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ORIGINAL ARTICLE

Why we should sample sparsely and aim for a higher target: Lessons from model-based therapeutic drug monitoring of vancomycin in intensive care patients

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Aims: To explore the optimal data sampling scheme and the pharmacokinetic (PK) target exposure on which dose computation is based in the model-based therapeutic drug monitoring (TDM) practice of vancomycin in intensive care (ICU) patients.

Methods: We simulated concentration data for 1 day following four sampling schemes, C_{min}, C_{max} + C_{min}, C_{max} + $C_{mid\text{-}interval}$ + C_{min}, and rich sampling where a sample was drawn every hour within a dose interval. The datasets were used for Bayesian estimation to obtain PK parameters, which were used to compute the doses for the next day based on five PK target exposures: AUC_{24} = 400, 500, and 600 mg·h/L and C_{min} = 15 and 20 mg/L. We then simulated data for the next day, adopting the computed doses, and repeated the above procedure for 7 days. Thereafter, we calculated the percentage error and the normalized root mean square error (NRMSE) of estimated against "true" PK parameters, and the percentage of optimal treatment (POT), defined as the percentage of patients who met 400 ≤ AUC_{24} ≤ 600 mg·h/L and C_{min} ≤ 20 mg/L.

Results: PK parameters were unbiasedly estimated in all investigated scenarios and the 6-day average NRMSE were 32.5%/38.5% (*CL*/*V*, where *CL* is clearance and *V* is volume of distribution) in the trough sampling scheme and 27.3%/26.5% (*CL*/*V*) in the rich sampling scheme. Regarding POT, the sampling scheme had marginal influence, while target exposure showed clear impacts that the maximum POT of 71.5% was reached when doses were computed based on AUC_{24} = 500 mg·h/L.

Conclusions: For model-based TDM of vancomycin in ICU patients, sampling more frequently than taking only trough samples adds no value and dosing based on AUC_{24} = 500 mg·h/L lead to the best POT.

KEYWORDS

vancomycin, TDM, model-based, Bayesian estimation, dose optimization, ICU patients

PI Statement: The authors confirm that the PI for this paper is Paul W.G. Elbers and that he had direct clinical responsibility for patients.

1 | INTRODUCTION

Vancomycin is an antibiotic with activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, and is widely used to prevent and treat sepsis in intensive care (ICU) patients.[1–3] The antimicrobial efficacy of vancomycin is both time- and concentration-dependent and is therefore mainly dependent on its pharmacokinetic (PK) exposure, defined by area under the concentration-time curve (AUC).[4] The most commonly used PK target associated with treatment efficacy for vancomycin is AUC_{24} ≥ 400 mg·h/L, assuming that the minimum inhibitory concentration (MIC) of the targeted pathogens is less than 1 mg/L.[1] On the other hand, it was shown that excessive PK exposure of vancomycin may result in toxicity and specifically that AUC_{24} above 600 mg·h/L was associated with a higher risk of acute kidney injury.[5] Compared to less severely ill patients, ICU patients are markedly unstable in physiology and show highly variable PK both between patients and within the same patient. As such, adequate dosing of vancomycin is particularly challenging for ICU healthcare professionals.[6]

Population PK (PopPK) model-based therapeutic drug monitoring (TDM) using Bayesian methodologies is often applied to optimize vancomycin dosing for individual patients. Within the Bayesian framework, the prior knowledge of the distribution of PK parameters, which is informed by PopPK models, is combined with the information from an individual patient's actual concentration-time data. Estimates of individual PK parameters can be obtained through the so-called maximum a posterior (MAP) procedure.[7] This allows the use of PopPK models with individually estimated PK parameters to simulate the time course of drug concentration based on specific input, i.e. a certain dose regimen and/or covariate. This better informs clinicians about how the considered dosing regimen is related to the drug exposure. Estimated PK parameters can be also used to directly calculate the optimal dosing regimen for an individual patient, considering the desired PK target.

Although model-based TDM is increasingly carried out, clinical practice can differ between settings. For instance, for monitoring AUC_{24}, the number of samples that should be taken into account for MAP estimation varies between settings. We may intuitively assume that taking more samples could lead to better estimates of individual PK parameters, and therefore in some clinical settings a peak and/or a mid-interval concentration sample is drawn in addition to the trough concentration.[8–10] However, taking more samples may require more clinical team management, and is more stressful for the patient and its cost-effectiveness is unknown. Furthermore, the optimal target exposure to use for the dose computation is unclear. AUC_{24} of 400 mg·h/L is perhaps mostly used to guide dose computation. However, patients may be undertreated if the dose is computed based on this cut-off value because individual PK parameters can never be estimated with perfect precision due to the presence of inter-individual variability (IIV), which is large for ICU patients, and residual error (RES). On the other hand, choosing a higher target exposure to avoid treatment failure is likely to come with a risk of overexposure and an accompanying risk of toxicity.[5] Trough concentration is often applied for monitoring purposes as the surrogate for AUC_{24} in some hospitals, since a trough concentration between 15 and 20 mg/L is believed to entail a good chance of AUC_{24} ≥ 400 mg·h/L.[11,12] However, it was previously shown that trough concentrations may have a poor relationship with AUC_{24}, and thus monitoring AUC_{24} may be favoured.[13,14]

In this study, we aimed to explore the optimal strategies of the commonly seen practices of model-based TDM for optimizing vancomycin dosing in ICU patients. Through simulation techniques, we investigated the impact of (i) the sampling scheme of the data that is taken into account in MAP estimation and (ii) the target exposure on which the dose computation is based, on the accuracy and precision of estimated PK parameters and the percentage of optimal treatment (POT).

