

**ARTICLE**

# Pharmacokinetic equations versus Bayesian guided vancomycin monitoring: Pharmacokinetic model and model-informed precision dosing trial simulations

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**Abstract**

The recently released revised vancomycin consensus guideline endorsed area under the concentration-time curve (AUC) guided monitoring. Means to AUC-guided monitoring include pharmacokinetic (PK) equations and Bayesian software programs, with the latter approach being preferable. We aimed to evaluate the predictive performance of these two methods when monitoring using troughs or peaks and troughs at varying single or mixed dosing intervals (DIs), and evaluate the significance of satisfying underlying assumptions of steady-state and model transferability. Methods included developing a vancomycin population PK model and conducting model-informed precision dosing clinical trial simulations. A one-compartment PK model with linear elimination, exponential between-subject variability, and mixed (additive and proportional) residual error model resulted in the best model fit. Conducted simulations demonstrated that Bayesian-guided AUC can, potentially, outperform that of equation-based AUC predictions depending on the quality of model diagnostics and met assumptions. Ideally, Bayesian-guided AUC predictive performance using a trough from the first DI was equivalent to that of PK equations using two measurements (peak and trough) from the fifth DI. Model transferability diagnostics can guide the selection of Bayesian priors but are not strong indicators of predictive performance. Mixed versus single fourth and/or fifth DI sampling seems indifferent. This study illustrated cases associated with the most reliable AUC predictions and showed that only proper Bayesian-guided monitoring is always faster and more reliable than equations-guided monitoring in pre-steady-state DIs in the absence of a loading dose. This supports rapid Bayesian monitoring using data as sparse and early as a trough at the first DI.

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## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Area under the concentration-time curve (AUC)-guided vancomycin monitoring was, recently, recommended using first-order pharmacokinetic (PK) equations or Bayesian software programs. Additionally, vancomycin trough-only monitoring was abolished.

### WHAT QUESTION DID THIS STUDY ADDRESS?

Are there any predictive performance differences between first-order PK and Bayesian-guided monitoring, between Bayesian-guided troughs versus Bayesian-guided troughs and peaks, and between monitoring at varying single or mixed pre- or at steady-state dosing intervals (DIs)?

### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Bayesian-guided AUC prediction has the potential to outperform equation-based AUC prediction, although not necessarily in all conditions. Underlying steady-state and model transferability assumptions are crucial for good predictive performance, although model diagnostics do not seem to be strong predictors of predictive performance. Rapid vancomycin Bayesian AUC-guided monitoring using only a trough that was obtained as early as at the first DI was quite supported by this study under certain conditions. Incremental improvements in AUC predictions accuracy and precision and reduction in bias were generally observed progressing between intervals from the first DI toward steady-state. Sampling from different DIs (i.e., the fourth and fifth) did not seem to have a detrimental impact on the AUC prediction.

### HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study supports the clinical implementation of rapid proper vancomycin Bayesian AUC-guided monitoring as early as at the first DI using sparse samples as sparse as a trough measurement and underscores the importance of satisfying the steady-state and model transferability underlying assumptions. This study will likely contribute to better vancomycin clinical monitoring and precision dosing by understanding contexts that might impact AUC predictions.

## INTRODUCTION

Vancomycin is widely used for suspected and confirmed serious invasive methicillin-resistant *Staphylococcus aureus* infections.<sup>1</sup> Recently, the revised consensus guideline abandoned the previously recommended use of vancomycin trough concentrations as surrogates to estimate the ratio of the area under the concentration-time curve (AUC) over 24 h to minimum inhibitory concentration (MIC).<sup>1,2</sup> Instead, the revised guideline recommended therapeutic target attainment through the means of AUC-guided dosing.<sup>1</sup> This AUC-guided dosing should be achieved by using (a) first-order analytic equations or (b) Bayesian software programs, with the latter approach being preferable.<sup>1</sup> This preference was attributed to reports suggesting that Bayesian approaches can provide rapid and reliable AUC predictions while requiring as few as one vancomycin measurement that is not necessarily obtained at steady-state.<sup>1,3</sup> Rapid achievement of the target AUC can be vital for effective therapy.<sup>1</sup> In contrast,

valid use of first-order analytic equations requires at least two post-distributional vancomycin measurements (preferably at the same dosing interval [DI]) obtained at or near steady-state.<sup>1</sup> The revised guideline, however, acknowledges difficulties determining steady-state conditions in clinical practice, being subject to variables such as changing renal function and loading dose.<sup>1</sup> Trough monitoring is preferred in certain settings according to a Canadian perspective on the revised guideline.<sup>4</sup>

Utilizing pharmacokinetic and/or pharmacodynamic (PK) models to optimize, guide, and individualize dosing using patients' covariates and drug concentrations is referred to as model-informed precision dosing (MIPD), Bayesian forecasting, or model-based precision dosing.<sup>5-7</sup> Reports exist suggesting MIPD (e.g., using Bayesian programs) can outperform clinician judgment in recommending vancomycin dosing regimens.<sup>3,8</sup> In principle, Bayesian programs incorporate prior knowledge and experiments, such as a developed PK model and its parameter values. This prior component is combined with the patients'

observed vancomycin concentrations to yield Bayesian posterior parameter distribution.<sup>5,6,9</sup> The revised guideline stated that Bayesian programs that implemented richly sampled Bayesian priors should be used.<sup>1</sup>

Despite the potentials of Bayesian-guided monitoring, equation-based AUC estimation was reported to result in an equivalent or better accuracy and bias compared to using five Bayesian programs.<sup>10</sup> Recent reports indicated that few hospitals in the United States implemented AUC-guided dosing.<sup>11,12</sup> For example, a recent survey indicated that 70.3% ( $n = 202$ ) of hospitals did not implement AUC-guided dosing with 43% of which had no plan to adopt it soon.<sup>12</sup> Bayesian-guided monitoring was implemented in only 12% of the hospitals surveyed.<sup>12</sup> This low rate of implementation is attributed, partly, to clinicians' unfamiliarity with Bayesian monitoring.<sup>11-13</sup>

