

ARTICLE

Optimized sampling to estimate vancomycin drug exposure: Comparison of pharmacometric and equation-based approaches in a simulation-estimation study

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Abstract

Vancomycin dosing should be accompanied by area under the concentration-time curve (AUC)-guided dosing using model-informed precision dosing software according to the latest guidelines. Although a peak plus a trough sample is considered the gold standard to determine the AUC, single-sample strategies might be more economic. Yet, optimal sampling times for AUC determination of vancomycin have not been systematically evaluated. In the present study, automated one- or two-sample strategies were systematically explored to estimate the AUC with a model averaging and a model selection algorithm. Both were compared with a conventional equation-based approach in a simulation-estimation study mimicking a heterogeneous patient population ($n = 6000$). The optimal single-sample timepoints were identified between 2–6.5 h post dose, with varying bias values between -2.9% and 1.0% and an imprecision of 23.3% – 24.0% across the population pharmacokinetic approaches. Adding a second sample between 4.5–6.0 h improved the predictive performance (-1.7% to 0.0% bias, 17.6% – 18.6% imprecision), although the difference in the two-sampling strategies were minor. The equation-based approach was always positively biased and hence inferior to the population pharmacokinetic approaches. In conclusion, the approaches always preferred samples to be drawn early in the profile (<6.5 h), whereas sampling of trough concentrations resulted in a higher imprecision. Furthermore, optimal sampling during the early treatment phase could already give sufficient time to individualize the second dose, which is likely unfeasible using trough sampling.

Study Highlights**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

Gram-positive anti-infective therapy using vancomycin should be supported by population pharmacokinetic models, especially in patients who are critically ill. Therefore, 1–2 plasma samples (ideally a sample from the early profile and

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a sample from the late profile) should be supplied to model-informed precision dosing software to ultimately predict precise individual doses.

WHAT QUESTION DID THIS STUDY ADDRESS?

Besides the influence of the models/approaches used for guidance, we hypothesize that the sampling time might alter prediction depending on the time under treatment or the number of samples and optimized sampling strategies might outperform currently recommended strategies.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The most informative sampling timepoints were identified to be from the early pharmacokinetic profile, whereas trough samples resulted in less-precise predictions.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The virtual study implies that model-informed precision dosing of vancomycin should be done informing population pharmacokinetic approaches with earlier samples (less than 6.5 h) rather than trough samples.

INTRODUCTION

To treat serious invasive infections by multiresistant Gram-positive bacteria, vancomycin is indisputably the key antibiotic, and therapeutic drug monitoring (TDM) in conjunction with individual dose adjustments is required to improve treatment outcomes.¹⁻³ The consensual pharmacokinetic (PK)/pharmacodynamic index to guide vancomycin is the area under the concentration-time curve (AUC) per 24 h divided by the minimum inhibitory concentration and values between 400 and 600 are considered optimal.⁴⁻⁶

Historically, the clinically relevant drug exposure was either approximated via a surrogate trough measurement in steady state or calculated with log-linear regression or trapezoidal formulas using multiple samples from the same individual.^{7,8} Another appealing approach is to estimate the individual PK parameters using sparse sampling in combination with population PK models to guide individual dosing decisions.⁹ This combination of present patient information and prior knowledge on drug PK (i.e., embedded in the population PK models) is usually termed *model-informed precision dosing* and has recently received increasing interest in treatment individualization at bedside.¹⁰⁻¹² The interest grounds on obvious benefits, such as adequately adjusting the treatment at early stages, the reduced burden to the patient caused through a lower sampling frequency, and a potentially higher rate of successful therapies, while reducing the overall costs.¹²⁻¹⁶

Nonetheless, it is crucial for precision dosing to select the correct model and assure that the data are accurately collected and the sampling time is adequately documented.^{17,18} However, the recommended number of

required samples per dosing interval and their optimal timing to achieve accurate and precise estimates of the individual PK has not been conclusively evaluated yet.¹⁹

The aim of the study was to find optimal sampling strategies in intermittent vancomycin therapy to determine the individual drug exposure in heterogenous patients using two previously developed multimodel approaches. These two approaches either automatically select the most suitable model from a set of candidate models per individual (model selection algorithm [MSA]) or average the predictions of the models according to their individual model fit (model averaging algorithm [MAA]).¹⁷ Therefore, the predictive performance of various one- and two-sampling strategies after the simulated first dose (FD) and in steady state (SS) were compared (i) within the two multimodel approaches; (ii) against a “classical” peak-trough sampling applied to the two multimodel approaches; and (iii) against an equation-based approach (EQA) that uses two predetermined vancomycin samples and simple analytic equations to calculate the area under a monoexponential curve.