What is already known about this subject

- Population pharmacokinetic model-based therapeutic drug monitoring (TDM) of vancomycin in intensive care (ICU) patients is a common practice in many clinical settings.
- In general trough samples are drawn in TDM practice, but more frequent sampling is believed to be able to optimise AUC estimation.
- Population pharmacokinetic model for vancomycin TDM is usually developed in sparse TDM data.
- Dose advice is often based on AUC_{24} = 400 mg·h/L.

What this study adds

- Due to the high pharmacokinetic variability in ICU patients, sampling more frequently than only taking trough samples does not have added value for TDM of vancomycin.
- Dose computation of vancomycin for ICU patients should be based on AUC_{24} = 500 mg·h/L to ensure a higher proportion of patients achieve optimal exposure.

2 | METHODS

PK data sets for the first day were simulated with various numbers of samples following a standard dosing regimen of 1000 mg b.i.d. The simulated data sets were then fitted to estimate the PK parameters, which were in turn used to compute the doses for the second day. The latter was done based on different target exposures for dose computation. We then simulated the PK data for the second day with the newly computed dose and the simulated data were fitted again to estimate the PK parameters. Subsequently, the doses for the third day were computed. This procedure was repeated until the seventh day and is further detailed in the sections below (Figure 1). Nonlinear mixed-effects modelling software (NONMEM, version 7.4.3; ICON Development Solutions, MD, USA) was used for both simulation and

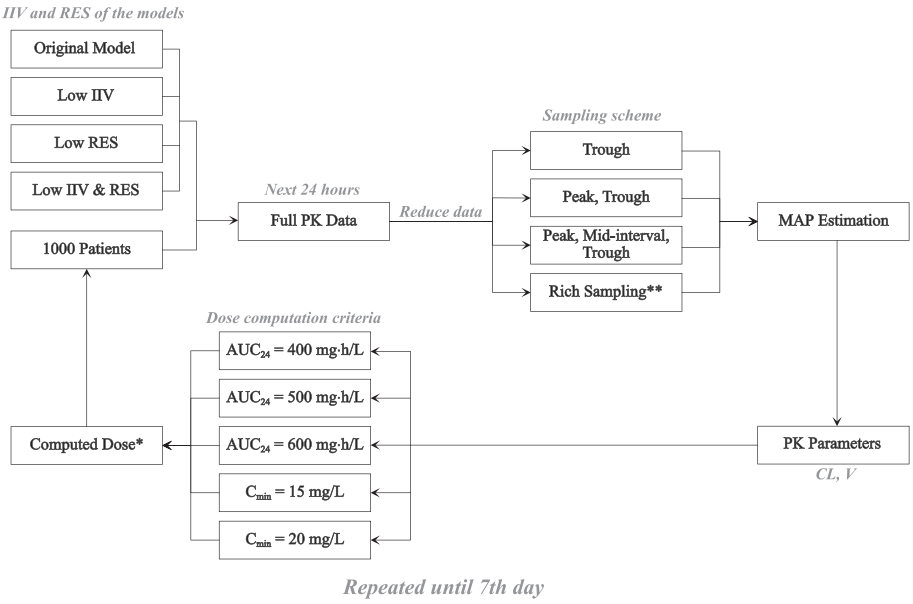

FIGURE 1 Scheme of study design. IIV, inter-individual variability; RES, residual errors; PK, pharmacokinetic(s); MAP, maximum a posteriori. *The doses were given b.i.d and a standard dose regimen of 1000 mg was adopted for the first iteration of scenarios of model-based dosing. **A sample was drawn every hour

estimation. Data organization and visualization were carried out with R (version 3.6.0; R-project.org).

2.1 | PopPK model and generation of virtual patients

A previously published one-compartmental PopPK model of vancomycin (Table 1) was adopted to execute both the PK simulation and MAP estimation in this study.[15] The model has been validated in our own ICU population, which turned out to best describe our data among all identified candidate models.[16] Like most PopPK models of vancomycin in ICU patients, this model was originally built with data from routine TDM data, i.e. sparse data. Since this study focuses on the application of existing PopPK models for TDM purposes, the choice for the model of Roberts et al[15] is well representative for the clinical reality. The model did not include an interoccasion variability (IOV) component nor did the model address time-varying covariates. We generated 1000 patients by sampling repeatedly from an existing data set of 579 ICU patients for whom the mean ± SD body weight was 82.0 ± 18.3 kg and the mean ± SD renal clearance was 81.8 ± 53.2 mL/min. Gender was balanced in the sampling process, i.e. 50% males and 50% females. For each patient, the random-effect parameters of IIV were sampled from their distributions according to the PopPK model. These random-effect parameters were used to calculate individual PK parameters, which are referred to as "true" in this study.