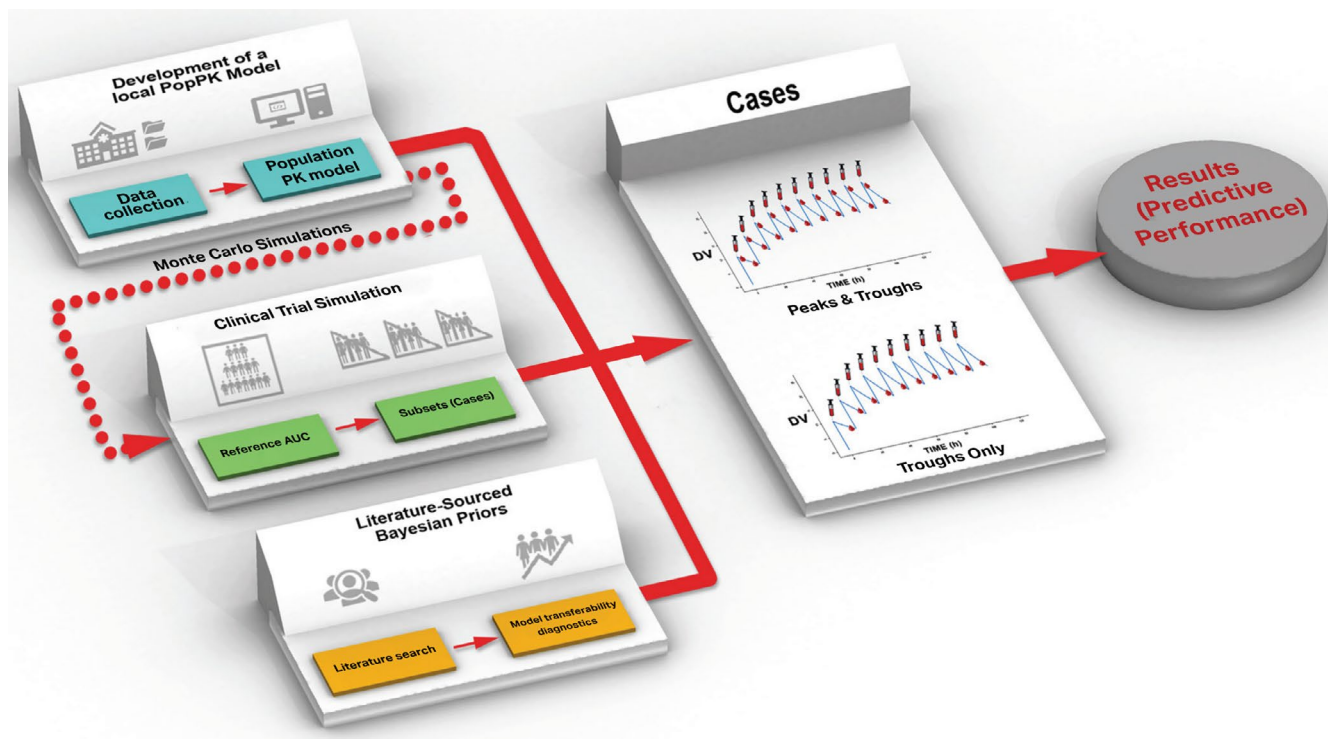
Although both methods (i.e., PK equations and Bayesian) were suggested in the revised guideline, a comprehensive analysis of their performances in predicting AUC under different real-life scenarios yet seems to be lacking. Using the population PK (PopPK) modeling approach and MIPD clinical trial simulations, the first of our threefold objective is to compare the predictive performance of PK equation- and Bayesian-based AUC methods under different conditions (e.g., variations of near and confirmed steady-state intervals using two vancomycin

measurements per the guideline recommendations), as depicted in Figure 1. We also aim at evaluating Bayesian-guided AUC prediction when using two compared to one measurement, because the latter was only moderately recommended.<sup>1</sup> Additionally, to increase familiarity with Bayesian monitoring, we aim at discussing proper Bayesian priors' selection, including the influence of using sparsely sampled PK-fitted models as priors, and the relative significance of satisfying underlying assumptions.

## METHODS

### Study design

Adult patients admitted at the McGill University Health Center (MUHC)-Royal Victoria Hospital during 2016 and 2017 were screened for this single-center retrospective study. Included patients received at least four vancomycin doses and had at least one measured plasma concentration. Exclusion criteria were one or more of the following: acute kidney failure, renal replacement therapy, extracorporeal support membrane oxygenation, end-stage renal disease, and intravenous fluids larger than 2 L within the last four vancomycin doses. Variables collected include vancomycin dosage and administration records, patients'



**FIGURE 1** Schematic roadmap of our study. The predictive performance (precision and accuracy) using the two main methods of first-order PK equations and the Bayesian approach for cases of peak and trough or trough only, each at six varying dosing intervals. This roadmap shows two parallel processes of selecting Bayesian priors, either obtained through the literature or the PopPK model developed here. PopPK, population pharmacokinetic

demographics, the main indication for vancomycin, comorbidities (e.g., obesity, neutropenia, liver disease, and renal insufficiency), admission to the intensive care unit, and laboratory, biochemistry, and microbiology data. This study was approved by the MUHC Institutional Review Board.

## Vancomycin and serum creatinine quantification

Vancomycin and serum creatinine were quantified using Beckman Coulter AU5800 (Beckman Coulter Inc.) with a quantification range of 2.5–100.0 mg/L and 4.4–4420  $\mu\text{mol/L}$  for vancomycin and serum creatinine, respectively. We used the QMS Vancomycin (VANCO) assay (Thermo Fisher; Microgenics Corp.) and creatinine enzymatic assay (Olympus OSR61204).