METHODS

The simulation-estimation study consisted of six partly repetitive main steps (Figure 1) and can be divided into the simulation part (i.e., creating the true parameters/drug exposure) and the estimation part (i.e., the estimation of the drug exposure using a reduced number of one or two samples per patient). Details of the study methods are described in the next section, and examples of the data, model codes, and output are provided in Appendix S1.

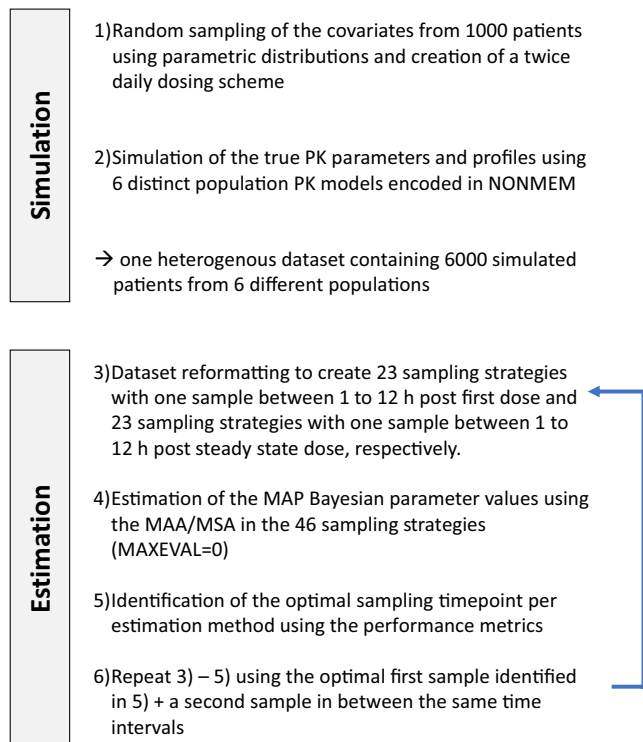


FIGURE 1 Workflow of the simulation-estimation study consisting of six main steps. MAA, model averaging algorithm; MAP, maximum a posteriori prediction; MAXEVAL=0, NONMEM-specific MAP estimation with fixed population parameters; MSA, model selection algorithm; PK, pharmacokinetics

The data preparation and all statistical and graphical evaluations were done in R (Version 4.0.2),²⁰ whereas the simulations and data-fitting processes were conducted in NONMEM® (Version 7.5; ICON plc).²¹

Simulation structure

A base set of 1000 virtual patients receiving a loading dose of 2000 mg and maintenance doses of 1250 mg every 12 h administered as 60-min infusions and with randomly sampled covariates was constructed once. The randomly acquired covariates were sampled from a normal (age and body height), log normal (body mass index [BMI], serum creatinine), or a binomial distribution (sex). To mimic an adult population with adequate covariate relationships and correlations, body height was sampled from a normal distribution depending on the sex (female, mean 1.65 m; male, 1.75 m [standard deviation, 0.035 m]), the corresponding body weight was calculated based on the simulated BMI and height, and age was truncated to values between 20 and 75 years.

To obtain a preferably heterogenous data set, the PK profiles and the “true” drug exposures were simulated in NONMEM via sampling from the eta-distribution of six

distinct population PK models, respectively. The resulting data set contained 1000 patients each (6000 in total, i.e., six times the base set) of the following populations: extremely obese using the Adane et al. model²²; after heart surgery, Mangin et al.²³; trauma, Medellín-Garibay et al.²⁴; critically ill, Revilla et al.²⁵; sepsis, Roberts et al.²⁶; and hospitalized using the Thomson et al. model²⁷ (model details can be found in Table S1).

The true drug exposures obtained via the individual simulated PK parameters (i.e., simulated AUC) were determined via numerical integration of the concentration-time profiles from 0 to 12 h (AUC_{0-12}) or from 48 to 60 h (AUC_{48-60}) for steady-state conditions.