TABLE 1 The vancomycin PopPK model[15]

Component	Equation
Pharmacokinetic parameters	CL (L/h) = 4.58·CrCL/100 × $e^{\eta 1}$
	V (L) = 1.53 × WGT × $e^{\eta 2}$
Interindividual variability	$\eta_1 \sim N(0, \omega_1^2)$ and $\eta_2 \sim N(0, \omega_2^2)$
	ω_1 = 0.389 and ω_2 = 0.374
Residual errors	Obs = Pred·(1 + ε_1) + ε_2
	$\varepsilon_1 \sim N(0, \sigma_1^2)$ and $\varepsilon_2 \sim N(0, \sigma_2^2)$
	σ_1 = 0.199 and σ_2 = 2.4 (mg/L)

CL, clearance; *V*, volume of distribution; CrCL, creatinine clearance in mL/min; WGT, body weight in kg; Obs, observed concentration; Pred, predicted concentration. The distributions of η_1 and η_2 are used as the prior distributions for the maximum a posteriori estimation.

2.2 | Data simulation, MAP estimation and dose computation

A common dose regimen of vancomycin was assumed in which doses were intravenously infused for a duration of 1 hour b.i.d. For each virtual patient, the data of a full PK profile from 0 to 24 hours was simulated based on the aforementioned "true" individual PK parameters, applying a starting dose regimen of 1000 mg b.i.d. The full PK profile data was then reduced to retain different numbers of samples based on four sampling schemes: (i) trough (C_{min}, at 12 hours post dose), (ii) peak (C_{max}, at 1 hour post dose) and trough (iii) peak, mid-interval (C_{mid}, at 6 hours post dose) and trough, and (iv) rich sampling with a sample drawn every hour within a dose interval for a total of 12 samples (Figure 1). Such a setting was adopted according to the Dutch guideline which advises that samples including peak concentrations and/or mid-interval concentrations are considered in addition to trough concentration.[17] Rich sampling was included for the purpose of exploring an "ideal" situation. Considering that in general only one or two samples are collected in clinical practice, such a rich sampling scheme should be able to reasonably reflect a situation with the best possible results. The data from the four sampling schemes of only the preceding one day which has been shown to be most optimal for Bayesian forecasting, was used to execute MAP estimation to calculate individual PK parameters, i.e. clearance (*CL*) and volume of distribution (*V*), for the next day.[18] Five different target exposures were tested to compute new doses for the next 24 hours:

(i) AUC_{24} = 400 mg·h/L, (ii) AUC_{24} = 500 mg·h/L, (iii) AUC_{24} = 600 mg·h/L, (iv) C_{min} = 15 mg/L, (v) C_{min} = 20 mg/L (Figure 1). An empirical standard dosing regimen was also considered for comparison. For this we adopted the Dutch guideline, which advices a vancomycin dose of 15 mg/kg before a concentration is available for TDM.[17] For AUC-based targets, the dose was computed based on dose = AUC × *CL* and capped to ensure trough concentration no higher than 20 mg/L. For C_{min}-based criteria, dose was reversely computed according to the following PK equation:

$$C_{min} = \frac{dose}{VkT} \cdot \frac{1-e^{-kT}}{1-e^{-k\tau}} \cdot e^{-k(\tau-T)} \quad (1)$$

where *k* is *CL*/*V*, *T* represents the infusion duration time (i.e. 1 hour), τ is the dose interval (i.e. 12 hours). C_{min} is either 15 mg/L or 20 mg/L, and the dose is to be calculated. Of note, only the dose was changed, not the dosing frequency. Thereafter, the full PK profile of each patient for the next 24 hours was simulated based on the "true" individual PK parameters but with the newly computed doses. This procedure was repeated for all 7 days (Figure 1).

2.3 | The accuracy and precision of MAP estimation

After MAP estimation with the reduced data sets, the percentage error (*PE*), defined in Equation 2, of estimated individual PK parameters against the "true" parameters was calculated as a measure of accuracy and visualized using boxplots. The normalized root of the mean square error (NRMSE), defined in Equation 3, was calculated to quantify the precision of estimated PK parameters.

$$PE = \left(\frac{P_{est} - P_{true}}{P_{true}}\right) \times 100\% \quad (2)$$

$$NRMSE = \sqrt{\sum_{i=1}^{n} (P_{est} - P_{true})^2 \times \frac{1}{n}} \times \frac{1}{\overline{P_{true}}} \times 100\% \quad (3)$$

where P_{est} and P_{true} denote the estimated and "true" individual PK parameters, respectively, $\overline{P_{true}}$ is the mean of "true" individual PK parameters and *n* is the number of patients, i.e. 1000.