## Population pharmacokinetic

Our first goal was to develop a local vancomycin PopPK model for the collected MUHC data. Vancomycin PopPK parameters were estimated using NONMEM (version 7.4; GloboMax LLC) within the PsN toolkit.<sup>14</sup> We used the first-order conditional estimation method with interaction (FOCE-I) to fit vancomycin concentration-versus-time profiles to a base one- and two-compartment model, while assuming log-normal between-subject variability (BSV) distribution on the typical parameter estimates. Multiple residual unexplained variability (RUV) models were tested, including additive, proportional, and mixed (additive and proportional) models. Allometric scaling of the effect of weight on vancomycin PK parameters was evaluated using the allometric theory.<sup>15</sup>

Biologically plausible variables were selected for multivariate analysis using stepwise covariate modeling.<sup>16</sup> We used ggplot2 in R ([www.r-project.org](http://www.r-project.org)) to produce all the plots.<sup>17</sup> Bootstrap analysis of 1000 replicates was conducted to evaluate uncertainty and 95% confidence intervals (CIs) around model parameters. Further PopPK modeling details are presented in Appendix S1: Section I.

## Individual reference AUC

Based on the PopPK model developed in the previous section, we conducted Monte Carlo simulations of 1000 virtual patients to obtain individual steady-state AUC ( $\text{AUC}_i$ ).<sup>18</sup> This simulated dataset will be referred to here

as the reference dataset. Conditions of this simulation are presented in Appendix S1: Section II.

## Prediction of reference AUC

In this section, our goal was to predict  $\text{AUC}_i$  at steady-state from using concentrations from different DIs (i.e., not the AUC of the respective interval) using methods detailed below, as were suggested in the revised guideline.<sup>1</sup>

### First-order PK analytic equations

As suggested in the revised guidelines, this method should be used with at least two measurements (peak and trough), obtained near steady-state.<sup>1</sup> The equations (given in Appendix S1: Section III) were coded in R and used in the MIPD clinical trial simulations section.

### Bayesian estimation

Bayesian estimation was performed using two approaches and algorithms: a conventional Bayesian using the FOCE algorithm and a full Bayesian using the Markov chain Monte Carlo (MCMC) algorithm. These two approaches are fundamentally different and a discussion about the Bayesian analysis can be found in Appendix S1: Section IV.<sup>9,19</sup>

#### *Selection of PopPK models to serve as Bayesian priors*

The goal of this step was to identify and systematically evaluate well-established PopPK models from the literature having similar study design and patient characteristics as MUHC data, to serve as Bayesian prior components. This assumes both subpopulations of the MUHC and the literature model were derived from one population with similar study designs.<sup>20,21</sup> Based on these assumptions, we conducted a literature survey to identify proper original or recycled models published from inception and up to January 2020 using the methodology detailed by Aljutayli et al.<sup>22</sup> These models were coded in NONMEM and evaluated according to transferability quality criteria discussed in ref. 20, including ranking by the objective function (OFV), Akaike Information Criterion (AIC), and the visual overlap between individual  $\eta_i$  distribution densities with the theoretical  $\eta$ -distribution  $N(0, \omega^2)$ , as well as simulation-based diagnostics, such as prediction-corrected visual predictive check (pcVPC) and normalized prediction distribution errors (NPDE). These models, in addition to our PopPK model developed above, will serve, each in turn, as Bayesian priors to drive AUC predictions in the MIPD clinical trial simulations section.



## MIPD clinical trial simulations

In this step, our goal was to estimate  $AUC_i$  under multiple realistic clinical scenarios. Using the reference dataset simulated in the Individual Reference AUC section, 14 subsets were created in R with each subset representing realistic clinical cases (Figure 1). These scenarios represent either a couple of peaks and troughs or only troughs, obtained from single or mixed DIs, spanning from the first to the fifth DI, as well as at a steady-state (i.e.,  $SS = 1$  in NONMEM). Using these scenarios and assuming an MIC value of 1 mg/L, three different clinical trials were conducted.

### MIPD clinical trial A: Using literature-sourced Bayesian priors

The goal of this trial was to compare the predictive performance of simple PK equations to Bayesian methods using Bayesian priors obtained from the literature. This trial simulation aimed at mirroring the implementation of Bayesian programs in clinical practice.

### MIPD clinical trial B: Using locally constructed PK model as Bayesian prior

In trial B, we used our local model (i.e., MUHC PopPK model), as a Bayesian prior for subsequent analyses. This is to isolate the influence of trial A model transferability assumptions, while examining and attributing results to the other remaining components, such as estimation methods and varying DIs.

### MIPD clinical trial C: Sampling from different dosing intervals

The goal of this trial was to study the effect of sampling from two different DIs. Using R, we randomly selected individual peaks and troughs from near steady-state intervals (i.e., the fourth and/or fifth DI). This trial investigates the guideline preference of using peaks and troughs from the same versus different DIs when the PK equations are applied.<sup>1</sup>

## Performance metrics

The predictive performance was evaluated in terms of relative bias (rBias) using relative mean percentage prediction error (rMPE) and relative mean absolute percentage prediction error (rMAPE) to assess accuracy, and using relative root mean squared error

(rRMSE) to assess precision. The equations are given in Appendix S1: Section V. Considering the narrow vancomycin AUC/MIC range for therapeutic effect, a very conservative range of rMPE to fall within  $\pm 20\%$  was considered tolerable bias. For example, for an  $AUC_i$  value of 500, a prediction within 400–600 will result in a tolerable rMPE. Cases that result in smaller rRMSE values were considered more favorable if the rMPE 95% confidence interval includes zero.

## Additional verification of results

For additional verification of results, we repeated steps 2.4 to 2.7 but with simulation from Colin et al.,<sup>23</sup> a well-established two-compartment PopPK model containing 8300 vancomycin measurements from 2554 patients across 14 centers. Trial simulations B and C were not repeated and the MCMC algorithm was not used here due to its intensive computational demand.