Estimation elements

Sampling strategies

The previously described 6000 patients were reformatted to data sets containing a single plasma measurement (i.e., coded as missing dependent variable (MDV) = 0, while all other samples were coded as MDV = 1) at the same timepoint between 1–12 h post start of first infusion (in 30 min increments) or between 49–60 h post start of first infusion, resulting in 23 data sets containing a single sample per patient in the FD and 23 single-sampling strategies in the fifth dosing interval (i.e., at approximate SS), respectively.

Furthermore, to create 23 data sets with two samples in the FD and SS, respectively, the optimal single-sampling strategies were identified (details in the [Approaches to Determine Drug Exposures](#) and [Identification of the Optimal Sampling Strategies](#) sections). The data sets therefore contained the identified best single timepoint of the multimodel approaches ([Identification of the Optimal Sampling Strategies](#) section) and an additional second sample drawn between 1–12 h after the start of infusion ([Figure 1](#), Step 6). The strategies that would draw the second sample at the timepoint of the optimal first sample were excluded. To compare the two-sampling strategies with the current gold standard in reduced sampling, a classical “peak-trough” strategy was prepared with samples drawn at 1 and 11.5 h after the start of infusion.

Approaches to determine drug exposures

Two different approaches to estimate the vancomycin AUC using the reduced sampling strategies (see the [Sampling Strategies](#) section) were compared and consisted of two multimodel approaches as well as an EQA.

The two multimodel approaches were applied to estimate the individual PK parameters (including the AUC) with each of the sampling strategies through maximum a posteriori Bayesian estimation (MAXEVAL = 0 procedure in NONMEM®). Therefore, the approaches either automatically estimated a weighted average of the individual drug exposure using a set of six population PK models simultaneously (i.e., MAA) or selected the individually best-fitting model from the same set of models (MSA), as described by Uster et al.¹⁷ In detail, these automated algorithms comprise three steps: (i) maximum a posteriori Bayesian estimation (MAXEVAL = 0) of the individual PK parameter and drug exposure with each model (i.e., AUC obtained via numerical integration), (ii) automated comparison of the individual model fit via the likelihood (LL), and (iii) adjustments of the predictions (i.e., the AUC) by the respective weighting (Equation 1) with the best-fitting model given the highest influence and either building a weighted average (MAA) or selecting the best model (MSA). The weighting scheme, therefore, compared the maximum LL obtained through the NONMEM objective function value (OFV) of the i th model relative to the set of n models included in the algorithms:

$$W_{OFV_i} = \frac{LL_i}{\sum_1^n LL_n} = \frac{e^{(-0.5 \times OFV_i)}}{\sum_1^n e^{(-0.5 \times OFV_n)}}. \quad (1)$$

The two approaches were compared to an EQA as proposed by Pai et al.,²⁸ which consisted of the following: a post distributional peak (i.e., 2 h after the start of infusion) and a trough measurement (0.5 h before the next dose) were used to determine the individual elimination rate constant (K_e) using the Sawchuk–Zaske method (Equation 2). Subsequently, the concentration at the theoretical start of infusion (C_{T0}) and the true trough concentration immediately before the next dose (C_{T12}) were back-extrapolated from the mono-exponential curve via transposing Equation (2) (details in Appendix S1):

$$K_e = \frac{\ln\left(\frac{C_p}{C_T}\right)}{T_T - T_P} \quad (2)$$

with C_p and C_T being the concentrations close to the peak and trough levels, respectively, and T_p and T_T being the timepoints of the concentrations, respectively. The AUC_{0-12} was then approximated via Equation (3):

$$AUC_{0-12} = \frac{C_{T0} - C_{T12}}{K_e}. \quad (3)$$

Given the statistical nature of the simulation to assign negative plasma measurements in some cases (2.7% of the patients), but the Sawchuk–Zaske method not allowing for

TABLE 1 Demographics of the simulated population ($n = 5925$)

Characteristics	Value, mean (range)
Age, years	50 (20–75)
Body mass index, kg/m ²	25 (18–34)
Height, m	1.7 (1.55–1.85)
Serum creatinine, μmol/L	82 (29–198)
Weight, kg	73 (50–102)

them, plasma concentrations smaller than 0.2 mg/L were fixed to 0.2 mg/L representing 10% of the typical lower limit of quantification for vancomycin.

