Novel approaches to improve model-informed precision dosing in haemophilia A and infectious diseases

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Predictions can be very difficult – especially about the future.

Niels Bohr (1885–1962)

I. List of publications

Original articles included in the cumulative dissertation

Uster DW, Wicha SG. Optimized sampling to estimate vancomycin drug exposure: comparison of population pharmacokinetic and equation-based approaches in a simulation-estimation study. CPT Pharmacometrics Syst. Pharmacol. XX, XX–XX. 2022.
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Heus A*, **Uster DW***, Grootaert V, Vermeulen N, Somers A, Huis in't Veld D, Wicha SG, De Cock P. Model-informed precision dosing of vancomycin via continuous infusion: a clinical fit-for-purpose evaluation of published PK models. Int. J. Antimicrob. Agents 59, XX–XX. 2022. (* equal contribution)
doi: 10.1016/j.ijantimicag.2022.106579

Uster DW, Chowdary P, Riddel A, Garcia CD, Aradom E, Musarara M, Wicha SG. Dosing for Personalized Prophylaxis in Haemopilia A highly varies on the underlying Population Pharmacokinetic Models. Ther. Drug Monit. XX, XX–XX. 2022.
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Uster DW, Stocker SL, Carland JE, Brett J, Marriott DJE, Day, RO, Wicha SG. A Model Averaging/Selection Approach Improves the Predictive Performance of Model-Informed Precision Dosing: Vancomycin as a Case Study. Clin. Pharmacol. Ther. 109(1), 175–183. 2021.
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Original articles

Bououda M, **Uster DW**, Sidorov E, Labriffe M, Marquet P, Wicha SG, Woillard, JB. A Machine Learning Approach to Predict Interdose Vancomycin Exposure. Pharm. Res. XX, XX–XX. 2022.
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Cunio CB, **Uster DW**, Carland JE, Buscher H, Thixin L, Day R, Wicha SG, Stocker SL. An evaluation of the predictive performance of pharmacometric models in ICU patients to facilitate model-informed precision dosing. Clinical Microbiology and Infection. 27, 783.e7–783.e14. 2020.
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Conference abstracts (oral/poster)

Kirubakaran R, **Uster DW**, Hennig S, Carland J, Day R, Wicha SW, Stocker SL. Matters close to the heart: adaptation of tacrolimus models to inform therapeutic drug monitoring using the PRIOR approach (virtual IATDMCT 2021). Rom, Italy. Sep. 19-22, 2021.
(poster presentation)

Uster DW, Heus A, Somers A, Grootaert V, Vermeulen N, Huis in't Veld D, De Cock P. Wicha SG. Evaluation of four distinct weighting schemes in a model averaging and selection approach in model-informed precision dosing of continuously infused vancomycin (virtual PAGE 2021). Ljubljana, Slovenia. Sep 2-7, 2021.
(poster presentation)

Uster DW, Heus A, Somers A, Grootaert V, Vermeulen N, Huis in't Veld D, De Cock P. Wicha SG. A model averaging approach performs superior over distinct population pharmacokinetic models in Bayesian forecasting of vancomycin administered as continuous infusion (virtual ECCMID 2021). Vienna, Austria. Jul 9-12, 2021.
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Uster DW, Stocker SL, Carland J, Day R, Wicha SG. Improved predictive performance using a model averaging algorithm in model-informed precision dosing of vancomycin (virtual PAGANZ 2021). Sydney, Australia. Jan 27-29, 2021.
(oral presentation)

Kirubakaran R, **Uster DW**, Hennig S, Carland J, Day R, Wicha SW, Stocker SL. Matters close to the heart: adaptation of tacrolimus models to inform therapeutic drug monitoring using the PRIOR approach (virtual PAGANZ 2021). Sydney, Australia. Jan 27-29, 2021.
(oral presentation)

Minichmayr IK, **Uster DW**, Fellhauer M, König C, Langebrake C, Wicha SG. A multicentre survey of vancomycin therapeutic drug monitoring practice in Austria and Germany (virtual IATDMCT Congress 2020). Banff, Canada. Sep 14-16, 2020.
(poster presentation)

Uster DW, Garcia CD, Aradom E, Riddel A, Musarara M, Hamid C, Tait C, Mangles S, Curry N, Chowdary P, Wicha SG. Differences in the prediction of the time above target in Hemophilia A patients using a chromogenic assay and a one-stage assay in model-informed precision dosing (virtual ISTH 2020). Milan, Italy. Jul 11-15, 2020.
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(oral presentation)

Uster DW, Garcia CD, Aradom E, Musarara M, Riddel A, Chowdary P, Wicha SG. Model based dose finding in Hemophilia A: Evaluation of the predictive performance of ten published pharmacometric models for Factor VIII (DPhG 2019) Annual Meeting. Heidelberg, Germany. Sep 01-04, 2019.
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Uster DW, Garcia CD, Aradom E, Musarara M, Riddel A, Chowdary P, Wicha SG. Predictive performance of population pharmacokinetic models for Bayesian forecasting of coagulation factor VIII in Hemophilia A (PAGE 2019). Stockholm, Sweden. Jun 11-14, 2019.
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Presentations without abstract

