

Evaluating Vancomycin Pharmacokinetic Models in Pediatric Oncology Patients Using Routine Clinical Care Data

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Background

Dose optimization of vancomycin in pediatric oncology patients is inherently complex due to a reported increased risk of augmented renal clearance in patients with hematologic malignancy or neutropenia compared to the general patient population.¹ Due to this risk, following conventional vancomycin dosing guidelines in this patient population may result in subtherapeutic vancomycin concentrations. Therefore, adopting vancomycin models tailored for this patient population may lead to better dose advice, improving treatment outcomes.

InsightRX provides two pediatric oncology and oncology-supporting vancomycin models in the Nova platform, which were developed to model the altered pharmacokinetics of vancomycin in patients with hematologic malignancy or neutropenia;^{2,3} and we have identified several more candidate models for this population following a literature search.⁴⁻⁷ However, vancomycin dose advice for most pediatric oncology 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.⁸ 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 developed on fourteen pooled data sets to characterize vancomycin pharmacokinetics across a broad range of patient populations, including those with extreme ages and weights, as well as specialized subpopulations.² One of these specialized populations included adults with hematological malignancy, and this model therefore included an effect of cancer status on clearance. InsightRX offers two versions of the Colin 2019 model in the Nova platform, both with and without this covariate effect, which we denote here as “Colin 2019 (Onc)” and “Colin 2019”.

The goal of this study was to compare the predictive performance across these eight models, in order guide model selection decisions for model-informed precision dosing (MIPD) of vancomycin in pediatric oncology patients, including those with hematologic malignancy or neutropenia.

Methods

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. These data included patient sex; height and weight; chronological and post-menstrual age at the time of the first dose of vancomycin; serum creatinine measurements; serum vancomycin measurements; the dose amount, timing, and infusion duration of vancomycin administered; cancer type; and neutropenia status.

Patients were included if they were under the age of 20 years, had at least one serum vancomycin level obtained as part of therapeutic drug monitoring (TDM), and were tagged as an oncology patient without concomitant drug treatments by the clinician during treatment.

Body temperature was not recorded for any patients; however, for patients with a known diagnosis of febrile neutropenia, body temperature was imputed to be 38.1°C (indicating the presence of a fever), and 37°C for all other patients (indicating the absence of a fever). The impact of this imputation was assessed by repeating the analysis with imputed values assuming all patients were with or without fever for the relevant popPK models.

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 pediatric oncology 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 dose gaps greater than 72 hours were present, TDMs were collected during infusion, one or more records had anomalous weights or heights for age based on CDC growth charts (< 0.1 or > 99.9th percentiles), or that had treatment courses beyond 60 days.

Following model-based predictions, patients whose predictions had an absolute conditional weighted residual (CWRES) greater than 4 for any model were considered for removal, since a residual more than four standard deviations larger than the expected residual variability likely indicates erroneous data. This was handled on a case-by-case basis, taking into consideration the quality of each patients' data, the number of records and models where their predictions had an absolute CWRES greater than 4, as well as the general performance of each model. The analysis pipeline was then repeated with these patients removed for the final results.

A sample of non-oncology 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-oncology patients from our datalake who were also receiving vancomycin and whose baseline characteristics were similar to our final sample of oncology 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 nearest neighbor propensity score matching without replacement using optimal matching. This matching specification yielded an improved balance; however, graphical checks revealed systematic differences in covariate balance, so we instead tried modifying the propensity score model to include interactions between all covariates. This yielded better balance than the original propensity score model and was selected as our final model for matching.