Identification of the optimal sampling strategies

To assess the sampling strategies of the multimodel approaches in FD or SS and to compare them with the EQA, trends of the median percentage error (MdPE; Equation 5) and the interquartile range (IQR; Equation 6) of the relative prediction errors (rPE; Equation 4) across the total population were evaluated:

$$rPE = \frac{\text{predicted AUC} - \text{simulated AUC}}{\text{simulated AUC}} * 100 \quad (4)$$

$$\text{MdPE} = \text{median}(\{rPE_0 \dots rPE_i\}) \quad (5)$$

$$\text{IQR} = \text{quartile}_3(\{rPE_0 \dots rPE_i\}) - \text{quartile}_1(\{rPE_0 \dots rPE_i\}) \quad (6)$$

with quartile_1 and quartile_3 being the 25th and 75th percentiles of all rPE of the AUC over the 6000 (= i) patients, respectively. Unbiased approaches should therefore result in an MdPE close to 0 and the IQR should be as low as possible, only being limited by the residual unexplained variability components of the simulation models.

To identify the optimal sampling timepoints of the multimodel approaches for the total population, the MdPE and IQR were separately evaluated with the best metric given the highest ranking (Table S2 contains an example). The best resulting ranking of the median and IQR (i.e., the minimum sum of both) together indicated the optimal single-sampling timepoint of the approach, that is, the ideal combination of a low bias and a small imprecision compared with the other sampling strategies within the respective approach. In case the combined ranking from the MdPE and IQR was equal at two or more timepoints per approach, a better IQR was prioritized. Subsequently, the identified single-sampling timepoint was used as first sampling in the two-sampling strategies (see the Sampling Strategies section).

RESULTS

Simulated study population

The study population consisted of 6000 individuals from six distinct populations with the representative covariate distributions displayed in Table 1 and Figure S1. To avoid unreasonable PK parameters, the eta values of the simulation models were restricted to ± 2.8 times standard deviation (i.e., covering 99.5% of the drawn values under ideal normal assumption), which resulted in the exclusion of 75 simulated patients in the subsequent analysis. The PK parameter distributions of the remaining 5925 patients are displayed in Figure S2. Implausible covariate relationships were avoided by restricting the age to 20–75 years and correlating body weight, height, and sex via BMI. The true individual PK profiles can be inspected in Figure S3

and resulted in true median AUC_{0-12} of 253 mg/L*h (IQR, 192–324 mg/L*h) and AUC_{48-60} of 299 mg/L*h (IQR, 226–399 mg/L*h).

Estimation of the AUC and identification of the optimal sampling timepoints

In the following, we depict the identification of the optimal sampling timepoints of the multimodel approaches in the simulated population ($n = 5925$) and therefore compare the predictive performance in the MAA and MSA, respectively. In general, the predictive performance of the two approaches resulted in MdPEs between -4.3% and 2.2% across the single-sample strategies, whereas the IQR followed an asymmetric positive parabolic pattern (Figure 2).