## RESULTS

### Patients

We included 116 patients, who satisfied the study criteria, having 326 measurements. Table 1 and Table S1 in Appendix S1 summarize the demographics and patient diagnosis of our MUHC data.

### Population pharmacokinetic modeling

A one-compartment model with linear elimination resulted in the best model fit, probably due to the sparse nature of our therapeutic drug monitoring (TDM) data (i.e., 88% troughs and 40% of patients had one measurement). Exponential and mixed (additive and proportional) models best described BSV and RUV, respectively. Introducing creatinine clearance (CL) on CL significantly reduced the objective function (i.e.,  $\Delta OFV -118.34$  at  $p < 0.01$ ), and therefore was included in the final model. Model and values of typical parameter estimates are shown in Table 2. The diagnostic plots for the final model are presented in Appendix S1: Figures S3–S6. The final model had successful minimization and covariance.

### Literature-sourced Bayesian priors

Seven vancomycin PopPK models were retained from the literature as Bayesian priors for subsequent analyses.<sup>23–29</sup>

Due to their TDM nature, literature-sourced models bared varying degrees of resemblances in design and population to the MUHC data. Nevertheless, we assumed a negligible influence arising from these differences on vancomycin PK parameter estimates that were not accounted for using model transferability diagnostics.<sup>22</sup> We produced diagnostic plots, including pcVPC and NPDE (Appendix S1: Table S2). Models were ranked according to OFV, AIC, and

visual overlap between individual  $\eta_i$  density distribution with the theoretical distribution (Table S3 and Figure S7). Results suggested that two models might be appropriate for MUHC data, namely Colin et al. and Yamamoto et al.<sup>23,27</sup> Other models resulted in varying degrees of some systematic under- or overprediction or misfit. It should be noted that the Colin et al. model was slightly modified per MCMC run requirements.<sup>23,30</sup>

**TABLE 1** Baseline demographics and clinical characteristics of MUHC participants

Variable	Value
Study size, <i>n</i>	116
Male/female, <i>n</i>	83/33
Vancomycin observations, <i>n</i>	326
Trough measurements	88%
Patients with one vancomycin observation	40%
Patients with one or two vancomycin observations	60%
Age, <sup>a</sup> years	67.8 ± 11
Weight, <sup>a</sup> kg	72 ± 8.6
Height, <sup>a</sup> cm	167.9 ± 4.9
BMI, <sup>a</sup> kg/m <sup>2</sup>	24.2 ± 3.1
Serum creatinine, <sup>a</sup> mg/dl	1.0 ± 0.5
Liver disease, <i>n</i>	5
Neutropenia, <i>n</i>	6

Abbreviations: BMI, body mass index; MUHC, McGill University Health Center.

<sup>a</sup>Data presented as mean ± SD.

## Clinical trial simulation

### MIPD clinical trial A: Using literature-sourced Bayesian priors

Results of MIPD trial A using literature-sourced Bayesian priors are presented in Figure 2 and Appendix S1: Figures S8–S10. The predictive performance of the Bayesian approach using literature-sourced Bayesian priors varied depending on multiple factors, including the DI, number of samples, and Bayesian algorithm. Some of these variables affected, as well, the predictive performance of PK equations.

#### *Influence of the dosing interval*

Trial A might suggest varying degrees of improved predictive performance moving from the first DI to steady-state regardless of the prediction method used, as can be seen with the percentage of patients within ±20% rMPE in Figure 2. The trend of improved predictive performance

**TABLE 2** MUHC vancomycin population PK model and the corresponding parameter estimates of the final model, as well as its bootstrap results

PK parameter	Final model estimates	% RSE <sup>a</sup>	Bootstrap value ( <i>n</i> = 1000) <sup>b</sup>		
			Mean	2.5th Percentile	97.5th Percentile
CL (L/h) = $\Theta_1 * (CL_{cr}/84)$					
$\Theta_1$	4.16	4.1	4.16	3.84	4.53
V (L) = $\Theta_2 * (WT/70)$					
$\Theta_2$	102.46	9.7	102.95	82.3	125.0
IIV					
$\omega_{CL}$ , <sup>c</sup> %	34.12	11.2	34.0	26.68	42.07
$\omega_V$ , <sup>c</sup> %	51.83	16.8	51.48	30.51	66.56
RUV					
$\sigma_{Proportional}$ , <sup>c</sup> %	13.95	29.9	13.59	4.41	21.6
$\sigma_{Additive}$ , mg/L	3.04	19.7	2.92	1.58	4.03

Abbreviations: CL, clearance;  $CL_{cr}$ , creatinine clearance; IIV, interindividual variability; MUHC, McGill University Health Center; PK, pharmacokinetic; RSE, relative standard error; RUV, residual unexplained variability; V, volume of distribution; WT, weight;  $\Theta$ , NONMEM fixed-effect PK parameter;  $\omega$ , standard deviation of the interindividual variation (i.e.,  $\eta_i$ );  $\sigma$ , proportional or additive residual variability.

<sup>a</sup>Relative standard error.

<sup>b</sup>95% success.

<sup>c</sup>Expressed as a coefficient of variation (CV).

was not observed for two Bayesian priors (i.e., Usman et al. and Kim et al.) used with the conventional Bayesian method.<sup>25,28</sup> Two models (i.e., Zhou et al. and Staatz et al.) had a relatively long half-life, which could explain the drastic improvement in predictive performance at confirmed steady-state intervals.<sup>26,29</sup> The estimated half-life for other models ranged from 5.77 to 9 h (Appendix S1: Table S3).