Pharmacokinetic Analysis

Eight population pharmacokinetic models (Chuphan 2022, Colin 2019, Colin 2019 (Onc), Hadi 2015, Le 2014, Shimamoto 2021, Wang 2020, Zhao 2014)²⁻⁸ 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) oncology patients, including those with hematologic malignancy or neutropenia. This search identified six suitable vancomycin models, given the availability of covariates in our data set (Chuphan 2022, Colin 2019 (Onc), Hadi 2015, Shimamoto 2021, Wang 2020, Zhao 2014). 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 | HT | WT | CR | CRCL | TEMP | HEEL | CANC |
|------------------------|-----|-----|----|----|----|------|------|------|------|
| Chuphan 2022 | — | — | — | X | — | X | — | — | — |
| Colin 2019 | — | X | — | X | X | — | — | — | — |
| Colin 2019 (Onc) | — | X | — | X | X | — | — | X | X |
| Hadi 2015 | — | — | — | X | — | — | — | — | — |
| Le 2014 | X | — | — | X | X | — | — | — | — |
| Shimamoto 2021 | — | X | — | X | — | X | X | — | — |
| Wang 2020 | — | — | — | X | — | X | — | — | — |
| Zhao 2014 | — | — | — | 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/1.73m²), TEMP = Body temperature (°C), HEEL = Heel-prick status, CANC = Cancer status

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 error, bias, and accuracy. Prediction error was quantified using root mean square error (RMSE); prediction bias was evaluated using mean percentage 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/dL or a relative error margin of 15% of the measured

concentrations. These metrics were calculated by comparing the (iteratively) predicted drug concentrations (pred or ipred) relative to the measured concentrations (obs) across N concentrations as follows:

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

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

For each metric, 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 error, bias, and accuracy were within a clinically acceptable range ($\text{RMSE} < 5$, $|\text{MPE}| < 0.25$, and $\text{Accuracy} > 0.60$), and the 95% CI of bias included zero.

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. Propensity score matching was performed using the MatchIt R package.

Results

Patient Characteristics

There were 371 pediatric oncology patients treated across 20 sites who met the inclusion criteria ([Table 2](#)). These 20 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 stemmed from one of three sites: 149 patients (40%) from a single site, followed by 64 patients (17%) from a second site, and 46 patients (12%) from a third. The remaining sites had

anywhere from 1 to 33 patients. Of these patients, 304 (82%) had a hematologic malignancy, 12 (3.2%) had a solid tumor, and 55 (15%) had an unspecified cancer; 48 (13%) patients were identified as neutropenic. Additionally, there was a good balance in the distribution of baseline characteristics between oncology and propensity-score matched non-oncology patients.

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

| Characteristic | Oncology | Non-oncology |
|--|------------------------------|------------------------------|
| Sites, N | 20 | 58 |
| Patients, N | 371 | 371 |
| Treatment courses, N | 592 | 502 |
| Doses, N | 7,498 | 6,280 |
| TDMs, N | 1,392 | 1,257 |
| Sex, n (%) | | |
| Female | 166 (45%) | 175 (47%) |
| Male | 205 (55%) | 196 (53%) |
| Age (years), median (IQR) [range] | 7.2 (3.4–13.3) [0.2–20.0] | 7.9 (3.9–14.1) [0.3–18.4] |
| Post-menstrual age (weeks), median (IQR) [range] | 413 (220–735) [51–1,081] | 454 (245–777) [56–998] |
| Height (cm), median (IQR) [range] | 123 (97–154) [58–187] | 126 (99–157) [55–195] |
| Weight (kg), median (IQR) [range] | 26 (15–51) [5–112] | 28 (16–52) [5–124] |
| Serum creatinine (mg/dL), median (IQR) [range] | 0.35 (0.24–0.49) [0.06–1.15] | 0.34 (0.23–0.50) [0.06–1.08] |
| Hematological malignancy, n (%) | 304 (82%) | 0 (0%) |
| Solid tumor, n (%) | 12 (3.2%) | 0 (0%) |
| Cancer (unspecified), n (%) | 55 (15%) | 0 (0%) |
| Neutropenia, n (%) | 48 (13%) | 4 (1.1%) |

The distribution of patient characteristics in our sample was similar to the Shimamoto 2021, Wang 2020, and Zhao 2014 models developed on pediatric oncology patients, as well as the Le 2014 model developed on a largely general population of pediatric patients ([Table 3](#)). The development population for the Colin 2019 meta-model included older adult patients, 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] for the Colin 2019, Le 2014, and Shimamoto 2021 models; and mean (SD) [range] for the Hadi 2015 model.