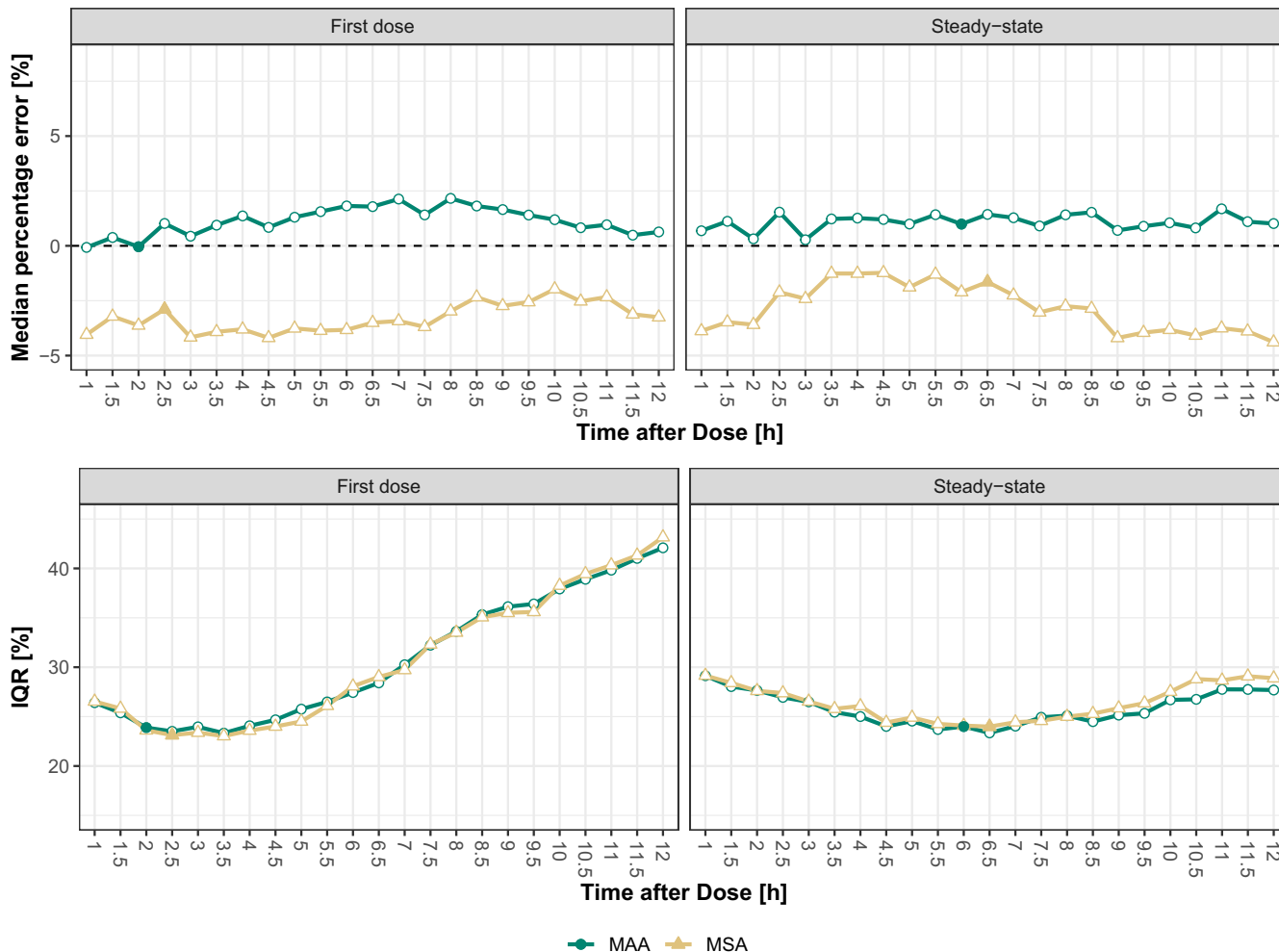


FIGURE 2 Performance metrics of the multimodel approaches using the single-sample strategies in the total population ($n = 5925$). The median percentage error and the interquartile range (IQR) of the relative prediction errors of the area under the concentration-time curve represent accuracy and imprecision, respectively. Time after dose indicates the timepoint of the single sample drawn in the 5925 patients either in the first dosing interval (i.e., first dose) or the fifth (i.e., steady state). The filled shapes indicate the optimal first sampling timepoint per approach identified via the metrics ranking. MAA, model averaging algorithm; MSA, model selection algorithm

Both approaches consistently estimated the AUC_{0-12} and AUC_{48-60} with a low bias, although the MSA resulted in slightly more negative MdPE (i.e., between -4.3% and -1.2%) across the single-sampling strategies. Sampling time intervals with favorable metrics in the FD were identified between 1.5 and 5.5 h. The IQR differed less across the single-sampling strategies, when being in SS, and resulted in a slightly later optimal time interval between 4.5 and 8.5 h. The best single-sampling strategies with the best metrics were identified at 2–2.5 h (FD) and 6–6.5 h (SS) and were statistically significant between the MAA and MSA (Table 2).

The sample at 2 h post start of infusion informed the two multimodel approaches to an extent, that the second sample mainly resulted in an improved precision. The IQR (ranging from 23.0% to 43.2% using the single-sampling strategies) was reduced to values between 17.3% and 21.9% in the FD and 18.0% and 20.7% in the SS (Figure 3). Therefore, the timing of the second sample seemed to be much less influential given the amplitude of the performance metrics in the two-sampling strategies was further reduced. Nonetheless, the time interval resulting in the best performance metrics of the MAA and MSA was identified between 4.5 and 6.0 h in both the FD and SS. The AUC predictions using the MAA resulted in MdPE values between -0.8% and 0.8% independently of the FD or SS, whereas the MSA resulted in slightly lower MdPE values (-3.0% to -0.7%). The optimal second sampling timepoint of the MAA was identified at 5 h in FD as well as in SS, while the MSA benefited most from a sample drawn at 6 h in FD and 4.5 h in SS.