2.4 | Percentage of optimal treatment

In order to evaluate the impacts of the different practices in model-based TDM of vancomycin, the percentage of optimal treatment (POT) was calculated, which was defined as the percentage of patients whose vancomycin exposure at steady state was 400 ≤ AUC_{24} ≤ 600 mg·h/L and C_{min} ≤ 20 mg/L. The more commonly used percentage of target attainment was not used since it does not take an upper limit of exposure into account, while avoiding overexposure seems to become increasingly important to prevent nephrotoxicity.[8,19] POT was calculated for all sampling schemes and target exposures over 7 days.

2.5 | Impact of interindividual variability and residual error

Given the fact that ICU patients show high PK variabilities, we further investigated the impact of the size of variability (IIV and RES) of the PK model used for TDM on the accuracy and precision of MAP estimation and POT. There may be uncaptured factors that influence the PK of vancomycin and its variability which were not taken into account in the original study in which the model was developed, such as structural and random changes within an ICU patient over time. This, however, should not affect our results since the data were generated using this model. Hence the model was the true reference model in the context of the simulated data set. Previous steps were repeated using the same model but with IIV and RES modified in the following ways: (i) IIV was lowered to about half of the original model for both *CL* and *V*, i.e. 20%, (ii) proportional RES was lowered to about half of the original model, i.e. 10%, and additive RES was lowered to 0.5 mg/L, and (iii) both IIV and RES were lowered to the aforementioned low levels (Figure 1). For simplicity, the sampling scheme with trough-only samples was used for both simulation and estimation steps, and dose computation was based on the optimal target exposure concluded from previous steps.

3 | RESULTS

3.1 | The accuracy and precision of MAP estimation

Both *CL* and *V* were unbiasedly estimated for all four sampling schemes (Figure 2). The precision of the parameter estimates was related to time and the sampling scheme. For *CL*, the precision of estimates (NRMSE) on the first day was about 38% for all sampling schemes but improved to 20% at day 6 on average. Such improvement was more pronounced in the sampling schemes of C_{max}, C_{mid}, C_{min} and rich sampling, with NRMSE at day 7 being, for example, 13.8% for rich sampling. For *V*, the precision of estimates shows an opposite trend, where NRMSE was lowest on the first day, with 18.3% for the rich sampling, and tended to increase to 31.5% over the 7 days (Figure 2). Such a trend was not apparent for low sample densities (e.g. the trough-only scheme). The higher the sample density, the more precisely *V* was estimated on the first day (Figure 2).

3.2 | Percentage of optimal treatment

POT increased over time in all scenarios except for patients treated with a standard dosing regimen (Figure 3). The sampling scheme did not show a clear impact on POT if doses were computed based on the same target exposure. In contrast, the target exposures did have an

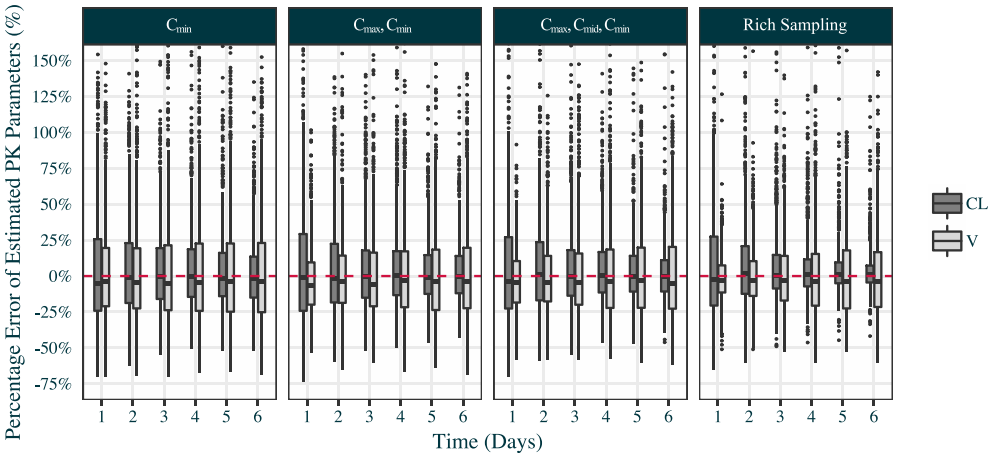

FIGURE 2 Percentage error of estimated PK parameters for all sampling schemes based on target exposure for dose computation of AUC_{24} = 500 mg·h/L. The lower and upper limits of the box are the first and third quartiles. The bold solid lines within each box are the median values. The red dashed lines highlight the percentage error of 0%