| Model | N | AGE | PMA | HT | WT | CR |
|----------------|------|-------------------|----------------|--------------------|------------------|------------------|
| Chuphan 2022 | 212 | 3.5 (0.9–10.9) | — | 95.5 (65–136) | 14.0 (7.2–30.4) | 0.38 (0.25–0.59) |
| Colin 2019 | 2554 | [0.00–101.00] | [23.5–5266.43] | [26–202] | [0.42–160.0] | [0.15–9.75] |
| Hadi 2015 | 95 | 6 (2.46) | — | 113.98 (15.6) | 19.6 (6.95) | 0.406 (0.118) |
| Le 2014 | 138 | 6.10 (2.20–12.20) | — | — | 22.2 (13.2–37.9) | 0.37 (0.30–0.50) |
| Shimamoto 2021 | 165 | [0.25–18.00] | — | — | 20.7 (13.5–46.5) | 0.34 (0.25–0.45) |
| Wang 2020 | 92 | 7.0 [0.4–17.1] | — | 124.0 [62.0–180.0] | 24.3 [7.0–70.0] | 0.48 [0.28–1.44] |
| Zhao 2014 | 70 | 5.6 [0.3–17.7] | — | — | 20.2 [5.6–71.0] | 0.34 [0.11–1.59] |

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

Comparison of Model Predictive Performance

Model prediction error ([Figure 1A](#)) was best for pediatric oncology patients using the Shimamoto 2021 model a priori. However, there was substantial overlap in the RMSE estimates most compatible with our data between the Shimamoto 2021 model and the Colin 2019 model for a priori predictions; and these were the only models whose RMSE estimates fell inside our chosen clinically acceptable range (RMSE < 5), although neither model's confidence intervals fell exclusively inside this range. For a posteriori predictions, the Colin 2019 and Shimamoto 2021 models produced the most precise predictions with near-identical performance, on average. Here, the Colin 2019 (Onc) and Le 2014 models were the only other models that had RMSE estimates that fell inside our chosen clinically acceptable range, although again, no model fell exclusively inside this range.

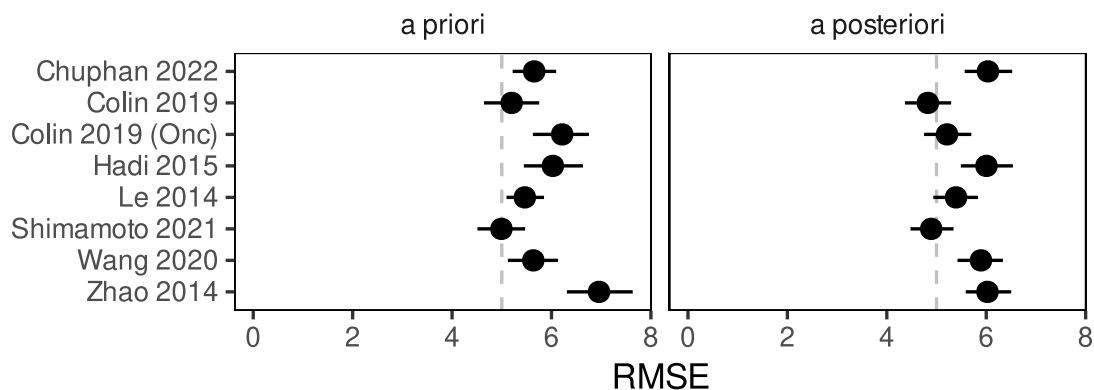
The Hadi 2015 model produced the least biased predictions a priori, and the Colin 2019 and Shimamoto 2021 models produced the least biased predictions a posteriori, with confidence intervals overlapping zero ([Figure 1B](#)). The Colin 2019, Wang 2020, and Zhao 2014 models also

met our chosen thresholds for a priori predictions ($|\text{MPE}| < 0.25$); and all models but Zhao 2014 fell exclusively in this range for a posteriori predictions.