When comparing the optimized sampling strategies with the “peak-trough” strategy using MAA or MSA, the optimal two-sample strategy (e.g., two samples drawn at 2.0 h and 5.0 h for the MAA in the FD; Table 2) outperformed the “peak-trough” strategy. Yet, the differences between the “peak-trough” and the optimal two-sample strategy were minor, for example, MdPE and IQR were -0.6% and 18.4% for the “peak-trough” compared with 0.0% and 18.1% for the optimal two-sample strategy of the MAA. The optimized single-sample strategy on the other hand resulted in less precise but comparably accurate predictions.

The AUC calculations over all 5925 patients using the EQA were positively biased using the samples (3.0 and 11.5 h) in FD (MdPE, 7.4%) or the samples (3.0 and 11.5 h) in SS (MdPE, 3.2%) with an imprecision of 26.0% (FD) and 21.8% (SS). Both multimodel approaches were outperforming the EQA even using the optimized single sampling. Given that the population was simulated using three one-compartment and three two-compartment models and that the EQA ignores the α -distribution phase, it might be expected that the EQA performs worse in the simulations

TABLE 2 Timing and performance metrics of the optimized single- and two-sampling and mainly recommended peak-trough strategies of the two multimodel approaches after the first dose of vancomycin as well as in steady state

	Single-sampling strategy ^a			Two-sampling strategy ^b			“Peak-trough” strategy ^c		
	First sample, h	Second sample, h	MdPE (95% CI), %	IQR, %	MdPE (95% CI), %	IQR, %	MdPE (95% CI), %	IQR, %	
First dose									
Model averaging algorithm	2	5	0.0 (−0.6, 0.6)	23.9	−0.2 (−0.6, 0.3)	17.6	−0.8 (−1.3, −0.2)	20.3	
Model selection algorithm	2.5	6	−2.9 (−3.5, −2.3)	23.1	−1.7 (−2.2, −1.3)	18.2	−2.3 (−2.9, −1.8)	20.5	
Equation-based approach ^d	3	11.5	—	—	7.4 (6.7, 8.0)	26.0	—	—	
Steady state									
Model averaging algorithm	6	5	1.0 (0.4, 1.6)	24.0	0.0 (−0.4, 0.5)	18.1	−0.6 (−1.0, −0.1)	18.4	
Model selection algorithm	6.5	4.5	−1.6 (−2.2, −1.0)	24.0	−0.9 (−1.4, −0.5)	18.6	−2.4 (−2.9, −1.9)	18.4	
Equation-based approach ^d	3	11.5	—	—	3.2 (2.7, 3.8)	21.8	—	—	

Note: The equation-based approach was added as reference. Abbreviations: MdPE, median percentage error; IQR, interquartile range; CI, 95 % confidence interval of the median percentage error in percentage.

^aPerformance metrics using the “first sample” timepoint.

^bPerformance metrics using the “first sample” and “second sample” timepoints.

^cPerformance metrics using a sample at 1 h and at 11.5 h after the start of infusion.

^dWith two fixed sampling times at 3 and 11.5 h after the start of infusion.