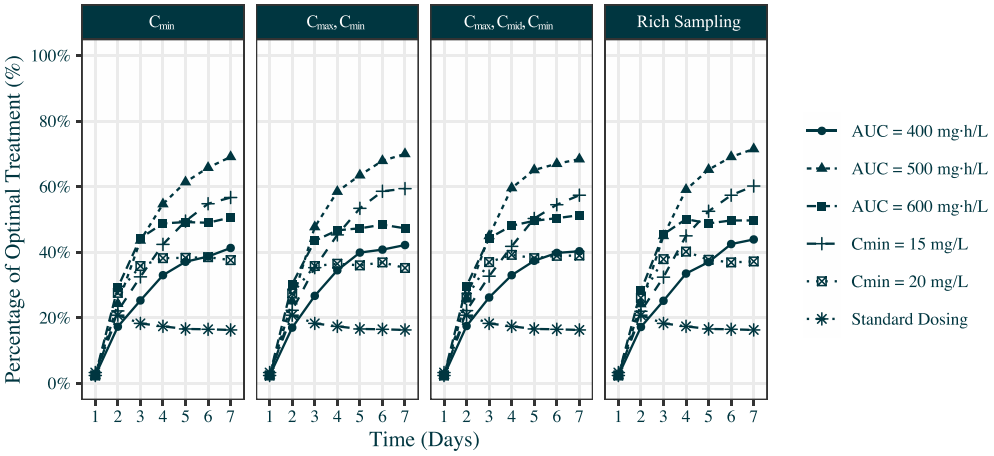

FIGURE 3 Percentage of optimal treatment (%). The percentage of patients whose PK exposure met the predefined definition was calculated for each day. For each day, the MAP estimation was executed, and the estimated PK parameters were used to calculate the dose for the next day either based on the standard dosing regimen or aiming the target exposure (legend on the right). Due to the relatively strict definition of optimal treatment (400 ≤ AUC_{24} ≤ 600 mg·h/L and C_{min} ≤ 20 mg/L), the percentage of optimal treatment does not go any higher than about 70%

impact on POT, which was highest on day 7, reaching 71.5% when doses were computed based on the target exposure of AUC_{24} = 500 mg·h/L, whereas POT was only 40.2% when doses were computed based on the target exposure of C_{min} = 20 mg/L. High target exposures (AUC_{24} = 600 mg·h/L and C_{min} = 20 mg/L) produced more overexposure and low target exposures (AUC_{24} = 400 mg·h/L and C_{min} = 15 mg/L) produced more underexposure (Figure 4).

3.3 | Impact of interindividual variability and residual error

The estimated PK parameters became more precise in all three investigated scenarios with a minimum NRMSE of 10.6% for *CL* and 15.2% for *V* (Figure 5). The improvement in the precision of parameter estimates relative to the original model was clearly present when IIV was

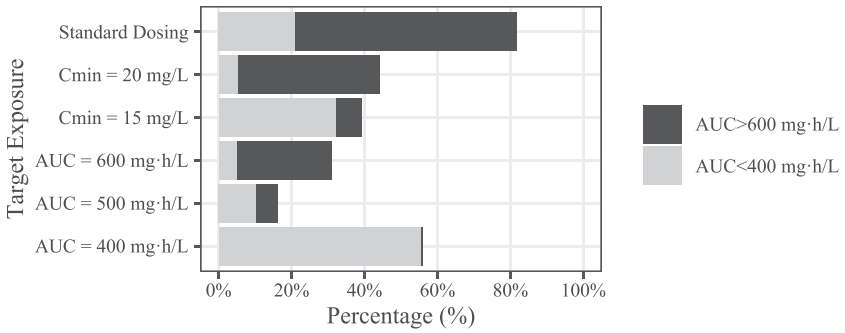

FIGURE 4 Percentage of patients for which AUC on day 7 was above 600 mg·h/L (black) or below 400 mg·h/L (light grey), when trough concentrations were used for MAP estimation

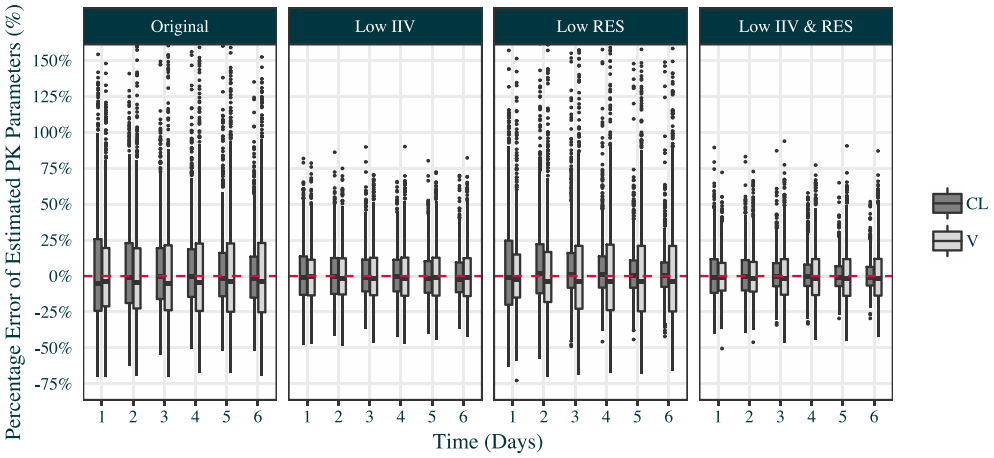

FIGURE 5 Percentage error of estimated PK parameters with low IIV (20% for both *CL* and *V*) and/or low RES (10% for proportional error and 0.5 mg/L for additive error) in the population PK model (%). Only trough samples were used in the MAP estimation and doses were computed based on the target exposure of AUC_{24} = 500 mg·h/L. The lower and upper limits of the box are the first and third quartiles. The bold solid lines within each box are the median values. The red dashed lines highlight the percentage error of 0%

at a lower level, while the improvement with RES at a lower level was modest, indicating that interindividual variability of a patient population takes precedence in MAP estimation. When both IIV and RES were at a lower level, the parameter estimates were most precise. The POT results show the same trend: the most optimal POT was reached in the case when both IIV and RES were at a low level, where POT was about 90% on day 7 (Figure 6).