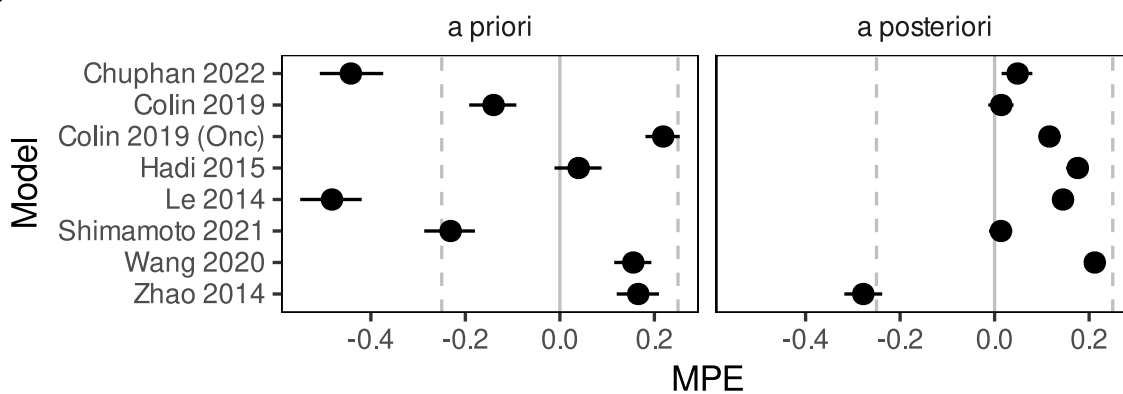
Model prediction accuracy ([Figure 1C](#)) was best for pediatric oncology patients using the Hadi 2015 and Colin 2019 models a priori, and the Colin 2019 model a posteriori. In the latter case, this was the only model whose accuracy estimates most compatible with our data fell inside our chosen clinically acceptable range (Accuracy > 0.60)—although barely and not exclusively. Otherwise, for both a priori and a posteriori predictions, accuracy estimates for all models fell exclusively outside our chosen clinically acceptable range.

On balance, the Colin 2019 model had the best performance across a priori and a posteriori predictions for pediatric oncology patients, and was the only model close to satisfying all our criteria for clinical acceptability a posteriori.

(A)



(B)



(C)

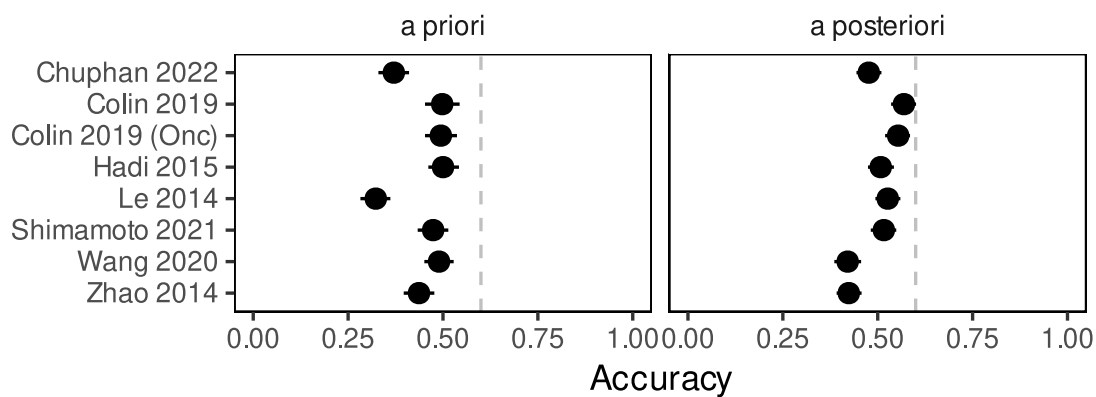
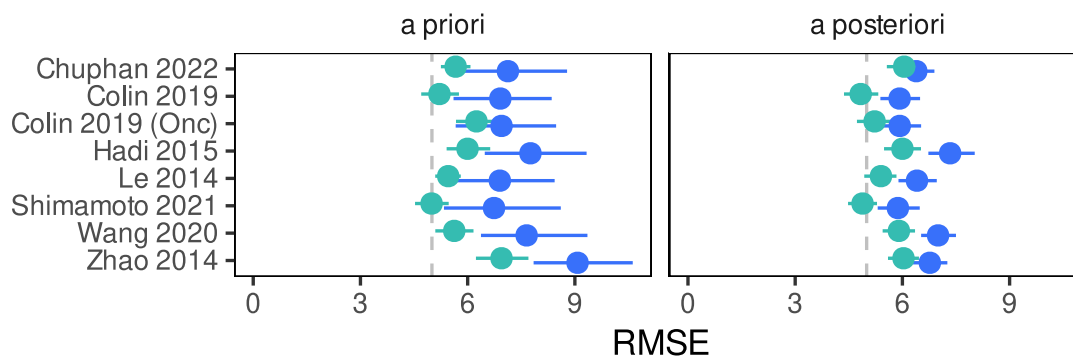