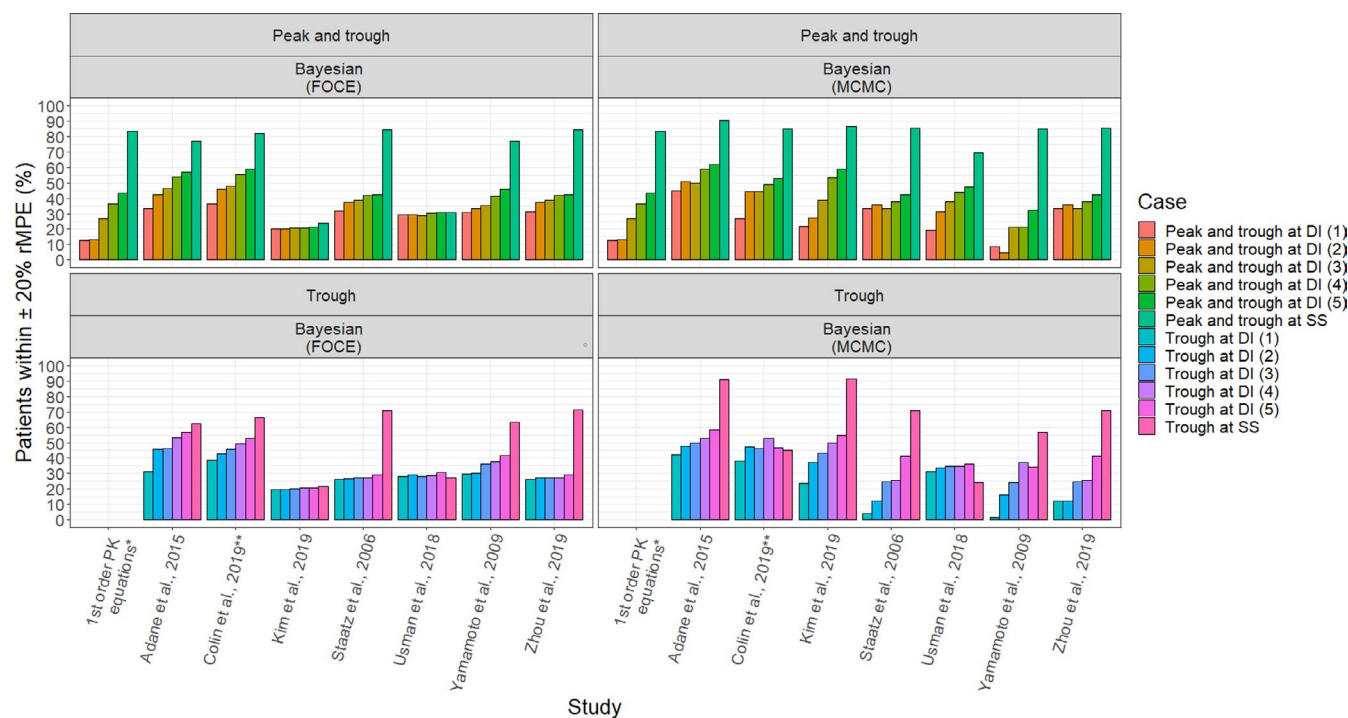
#### *Influence of peak and trough versus trough only*

In trial A, Bayesian prediction using two samples compared to one sample demonstrated a slightly better overall predictive performance. In our study, the influence of DIs was more pronounced. Examples can be given for the two most appropriate priors for MUHC data (i.e., Colin et al. and Yamamoto et al.<sup>23,27</sup>). Across the first, second, third, fourth, and fifth, and at steady-state DIs using the FOCE algorithm, Colin et al. prior achieved 36.3%, 46.1%, 48%, 55.2%, 59.1%, and 81.8% patients within  $\pm 20\%$  rMPE using two samples (i.e., peak and trough) versus 38.8%, 42.8%, 45.8%, 49.5%, 53%, and 66.5% patients within  $\pm 20\%$  rMPE using one sample (i.e., trough only), whereas Yamamoto et al. prior achieved 30.7%, 33.3%, 35.1%, 41.3%, 46.1%, and 77% patients within  $\pm 20\%$  rMPE using two samples

(i.e., peak and trough) versus 29.6%, 30.4%, 36.2%, 37.8%, 41.6%, and 63.3% patients within  $\pm 20\%$  rMPE using one sample (i.e., trough only). It should be noted that PK equations require at least two samples.

#### *Influence of the Bayesian algorithm*

Results of trial A did not support any generalized conclusion comparing the full- to conventional-Bayesian approach. For example, a higher percentage of patients within  $\pm 20\%$  rMPE, particularly at steady-state, was observed when using full-Bayesian compared to the respective conventional-Bayesian cases with Usman et al.<sup>25</sup> and Kim et al.<sup>28</sup> In contrast, Yamamoto et al.<sup>27</sup> showed better predictive performance and a significantly higher percentage of patients within  $\pm 20\%$  rMPE using the conventional Bayesian approach. In terms of rRMSE, Bayesian priors that consistently achieved a relatively low rRMSE were Colin et al.<sup>23</sup> and Adane et al.<sup>24</sup> in the cases of peaks and trough using full-Bayesian, and Zhou et al.<sup>26</sup> as well as Yamamoto et al.<sup>27</sup> in the cases of peaks and trough using conventional-Bayesian. Overall, peaks and troughs with the conventional Bayesian approach resulted in a higher number of points with low rRMSE (defined as below 75 rRMSE).