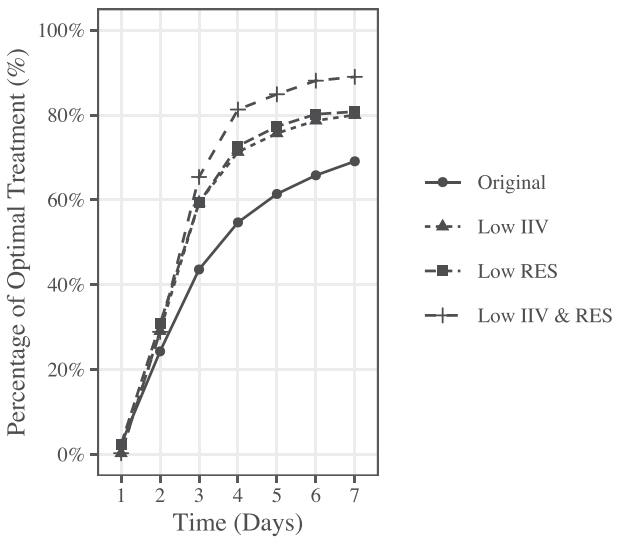

FIGURE 6 Percentage of optimal treatment with low IIV (20% for both *CL* and *V*) and/or low RES (10% for proportional error and 0.5 mg/L for additive error) of the model (%). Only trough samples were used in the MAP estimation and doses were computed based on the target exposure of AUC_{24} = 500 mg·h/L. The percentage of patients whose PK exposure met the predefined definition was calculated for each day

4 | DISCUSSION

This study is the first to explore the implications of different sampling protocols and target exposures when performing model-based TDM for optimizing vancomycin dosing in ICU patients. Perhaps surprisingly, we show that obtaining more samples than just trough samples does not improve estimation of PK parameters. In addition, computing the dose based on a target exposure of AUC_{24} of 500 mg·h/L was shown to lead to optimal POT.

Overall, the estimates of PK parameters are not very precise (Figure 2). Precision of *CL* estimates improved over days, while precision of *V* estimates worsened. This may be attributed to the declining influence of *V* on the concentration while approaching steady state. When concentration increases, it is more driven by *CL* rather than *V*. Thus, a concentration that is close to steady state carries more information about *CL* than *V*. An extreme instance in this respect is the continuous infusion process, which mathematically can be seen as intermittent dosing with a dosing interval of infinitely close to zero. Under such circumstances, the steady-state concentration is completely steered by *CL* and infusion rate only and thus is independent from *V*. In our study, an intermittent dosing schedule was simulated as this is most frequently practiced at ICUs in the Netherlands. As shown, NRMSE of *V* got worse over time when concentrations gradually accumulated to reach steady state. Meanwhile, as *CL* may dominate the concentration in later days, *CL* was getting more precisely estimated over time (Figure 2). Of note, only the data from the preceding one day were included for the MAP estimation in each iteration. This was evident from another study by our group in which we found that including the data from only the preceding one day led to the smallest bias for Bayesian forecasting.[18] This is likely due to the fact that ICU patients vary rapidly and as such the information from historical data earlier than the preceding one day do not contain

additional information of much value for prediction of the concentration in the future.

The results also show that when applying more dense sampling schemes, the precision of parameter estimates improved during the MAP estimation process, but not as much as one might have expected (Figure 2). The NRMSE only marginally improved relative to the scheme with only trough concentration, especially in the clinically realistic scenarios where only a peak and/or mid-interval concentration was sampled on top of trough concentrations. This phenomenon could be explained by the intrinsic mechanism of MAP estimation. The objective function of MAP estimation can be written in a simplified form as follows:

$$fa(P_{ind}) = \sum \frac{(C_{obs} - C_{pred})^2}{\sigma^2} + \sum \frac{(P_{ind} - P_{pop})^2}{\omega^2} \quad (4)$$