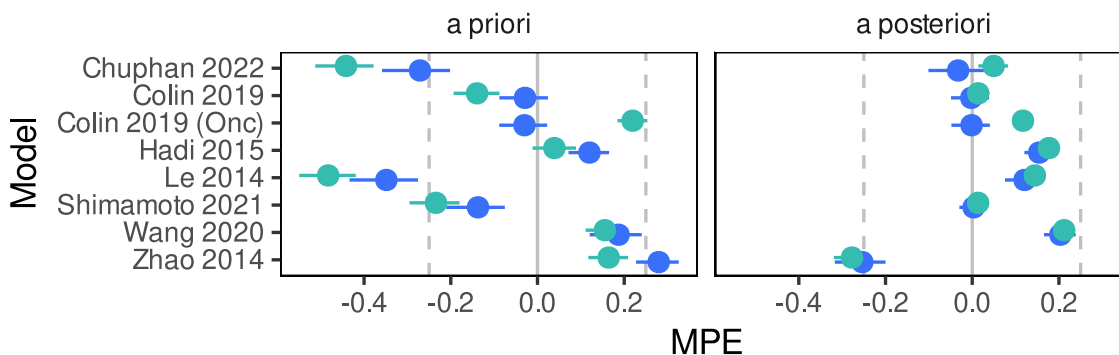
Figure 1: Predictive performance of published pharmacokinetic models for pediatric oncology patients dosed with vancomycin, assessed by RMSE, MPE, and accuracy. Error bars represent the point and 95% confidence interval estimate for each model. For RMSE and accuracy, the dotted lines represent the upper 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-oncology patients, the Colin 2019 model also had the best overall performance across a priori and a posteriori predictions. However, relative to oncology patients, predictive performance was similar or worse across all metrics, with the exception of a priori predictive bias. In general, this pattern held true across all models.

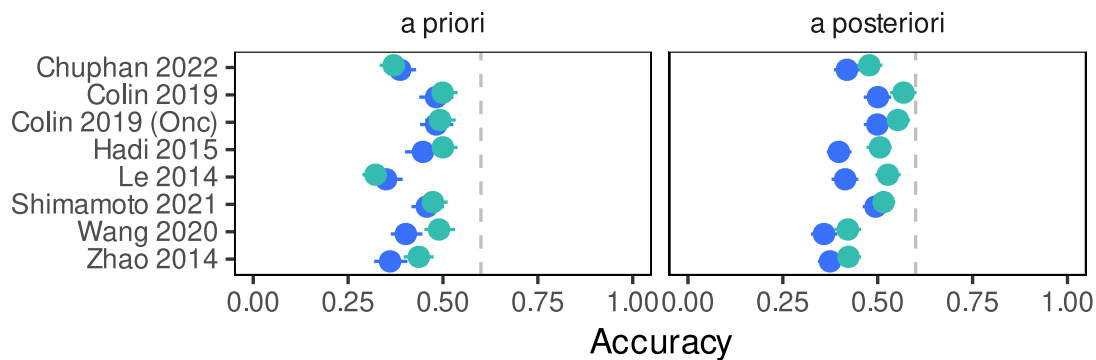
(A)



(B)



(C)



Group ● Non-oncology ● Oncology

Figure 2: Predictive performance of published pharmacokinetic models for pediatric oncology patients and matched non-oncology 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.

