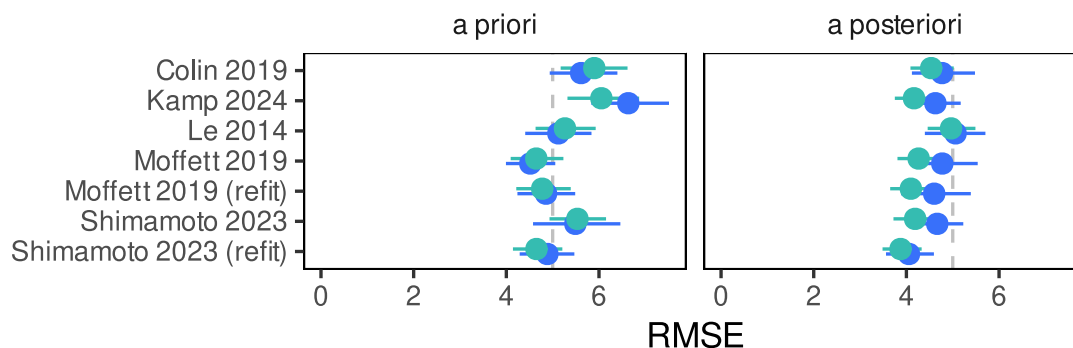


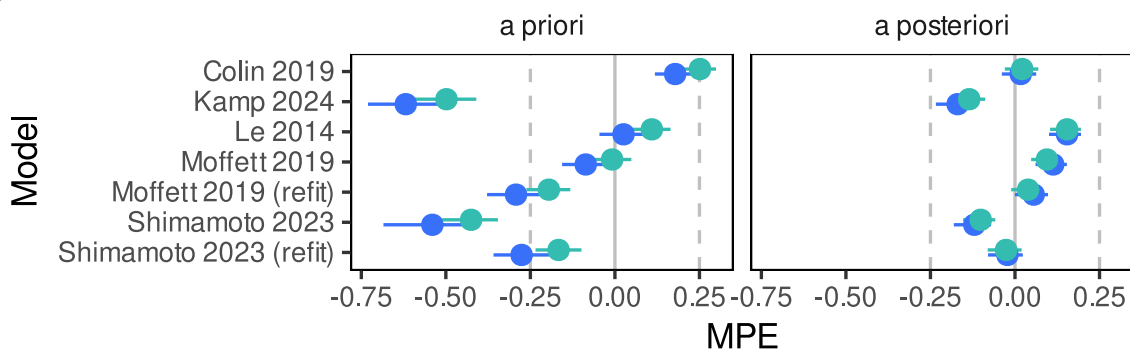
Figure 1: Predictive performance of published pharmacokinetic models for pediatric CVICU patients dosed with vancomycin, assessed by RMSE, MPE, and accuracy. Error bars represent the point and 95% confidence interval estimate for each model. For RMSE and accuracy, the dotted lines represent the upper and lower limits of the clinically acceptable range, respectively. For MPE, the dotted lines represent the lower and upper limits of the clinically acceptable range, and the solid line represents a target value of zero bias.

In matched non-CVICU patients, predictive performance was highly similar to that of CVICU patients across all models ([Figure 2](#)).

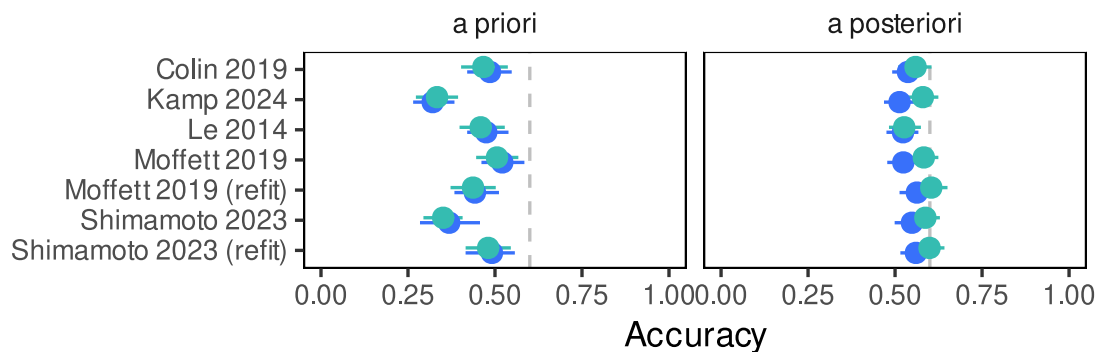
(A)



(B)



(C)



Group ● Non-CVICU ● CVICU

Figure 2: Predictive performance of published pharmacokinetic models for pediatric CVICU patients and matched non-CVICU patients dosed with vancomycin, assessed by RMSE, MPE, and accuracy. Error bars represent the point and 95% confidence interval estimate for each model. For RMSE and accuracy, the dotted lines represent the upper and lower limits of the clinically acceptable range, respectively. For MPE, the dotted lines represent the lower and upper limits of the clinically acceptable range, and the solid line represents a target value of zero bias.

## Discussion

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This study evaluated the predictive performance of two general (Colin 2019, Le 2014) and three specialized (Kamp 2024, Moffett 2019, Shimamoto 2023) vancomycin models in a multi-site sample of 219 pediatric CVICU patients receiving routine clinical care.

The two best-performing one-compartment (Moffett 2019) and two-compartment (Shimamoto 2023) models were also refit to evaluate if predictive performance could be further improved, and whether or not there is a benefit to using two-compartment models in pediatric CVICU patients dosed with vancomycin. Refitting these models resulted in an increase in inter-individual variability compared to the published models, which reflects the real world, routine clinical care nature of this data.

In terms of model selection decisions for MIPD of vancomycin in pediatric CVICU patients, InsightRX currently recommends the Colin 2019 model for all patients treated with vancomycin. However, in this study we found that the refit Shimamoto 2023 model had the best overall performance across a priori and a posteriori predictions, suggesting that an appropriately specified two-compartment vancomycin model may be beneficial in pediatric CVICU patients. Although this model failed to meet all our criteria for clinical acceptability—with substandard a priori bias and accuracy (and to a lesser extent, precision), and a posteriori accuracy—it outperformed the Colin 2019 model in this subpopulation and is likely better than dosing without a model. Considering other models: The published Moffett 2019 model performed best a priori, but had comparatively worse performance a posteriori; and the published Colin 2019, Kamp 2024, Le 2014, and Shimamoto 2023 models all performed poorly prior to incorporating subsequent TDM data. Therefore, further data are needed to understand the implications of applying these (specialized) vancomycin models for MIPD in clinical practice with pediatric CVICU patients.

Similar to our previous work, we found that MAP Bayesian estimates of individual PK parameters attenuated the differences in predictive performance between models.<sup>6</sup> Therefore, clinicians could collect earlier and more frequent drug levels to improve dose optimization in cases where a pharmacokinetic model appears to be a poor fit for a patient, or uncertainty in covariate values is suspected. For models that continue to fit poorly, selecting another model that better reflects patient covariates or subpopulation, or using clinical judgment to adjust dosing from model predictions, may improve dose optimization for an individual patient.<sup>7</sup>

## Conclusion

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The refit Shimamoto 2023 model had the best overall performance for MIPD of vancomycin in pediatric CVICU patients.

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