**FIGURE 2** Bar Plot of the percentage of patients within the tolerable rBias range of  $\pm 20\%$  rMPE from MIPD clinical trial simulation A. Each subplot represents a combination of using a peak and a trough or a trough only at varying dosing intervals (DIs; i.e., the first, second, third, fourth, and fifth, and at steady state [SS]) with the full-Bayesian and the conventional Bayesian approach. For reference, results using the first-order PK equations were plotted. Each color represents a case. \*For reference as the first-order PK equations should be used with near or at steady-state samples. \*\*Colin et al. model was modified for MCMC runs. FOCE, first-order conditional estimation method; MCMC, Markov chain Monte Carlo; MIPD, model-informed precision dosing; rBias, relative bias; rMPE, relative mean percentage prediction error

### *Variability in predictive performance between Bayesian priors and model transferability diagnostics*

Conducted model transferability diagnostics (literature-sourced Bayesian priors section) might suggest an overall relation to the predictive performance that was not as strong as we expected. For example, despite the Yamamoto et al.<sup>27</sup> model having better transferability diagnostic plots compared with other models, and similar clinical population and design as our MUHC study, only 2% of patients were within  $\pm 20\%$  rMPE in the case of full-Bayesian monitoring at the first DIs, being the lowest among all results in our study, Figure 2. In contrast, Adane et al.<sup>24</sup> transferability diagnostic plots suggested incompatibility while its population was limited to extremely obese, unlike most of the MUHC population. Yet, the overall predictive performance was one of the best. It is worth mentioning that Adane et al.<sup>24</sup> was included as a prior as the MUHC population had obese patients and based on the premise that obese vancomycin CL is not significantly different from non-obese.<sup>22</sup>

### *Literature-sourced Bayesian priors versus PK equations*

The predictive performance of the Bayesian approach using literature-sourced Bayesian priors was better overall than the performance of PK equations in pre-steady-state DIs (i.e., 1–3), except for Yamamoto et al.<sup>27</sup> (using the full-Bayesian method) and Kim et al.<sup>28</sup> (using the conventional-Bayesian). However, no similar conclusion could be made when sampling near or at steady-state DIs. The 95% CI for most cases did not include zero, except for most of Colin et al.<sup>23</sup> using the conventional-Bayesian approach, Adane et al.<sup>24</sup> using the full-Bayesian approach, and for PK equations at steady-state (Appendix S1: Figure S14).

Trial B results are shown in Figure 3 and Figures S11–S13 in Appendix S1. Unlike some cases in trial A, trial B showed an overall systematic and incremental gain in predictive performance (increased accuracy and precision and reduced bias) progressing between intervals toward steady-state. In trial B, Bayesian approaches with peaks and troughs consistently outperformed using only troughs, which translated into 2% to 15% more patients achieving  $\pm 20\%$  rMPE when using peaks and troughs. In our case, the use of local Bayesian priors outperformed the use of literature-sourced priors, including the two priors with the best transferability diagnostics (i.e., Colin et al. and Yamamoto et al.<sup>23,27</sup>), in the majority of the performance metrics.

The Bayesian approach used in trial B consistently outperformed the respective cases using first-order PK equations, with 20–25% more patients within the desired  $\pm 20\%$  rMPE target at the third, fourth, or fifth DIs. Further, using the first-order PK equations performed very poorly

at the first and second DIs, as expected, in which less than 13% were within  $\pm 20\%$  rMPE target, compared to 45% to 53% using Bayesian methods at the respective cases of trial B. Bayesian methods used in trial B appeared more precise and accurate compared to the first-order equations, as indicated clearly by rRMSE and rMAPE results. Further, first-order equations resulted in a systematic bias as indicated by the persistent underprediction in every non-steady-state interval as explained in ref. 31; a trend that was not observed for the respective cases using Bayesian methods. Finally, rMPE 95% CI favored Bayesian-guided AUC estimation over the corresponding cases using first-order PK equations. These observations extend as well to Bayesian approaches with a trough only, as Bayesian methods resulted in 15% to 35% more patients within the  $\pm 20\%$  rMPE target in every non-steady-state DI, compared to the respective cases using first-order PK equations.

### MIPD clinical trial C: Sampling from different dosing intervals

Results of using the first-order PK equations with two levels from the fourth and/or fifth DIs were consistent with the trend of incremental gain in predictive performance progressing between intervals toward steady-state, as shown in Figure 4 and Figures S15–S17 in Appendix S1. In contrast, using Bayesian approaches with two levels from the fourth and/or fifth DIs did not show a similar trend but rather showed comparable results to using only the fourth DI.