Pharmacokinetic Model Refitting

Because the standard Colin 2019 model outperformed the Colin 2019 (Onc) model—despite our sample consisting exclusively of oncology patients—we decided to repeat this analysis on a refit version of the Colin 2019 (Onc) to see if model predictions could be improved. The model was refit using NONMEM on the sample data for oncology patients and matched non-oncology patients. 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. The re-estimated model parameters are shown in [Table 4](#). In general, the re-estimated parameters were similar in our sample compared to the published values; notably however, the effect of cancer status on vancomycin clearance was considerably lower with a value overlapping zero, indicating that with the information in our sample we were not able to distinguish a significant difference in clearance between oncology and non-oncology patients.

Table 4: Model parameters from the published and refit Colin 2019 (Onc) models.

| Parameter | Colin 2019 (Onc) | | Colin 2019 (Onc) refit | |
|---------------------|------------------|------|------------------------|------|
| | Estimate | SE | Estimate | SE |
| θ_{CL} | 1.67 | 0.03 | 1.51 | 0.02 |
| θ_{V1} | 3.75 | 0.07 | 3.57 | 0.03 |
| θ_{V2} | 3.73 | 0.13 | 3.91 | 0.06 |
| θ_{Q2} | 1.17 | 0.08 | 0.81 | 0.13 |
| θ_{CANC} | 0.29 | 0.03 | 0.06 | 0.40 |
| θ_{PROP} | 0.21 | 0.01 | 0.22 | 0.04 |
| θ_{ADD} | 1.23 | 0.12 | 0.81 | 0.14 |
| ω_{CL} (IIV) | 0.27 | 0.01 | 0.26 | 0.08 |
| ω_{V1} (IIV) | 0.27 | 0.03 | 0.41 | 0.13 |
| ω_{V2} (IIV) | 0.83 | 0.05 | 0.93 | 0.07 |

Abbreviation: CL = Clearance (L/hr), V = Volume of distribution (L), Q = Intercompartmental clearance (L/h), CANC = Cancer status, PROP = Proportional error (%), ADD = Additive error (%), IIV = Interindividual variability (%)

Effect of Imputing Body Temperature on Shimamoto 2021 Model Predictions

The Shimamoto 2021 model uses body temperature as a flag for whether or not a patient has a fever (BT $\geq 38.0^{\circ}\text{C}$, flag = 1; BT $< 38.0^{\circ}\text{C}$, flag = 0), which multiplies the estimated value of

vancomycin clearance by 1.12 when present. Body temperature was not recorded for any patients in our sample; however, for patients with a known diagnosis of febrile neutropenia, body temperature was imputed to be 38.1°C (indicating the presence of a fever), and 37°C for all other patients (indicating the absence of a fever). To assess the impact of imputing body temperature on predicting vancomycin pharmacokinetics for the Shimamoto 2021 model, we compared model predictions made using this imputation method to predictions where we assumed all patients either did or did not have a fever.

Prediction error ([Figure 3A](#)) was similar across all imputation methods a priori and a posteriori. Prediction bias ([Figure 3B](#)) improved a priori when assuming all patients had a fever relative to the other imputation methods, but worsened a posteriori under the same assumption.

Prediction accuracy ([Figure 3C](#)) was largely similar across all imputation methods a priori and a posteriori. Keeping in mind that in our sample, only a small minority of patients were known to have fever based on their neutropenia status ([Table 2](#)), these results may suggest that a positive neutropenia diagnosis was not recorded in many cases, based on the improved a priori predictive bias when assuming all patients had a fever. However, in either case, it would seem that for the Shimamoto 2021 model, wrongly assuming patients have or do not have a fever may have a measurable influence on predictive bias, but not error or accuracy.