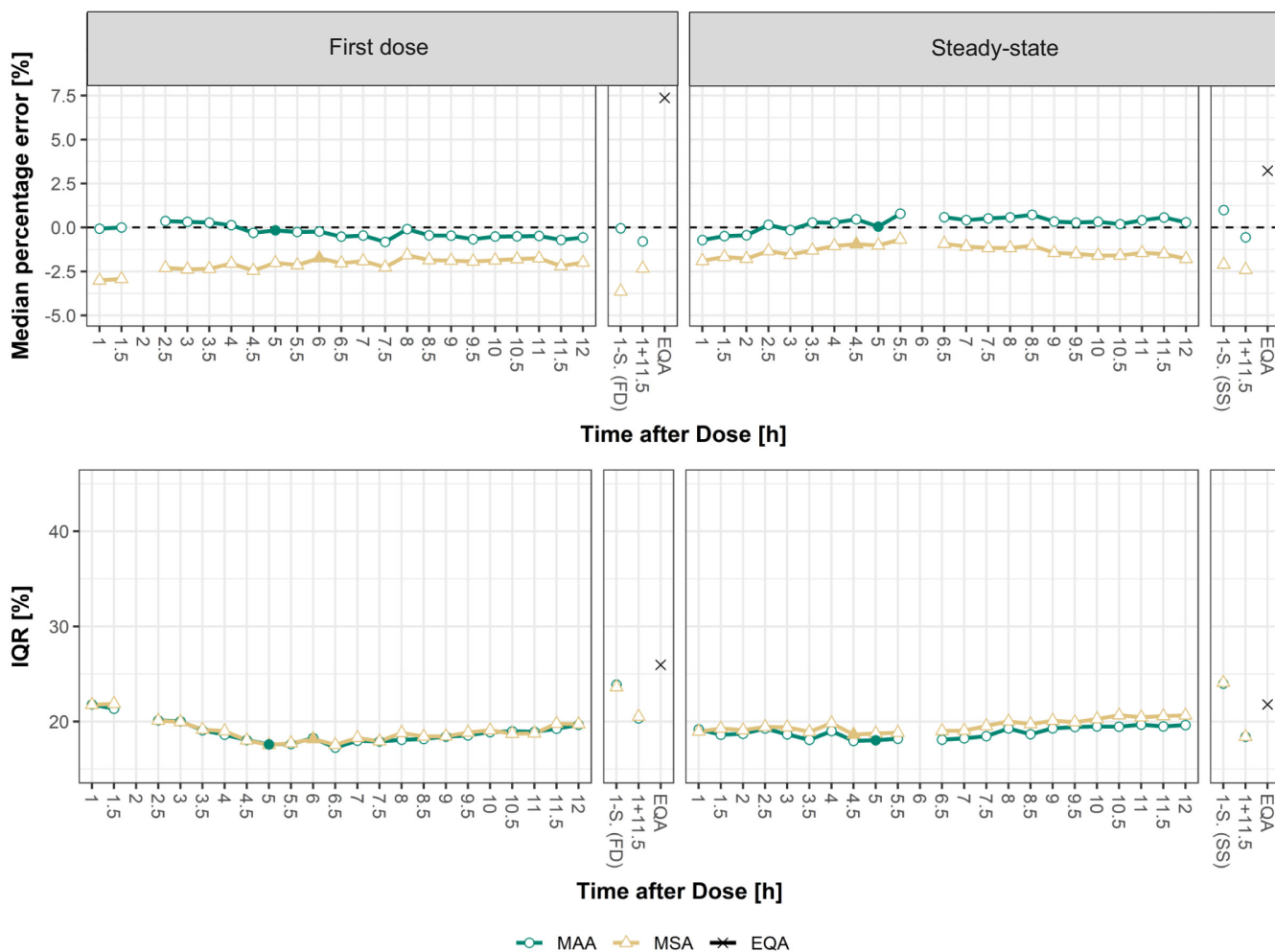


FIGURE 3 Performance metrics of the multimodel approaches using the optimized first sample and a second sample drawn in between 1–12 h after the start of infusion. Time after dose indicates the timepoint of the second sample drawn in the 5925 patients either in the first dosing interval (i.e., first dose) or the fifth (i.e., steady state) additionally to the optimal first sampling timepoint, which is indicated with the gap in the lines. The filled shapes indicate the optimal second sampling timepoint per approach identified via the metrics ranking. 1-S. displays the performance metrics of the optimal single-sample strategy of the two approaches (see Table 2); 1 + 11.5 represents the performance metrics of the gold standard “peak-trough” sampling strategies in the two approaches. Black ‘x’ indicate the performance metrics of the EQA as a reference. EQA, equation-based approach; FD, first dose; IQR, interquartile range of the relative prediction errors of the area under the concentration-time curve; MAA, model averaging algorithm; MSA, model selection algorithm; SS, steady state

from two-compartment models. However, a subpopulation analysis (Figure S4) revealed no such trends. In fact, the calculations were more precise in the simulation from the two-compartment Thomson et al. model²⁷ (i.e., TDM population; IQR, 20.2% [FD] and 20.9% [SS]) compared with simulations from the one-compartment Adane et al.²² and Roberts et al.²⁶ models (IQR, 22.5%–29.1%).