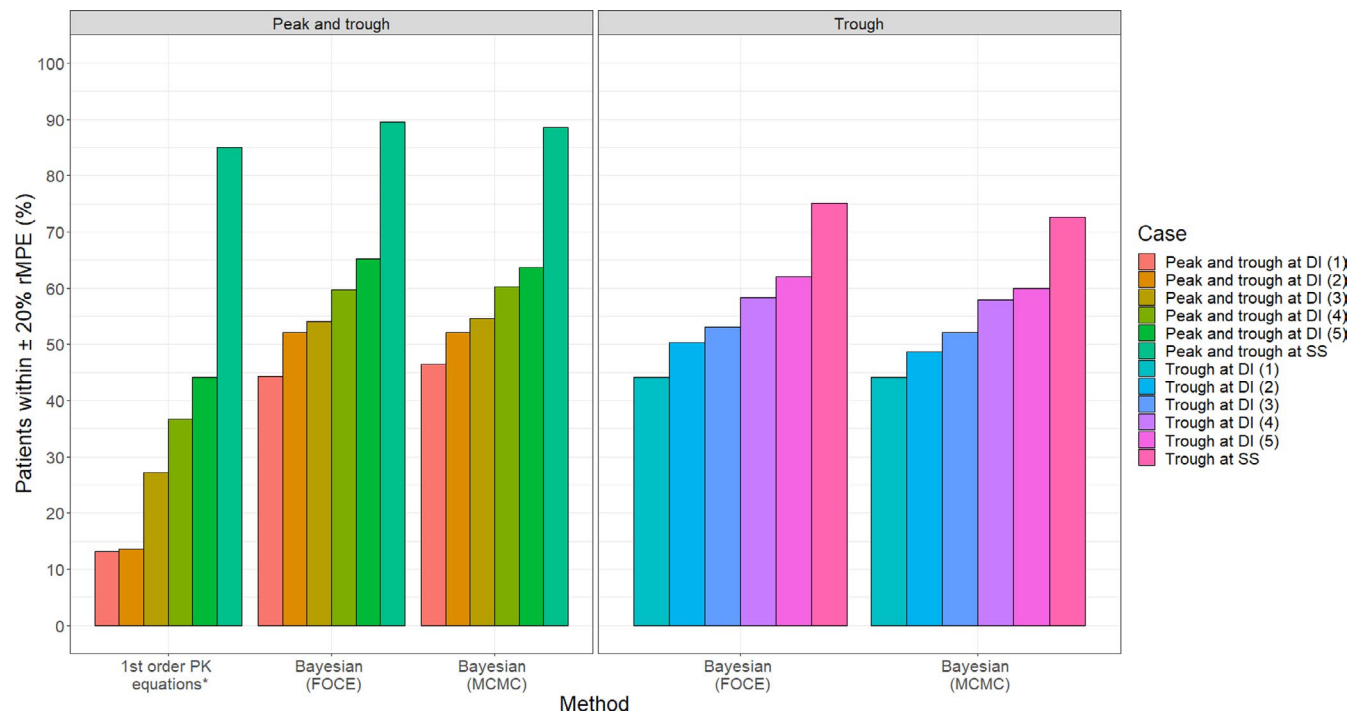
### Additional verification of results

Predictive performance of simulations from Colin et al.,<sup>23</sup> instead of the MUHC model, seemed to support general observations reported in the MIPD clinical trial A: using literature-sourced Bayesian priors section, comparing Bayesian to PK equations, Figure S19 in Appendix S1. This might suggest that our results apply beyond MUHC data and the model (i.e., one- versus two-compartment or the parameter estimates).

## DISCUSSION

In this study, the predictive performance of the two recommended AUC-guided monitoring methods<sup>1</sup> was compared in an array of realistic clinical cases, ranging from a practical early trough to late peaks and troughs sampling near or at steady-state. Results varied significantly depending on a combination of the estimation





**FIGURE 3** Bar plot of the percentage of patients within the tolerable rBias range of  $\pm 20\%$  rMPE from MIPD clinical trial simulation B. Each subplot represents either the case of a peak and a trough or a trough only at varying dosing intervals (DIs; i.e., the first, second, third, fourth, and fifth, and at steady-state [SS]) with the full-Bayesian and the conventional Bayesian approach. For reference, results using the first-order PK equations were plotted. Each color represents a case. \*For reference as first-order PK equations should be used with steady-state samples. FOCE, first-order conditional estimation method; MCMC, Markov chain Monte Carlo; MIPD, model-informed precision dosing; PK, pharmacokinetic; rBias, relative bias; rMPE, relative mean percentage prediction error

method, case, and the relative influence of not satisfying assumptions required for PK equations and PopPK model transferability. Further, we presented the potential influence of sampling from mixed versus single near steady-state DIs.

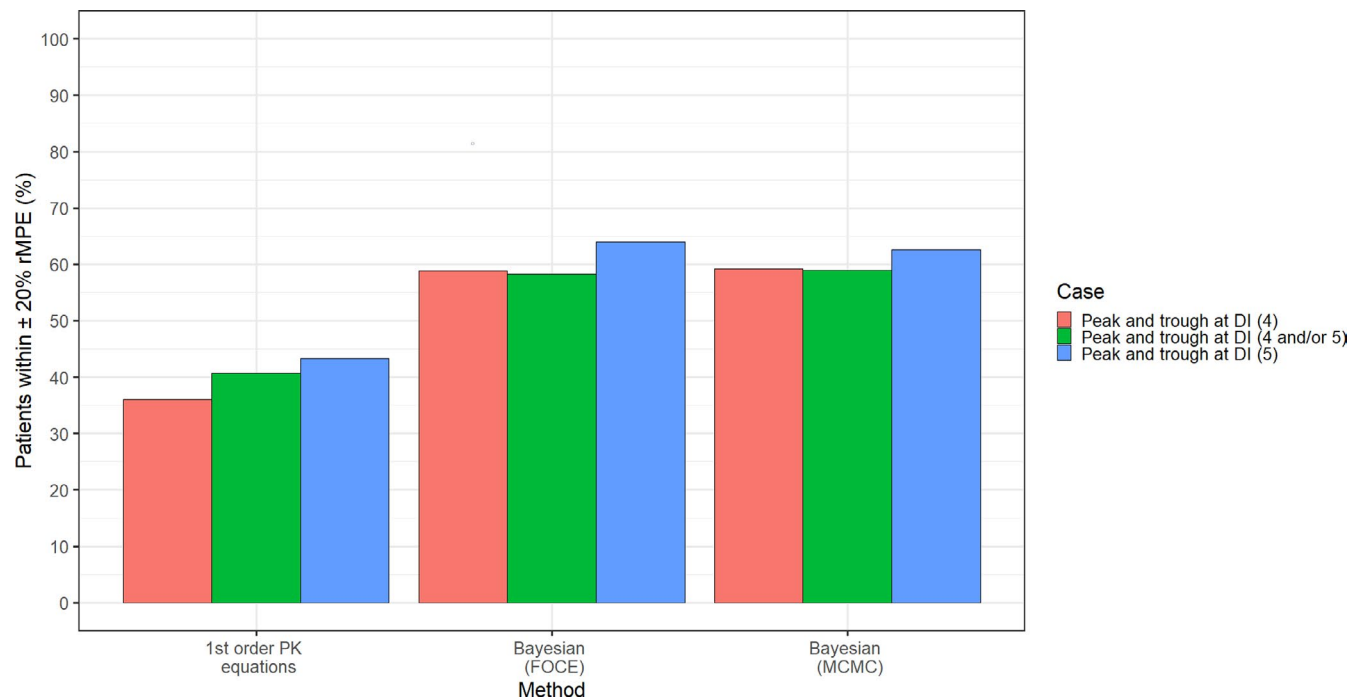
We aimed to assess whether equation-based AUC predictions resulted in an equivalent or better accuracy and bias compared to using five Bayesian software programs.<sup>10</sup> Trial A (using the MUHC and Colin et al. model-based simulations, one- and two-compartment models, respectively) did not seem to support a generalized conclusion. This is unlike trial B that showed monitoring using Bayesian methods with troughs only, as early as the first DI, showed comparable results to near steady-state monitoring using PK equations (i.e., peak and trough at the fifth DI), which resulted in 43% of the patients within this study's desired rMPE limits. These results as well as the desired rapid achievement of the therapeutic target and the ability to update current knowledge might favor Bayesian-guided monitoring.<sup>1,3,6</sup> A potential clinical exception, however, is the case of a loading dose at which therapeutic concentrations can be achieved fast. In this case, it is unclear if the Bayesian approach will maintain being favorable.