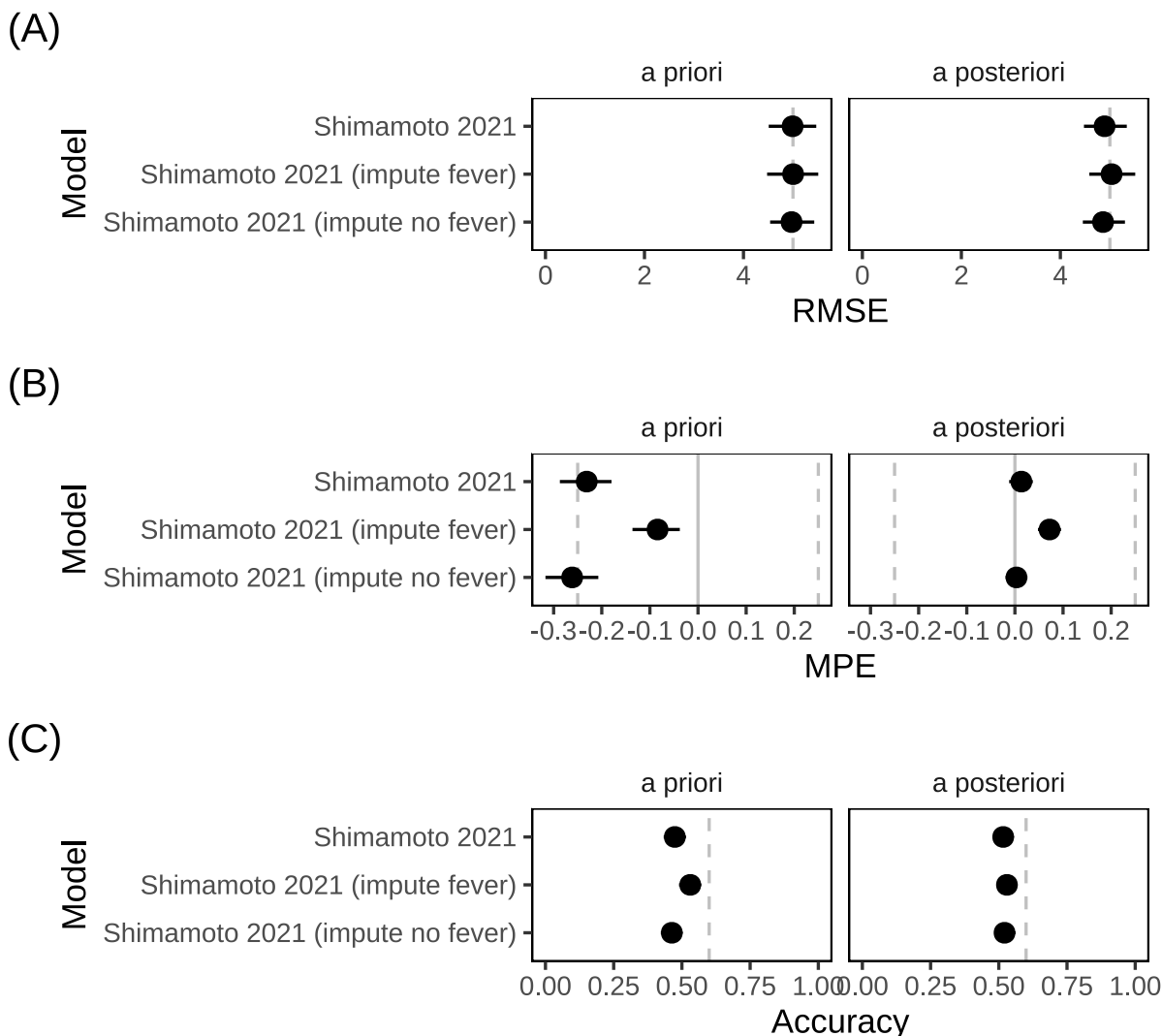


Figure 3: Predictive performance of published Shimamoto 2021 models with and without imputed body temperature for pediatric oncology patients dosed with vancomycin, assessed by RMSE, MPE, and accuracy. Error bars represent the point and 95% confidence interval estimate for each model. For RMSE and accuracy, 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