For completeness, the six mono models used for simulating the patients were evaluated in estimating the AUC_{0-12} and AUC_{48-60} using the same sampling strategies (see the Sampling Strategies section) in the 5925 patients (Figures S5 and S6). Expectedly, these models developed in special populations performed highly variable in the heterogenous total population (Figure S5). Nonetheless, the optimal timepoint to draw a single sample was

always identified to be before 6.5 h in FD and 8.0 h in SS (Table S3). The two-sampling strategies indicated that the second sample provides the most information, if drawn in the time interval between 1–5 h, except estimating with the Mangin et al.²³ model (Figure S6). The optimized two-sampling strategies outperformed the “classical peak-trough” strategies in the models, respectively (Table S3).

DISCUSSION

For accurate dose adjustments, model-informed precision dosing needs reliable estimates of the individual PK. Therefore, the optimal sampling time as well as the number of samples is complementing the challenge of

selecting the correct model and minimization of documentation errors.^{17,18} In this study, we evaluated the influence of sampling time and number in two multimodel approaches and demonstrated that the optimal sample was never identified at trough levels.

The multimodel approaches (MAA, MSA) preferred an FD sample around 2 h after the start of infusion to optimally estimate the AUC, and later sampling times negatively affected the precision of the AUC estimate. In SS conditions, the optimal single-sampling timepoint shifted to later timings around 6 h after the start of infusion. Yet, a smaller amplitude of performance metrics implied that a larger interval of sampling times ranging from 4.5 to 8.5 h can lead to optimal estimation of the AUC in SS.

A second sample in addition to the optimal single sample improved the precision of the AUC prediction. Interestingly, the timing of second sample was less important, in particular in SS. Furthermore, the classical “peak-trough” strategy resulted in acceptable predictions of the AUC when using a model-based approach.

The EQA provided positively biased estimates of the AUC, and the imprecision of the AUC estimates even exceeded the optimized single-sampling strategies using the multimodel approaches in FD. Hence, the simplicity of the EQA, as its major advantage, was opposed by the persistent overprediction, which is also discussed but de-emphasized by the authors themselves.²⁸ In addition, the approach always requires two samples.

Although adjustments in the later stages of the antibiotic therapy might be important to reduce toxicity, it is essential to achieve optimal drug exposure as early as possible to ensure a rapidly effective antibiosis.²⁹ The identified early FD optimal sampling time windows allow—if rapid bioanalytics of the vancomycin plasma concentration are available—dose adjustments within the first dosing interval. This might give sufficient time to already individualize the second dose, which is impossible with trough sampling.

The study by Shingde et al. investigated the predictive performance of seven population PK models when supplied with a single sample at different timepoints from 22 patients after the first dose of vancomycin.³⁰ Another large prospective study by Neely et al. compared a nonparametric dose optimization tool among others and revealed that 79% of the optimal sampling timepoints were not at the trough.³¹ Both studies were in line with our findings and emphasize that pretrough measurements should be preferred in drug exposure estimation even when using model-informed approaches. Another study evaluated the accuracy and precision of one- and two-sample based Bayesian AUC estimations in 12 richly sampled patients under tobramycin therapy. The samples drawn at less than 3 h were less biased.³²

Further studies compared the performance of various vancomycin PK models but focused on the model structure and the underlying population instead of the exact sample timing.^{13,33–37}

A strength of the study is the broad heterogeneity of the virtual population simulated with six distinct and clinically relevant models. This comes along with the drawback of every simulation being on a conceptual level. Given that the vancomycin samples were purely measured for the purpose of AUC calculation and to solely derive optimized sampling timepoints, this study did not investigate different dosing regimens or variability of the sampling times. Yet, small-scale investigations with clinical data sets are in line with our findings.^{30–32} Nonetheless, these results should be validated in prospective clinical studies covering the influences of different dosing intervals, dosing adjustments, and sampling/dose timing uncertainties. Therefore, our results could directly indicate the ideal and reduced sampling intervals to lessen the burden on patients.

In conclusion, our study suggests that a single sample drawn in the first 6.5 h of the dosing interval is preferred over sampling once at trough to predict the vancomycin drug exposure using the MAA and MSA. This seems particularly useful after the FD and gives sufficient time to already individualize the subsequent dose. For two-sampling strategies, the impact of the second sampling time was less marked. This implies a reduced need of resource allocation when sampled twice as the algorithms do not demand samples at extremely small time windows. The nonmodel based EQA, although always requiring two samples, displayed biased estimates of the AUC and was inferior compared with the optimized single- and two-sampling strategies of the multimodel approaches.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

D.W.U. and S.G.W. wrote the manuscript, designed the research, performed the research, and analyzed the data.

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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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