We included results that violated steady-state assumptions essential for PK equations in order to gain insights into the prospective impact of violating such assumptions

and for relative comparison with Bayesian methods. The revised guidelines highlighted the difficulty in determining steady-state conditions in practice and stated the strong preference for the two measurements to be near steady-state.<sup>1</sup>

Part of our simulations might support rapid Bayesian vancomycin monitoring using sparse data, as sparse as only a trough that is obtained as early as at the first DI. MIPD trial B showed that peaks and troughs compared to trough-only Bayesian monitoring were not very different. For example, the percentage of patients within  $\pm 20\%$  rMPE at the first DI was 46% and 44% for the peak and trough and trough only cases, respectively. Waiting to the fifth DI increased the percentage of patients within our desired  $\pm 20\%$  rMPE target to roughly 64%.

Bayesian-guided AUC monitoring might be affected by the quality of data used to build the prior.<sup>6,9</sup> The revised guideline only recommended Bayesian programs that implemented richly sampled Bayesian priors.<sup>1</sup> Yet, the availability of such models in the literature might be limited for many patient populations.<sup>22,32</sup> This can be attributed to previous TDM practices comprised of trough-only monitoring that resulted in many PopPK-fitted models using sparse samples.<sup>22,32</sup> Most priors used in our study were fitted using sparsely sampled TDM data, including our



**FIGURE 4** Bar plot of the percentage of patients within the tolerable rBias range of  $\pm 20\%$  rMPE from MIPD clinical trial simulation C, representing a peak and a trough obtained from varying dosing intervals (i.e., fourth, fifth, or both) with the full-Bayesian, the conventional Bayesian, and first-order PK equations. The revised guidelines recommendation of sampling within the same dosing interval was for the first-order PK equation. FOCE, first-order conditional estimation method; MCMC, Markov chain Monte Carlo; MIPD, model-informed precision dosing; PK, pharmacokinetic; rMPE, relative mean percentage prediction error

MUHC model. This sparse nature and our conservative rBias limits, might explain the capping of the percentage of patients within  $\pm 20$  rMPE at 65% and 90% for the fifth and confirmed steady-state DI, respectively.

Implementing MIPD using literature-sourced Bayesian priors might require a systematic model evaluation and validation and expertise, as performed by some of the Bayesian TDM programs.<sup>6,20,33,34</sup> The results of conducted systematic model evaluation varied with DIs, the number of measurements, and the algorithm used, and did not seem to suggest strong relation with predictive performance (trial A). This assumes little influence of unsatisfied underlying assumptions (i.e., populations driven from one population and similar study design).<sup>20,21</sup> One can argue, having collected local data, that developing local PopPK models for subsequent local studies can be more efficient and less assumption-demanding compared to adopting and validating varying vancomycin PopPK models, as demonstrated in trial B (local prior) compared to trial A (literature-sourced priors). Ideally, however, all previous experiments could be incorporated in the Bayesian prior components. In addition, other approaches, such as automated model selection or model averaging algorithms, can be used.<sup>5,20</sup>

Despite the simulation nature of AUC in this study (the gold standard of real AUC data was not available),

key points seem relevant to clinical practice and can help optimize vancomycin TDM. Although the performance of some priors might be limited to the MUHC and it might be expected that others report different or similar results,<sup>33,35</sup> the premise of this paper was not to advocate for a specific prior but to increase familiarity with important aspects of AUC-guided monitoring, uncover its case-specific performance and limitations, such as when using sparse nonoptimally sampled TDM data, and help transition into AUC-guided monitoring. The additional simulations from a well-established model did not seem to contradict our general observations despite that predictive performance can be expected to vary depending on many conditions, such as the relatively long average half-life of MUHC models that exceeded the DI length, the type and magnitude of the PopPK error model used, the narrow sampling window, and the varying levels of biased parameter estimates. Finally, this work was based on the premise that improved AUC prediction might yield improved outcomes. We focused only on evaluating methodology, so the gold standard PopPK modeling software NONMEM seemed more suitable to use rather than a commercially available TDM program with specific pre-built PopPK models.

In conclusion, this study will likely contribute to better vancomycin clinical monitoring and precision dosing by

understanding contexts that might impact AUC predictions in TDM settings. It shows that Bayesian-guided AUC monitoring has the potential to outperform first-order PK equations AUC monitoring, mostly in pre-steady-state dosing intervals in the absence of a loading dose. This study also supports rapid vancomycin Bayesian AUC-guided monitoring using only a trough that was obtained as early as at the first dosing interval.

## CONFLICT OF INTEREST

The authors declared no competing interests for this work.

## AUTHOR CONTRIBUTIONS

A.A., D.T., and F.N. wrote the manuscript. A.A., D.T., and F.N. designed the research. A.A. performed the research. A.A. and G.B. analyzed the data. F.N. contributed analytical tools.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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