This study evaluated the predictive performance of two general (Colin 2019, Le 2014) and six specialized (Chuphan 2022, Colin 2019 (Onc), Hadi 2015, Shimamoto 2021, Wang 2020, and Zhao 2014) vancomycin models in a multi-site sample of 371 pediatric oncology patients

receiving routine clinical care. We found that the Colin 2019 model had the best overall performance across a priori and a posteriori predictions, suggesting that a well-specified general model may be suitable in this patient population over specialized models.

In terms of model selection decisions for MIPD of vancomycin in pediatric oncology patients, InsightRX currently recommends the Colin 2019 model for all patients treated with vancomycin, and this version of the model appears more suitable in pediatric oncology patients over the Colin 2019 (Onc) version of the model. However, it is worth noting that the Colin 2019 model failed to meet all our criteria for clinical acceptability in our sample of pediatric oncology patients—with substandard a priori error, bias, and accuracy, and a posteriori error and accuracy—even if it outperformed other models in this subpopulation and is likely better than dosing without a model. Therefore, further data are needed to understand the implications of applying this and other (specialized) vancomycin models for MIPD in clinical practice with pediatric oncology patients. In particular, future studies in this patient population may benefit from better tagging of patients' cancer and neutropenia status (or extracting this information from electronic health records), and the recording of potentially explanatory variables such as body temperature,^{3,9} which would allow for fairer, more accurate model comparisons when these covariates are used in a model.

The Colin 2019 (Onc) model was also refit to evaluate if predictive performance could be improved, with particular interest in how the estimate for the effect of cancer status on vancomycin clearance changed between published and refit values. Refitting this model resulted in generally similar parameter estimates compared to the published values; however, the effect of cancer status on vancomycin clearance was considerably lower with a value overlapping zero, indicating that this information was not informative for estimating clearance in our sample. The cancer status covariate in the Colin 2019 (Onc) model was a study-specific parameter that came from adult oncology patients who had significantly higher clearance relative to patients from other studies in their meta-analysis.^{2,10} Although previous studies have reported higher clearance in pediatric oncology patients,^{7,11} we are unaware of any published pharmacokinetic models that have estimated the magnitude of additional clearance attributable to cancer status in this population. Instead, these reported differences have been based on either mean differences between oncology and non-oncology patients¹¹ or nominal comparisons between studies.⁷

Pediatric popPK studies that have tested the effect of cancer status⁴, type of hematological disease^{6,7}, or primary diagnosis³ on vancomycin clearance all discarded these covariates from

their final model, suggesting that cancer itself may not be an independent risk factor for augmented renal clearance or altered vancomycin PK. This assertion is supported by Hirai and colleagues¹², who found that febrile neutropenia—but not cancer, other critical illnesses, or surgery—significantly increased the risk of augmented renal clearance in pediatric patients, indirectly influencing vancomycin clearance. Therefore, it is likely that the reported effect of cancer status on vancomycin clearance in the published Colin 2019 (Onc) model was either age-specific or a batch effect (i.e., related to that particular data set and not the underlying biology). Future research should explore covariates that might better explain augmented renal clearance in pediatric oncology patients, such as body temperature³ or neutropenia status.

Similar to our previous work, we found that MAP Bayesian estimates of individual PK parameters attenuated the differences in predictive performance between models.¹³ 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.¹⁴

Conclusion

The standard Colin 2019 model had the best overall performance for MIPD of vancomycin in pediatric oncology patients. We should communicate this as our recommendation in this population despite the availability of the Colin 2019 (Onc) model, whose performance was worse in comparison.

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