where C_{obs} and C_{pred} denote observed and predicted concentrations, respectively, P_{ind} and P_{pop} denote the individual and population PK parameters vectors, respectively, σ is the standard deviation (SD) of RES and ω is the SD of IIV. The PK parameter values that minimize Equation 4 are the so-called parameter estimates. The estimates are determined by two terms: likelihood of the data (first summation in Equation 4) and prior distribution of the parameters of interest (second summation in Equation 4). These two terms are weighted competing to each other, since their values change towards opposite directions when P_{ind} changes. The final estimates of PK parameters are the ones that minimize the entire function by compromising both terms. Obviously, the data term is weighted by σ^2, which indicates that the importance of the data is related to the RES. When RES is relatively low compared to IIV, the estimates will lean towards minimizing the data term and thus data will have more influence on the MAP estimation, which indicates that including extra data is more likely to improve the estimation. To better validate our reasoning, we simulated a data set in an extreme condition where the RES was set to be 1% for proportional error and 0.1 mg/L for additive error, and executed MAP estimation. The results demonstrated that the precision of PK parameter estimates was already greatly improved when a peak sample was additionally included, compared to when only a trough concentration was drawn (Figure 7). Such results imply that a model with very low RES could be beneficial for model-based TDM. As we did not primarily focus on studying IIV or RES themselves, we did not study a scenario with large IIV and RES to prevent results from becoming too extensive and to facilitate overview. The results of such a case will obviously be the opposite. Nevertheless, one should keep in mind that this does not suggest that one should simply select a published model with low RES for clinical use. The RES of a model for ICU patients is usually high due to the unstable physiology, which is hard to cover completely in a model.[6] Therefore, significant reduction of RES would be very unlikely. Instead, a suitable model should be developed for the population in which it will be used to minimize the risk for biased estimates. Improving the quality of data determination, the compliance in data collection, etc. that also influence the RES of the model could probably be helpful. Inclusion of IOV may be able to reduce the RES as well. From a different perspective, when only PK models are available with high RES (20% and above), which is most likely to be the case, there doesn't seem to be much added value in collecting more samples than only one, which might be a trough level or, maybe even better, an optimally timed sample.[20] To further support this finding, we additionally repeated an important part of the study using a two-compartment model which was built in an ICU dataset with rich serial vancomycin plasma concentration samples.[21] Thus, the model features both rich sampling and better parameterization. Similar to our original analysis, we first used this model to simulate the concentration-time data and then re-estimated the PK parameters based on the same sampling schemes on days 1, 3 and 5. The results were in agreement with the current findings that the parameter estimation did not improve much, especially for *CL* when using more samples than only C_{min} (Supporting Information Figure S1).

In addition, the results show that the target exposure used for dose computation has a large impact on POT. AUC_{24} of above 400 mg·h/L has been adopted as the target for effective vancomycin dosing.[1,12,22] Given the current evidence that the risk of vancomycin-associated nephrotoxicity seems to increase with increasing vancomycin exposure, the optimal dose regimen for vancomycin should be able to maintain AUC_{24} between 400 and 600 mg·h/L and C_{min} not above 20 mg/L.[5] We accordingly calculated POT based on these conditions

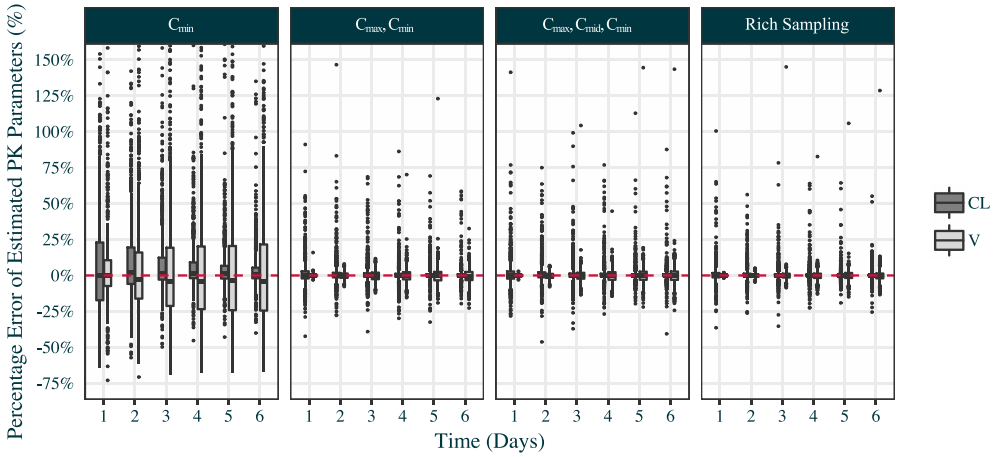

FIGURE 7 Percentage error of estimated PK parameters with extremely low RES (1% for proportional error and 0.1 mg/L for additive error) of the model for all sampling schemes based on the target exposure of AUC_{24} = 500 mg·h/L (%). The lower and upper limits of the box are the first and third quartiles. The bold solid lines within each box are the median values. The red dashed lines highlight the percentage error of 0%

in this study. In clinical practice, to our knowledge, the cut-off value of AUC_{24} of 400 mg·h/L is most commonly used when computing vancomycin doses and C_{min} of 15 mg/L as the surrogate of AUC_{24} of 400 mg·h/L is also often used, although the correlation between AUC_{24} and C_{min} is weak.[5] We show that dose computation based on the cut-off value for effective vancomycin exposure of AUC_{24} = 400 mg·h/L leads to suboptimal POT (Figures 3 and 4). This is primarily due to the imprecision of parameter estimates, as mentioned earlier. Although barely biased in general, the parameter estimates for a given individual could be biased, which in turn would introduce error in the dose computation. This indicates that dosing aiming at a target does not guarantee the achievement of that target. The simulations show that if a dose is computed based on a higher target exposure than the actual PK target, a better chance of adequate exposure can be expected. However, since using higher target exposures shifts up the whole range of computed doses synchronously, using an AUC_{24} of 600 mg·h/L for dose computation causes increased overdosing (Figures 3 and 4). For the same reason as discussed regarding MAP estimation, there were only marginal differences in POT when different numbers of samples were taken into account (Figure 3). The POT reached only about 70% when doses were computed based on AUC_{24} of 500 mg·h/L. Our study defined the POT as AUC_{24} between 400 and 600 mg·h/L and C_{min} not above 20 mg/L, which was slightly conservative, particularly regarding the AUC upper boundary. The main reason was that there is no clear definition yet for the upper cut-off value of the therapeutic window. Here, an MIC of 1 mg/L is also assumed, which is the worst-case scenario (the highest MIC that can be safely treated with vancomycin). We therefore chose the conservative value based on current evidence to reduce the risk of toxicity and maximize the therapeutic efficacy. Such a definition could explain why the POT based on the target, e.g. C_{min} of 20 mg/L, was lower than instead of around 50%, as should be the case for the more commonly used metric of probability of target attainment. The real POT might be different from what was observed in this study, depending on the definition. Nevertheless, we observed increases of POT in the case of low IIV and/or low RES, as both IIV and RES of a model have impacts on the MAP estimation process and ultimately POT (Figure 6). Part of the reason has been explained in detail previously in the case when RES was small. A similar reason applies to the case of low IIV as well. IIV is a measure of the dispersion of individual PK parameters and the estimates tend to reduce towards the population value. Thus, low IIV indicates that individual PK parameters are closer to the population value and consequently the estimates have a greater chance of reducing to the right values. It is worth noting that reducing IIV requires improvement of the model building, e.g. sufficient capture of covariate effects, proper construction of the model etc., although the reduction of IIV is not always guaranteed.[23]

There are several points worth mentioning. First, this is a simulation study and results were not validated in a real-world setting. To minimize the gap between simulation and the real world, we simulated the data based on a large real ICU patient population using a model that was well validated in the concerning population. Second, the model used in the study is not an ideal model. On one hand, as previously reported, the vancomycin molecule can distribute into tissue and thus vancomycin PK has also been described by a two-compartmental model.[24] In such a case, vancomycin PK undergoes a biphasic process, and this may have an effect on the impact of the sampling scheme on the MAP estimation. However, the resulting loss of only using a one-compartmental model may be negligible compared to many other sources of imprecision and error in clinical practice. This model was identified in the literature and externally validated in our own ICU patients and proved to be able to adequately describe our data. The fact that our data favoured this one-compartment model over the others actually supports the judgment we made. On the other hand, the model was not built in rich sampling data, which may eliminate the possibility to overview the full picture of vancomycin PK profile. To the best of our knowledge a rich sampling model of vancomycin for routine clinical practice does not seem to exist in the literature. Applying a sparse data-based model using sparse data is a clinical reality and thus our study is representative of such a setting. Third, as previously discussed, PK stages (steady state and nonsteady state) influence PK parameter estimation. Since we also wanted to study the accumulation phase after the start of therapy when evaluating different sampling designs, we did not consider a loading dose at the start of the simulation. Nonetheless, the results of later days (e.g. the fifth and sixth days) are expected to be roughly the same as when loading doses were applied. Fourth, our study did not involve the IOV or time-varying covariates. As being said, the health conditions of ICU patients are usually markedly variable both between- and within-patients. The POT might be negatively influenced by within-patient variability. These time-varying factors are not captured in our simulation study as the model we used or other identified models from the literature did not contain any parameters that allowed variation of PK parameters over time within a patient. Fianlly, the model used in this study was built with sparse data and consequently contained no IOV and high RES. Such a model may not be suitable to fully study the effect of rich sampling schemes on the accuracy and precision of PK parameter estimation. A model developed with rich data would probably have lower RES and would be more suitable for dose computation. However, this also requires the TDM data to be of good quality with few errors, which in the ICU ward is difficult. Thus, using a model including IOV might not have a pronounced impact on dose computation. However, considering that the majority of model sources for vancomycin are without IOV and not developed from rich data, our findings should be valid for the current clinical reality. Further validation of our findings in a real-world ICU setting is needed when both rich sample-based models and rich sampling TDM data are available.

In conclusion, our study shows that obtaining more samples than just trough samples fails to improve estimation of PK parameters and has no added value for POT. In addition, dosing based on a target exposure of AUC_{24} of 500 mg·h/L was shown to lead to optimal POT.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

P.W.G.E. and T.G. conceived the idea. T.G., R.M.vH. and J.G.C.vH. designed the study. T.G., R.M.vH. and R.A.A.M. performed the analysis and drafted the manuscript. L.M.F., L.F.R., R.J.B., P.H.J.vdV. and A.R.J.G. collected the clinical data.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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