Uster DW, Wicha SG. Hämophilie A - Kann computergestütztes Therapeutisches Drug Monitoring (TDM) die Therapie optimieren? Tag der Pharmazie. Hamburg, Germany. Jun 26, 2019.
(oral presentation)

II. Contents

III. List of abbreviations

ADME	absorption, distribution, metabolism, excretion
AMR	antimicrobial resistance
AUC	area under the concentration-time curve
COLE	continuous learning
CSA	chromogenic substrate assay
ELS	extended least squares
EQA	equation-based approach
FVIII	factor VIII
IOV	inter-occasion variability
LLOQ	lower limit of quantification
MAA	model averaging algorithm
MAP	maximum *a posteriori*
MIPD	model-informed precision dosing
MRSA	methicillin-resistant *Staphylococcus aureus*
MSA	model selection algorithm
NLME	non-linear mixed effects
OFV	objective function value
OSA	one-stage clotting assay
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
TAT	time above a concentration threshold
TDM	therapeutic drug monitoring
VPC	visual predictive checks

IV. Zusammenfassung

Das digitale Zeitalter schreitet insbesondere im gesundheitsbezogenen Kontext rasant voran. Unmengen an Gesundheitsdaten, computertechnologische Fortschritte und die ständig wachsenden Erkenntnisse über Krankheiten machen es erforderlich, neue Technologien zu entwickeln und zu evaluieren, um die gewonnenen Erkenntnisse in individualisierte Therapien einzuweben. Während das therapeutische Drug Monitoring (TDM) bei lebensbedrohlichen und kostenintensiven Krankheiten wie der Hämophilie A oder (schweren) Methicillin-resistenten *Staphylococcus aureus* (MRSA)-Infektionen inzwischen gängige Praxis ist, ist der Nutzen der Therapieindividualisierungen noch nicht vollständig ausgeschöpft. [1], [2] Sogenannte pharmakometrische Ansätze haben das Potenzial, die Effektivität und Sicherheit des Arzneimittels zu erhöhen. Dies setzt jedoch voraus, dass (i) die Ansätze für den beabsichtigten Zweck geeignet sind, (ii) sie sorgfältig evaluiert und validiert werden und (iii) die korrekte Anwendung durch das medizinische Fachpersonal gewährleistet ist.

Ziel des vorliegenden Dissertationsprojekts ist es, neue Erkenntnisse in individualisierten Therapien anhand zweier exemplarischer Krankheiten (Hämophilie A und mit Vancomycin behandelte Infektionen) zu gewinnen. Durch die Entwicklung und Evaluierung neuer und bestehender pharmakometrischer Ansätze soll der Aufwand für die Implementierung pharmakometrischer Ansätze am Krankenbett verringert werden.

In der Publikation I wurden 12 verschiedene Populations-pharmakokinetische (PK) Modelle hinsichtlich ihrer Vorhersagegenauigkeit der Zeit oberhalb des Faktor VIII (FVIII)-Zielwerts in 39 erwachsenen Hämophilie-A-Patienten bewertet. Den Patienten wurden verschiedene FVIII-Produkte verabreicht und im Anschluss fünfpunkt PK Daten für die externe Validierung erhoben. Im Durchschnitt überschätzten die Populationsmodelle die wahren Werte (z.B. *a priori* Richtigkeit: -3.8 Stunden bis 49.6 Stunden). Das Modell von Abrantes *et al*.[3] schnitt in der gesamten Population am besten ab (Richtigkeit: -3.8 Stunden *a priori*; -1.0 Stunden *a posteriori*; 0.6 Stunden *general model fit*) und wies eine akzeptable Vorhersage in bis zu 90 % der Patienten auf. Das Modell wurde in die frei verfügbare modellgestützte Präzisionsdosierungs (MIPD)-

Software 'TDMx'[4] implementiert, um es medizinischem Fachpersonal zu ermöglichen, eigenständig patientenindividuelle FVIII-Dosierung zu erstellen und zu bewerten.

Abseits der Hämophilie A wurde in Publikation II die Vorhersagegenauigkeit von 23 Populations-PK Modellen mittels umfangreicher TDM-Daten (923 Proben) von 169 erwachsenen Patienten, die kontinuierlich infundiertes Vancomycin erhielten, bewertet. Die Studie identifizierte das Modell von Okada *et al.*[5] (Richtigkeit: < -0.1 mg/L) und ein Modell aus gepoolten Daten von Colin *et al.*[6] (Richtigkeit: < -1.1 mg/L) als am besten geeignete Modelle. Im direkten Vergleich des Datenalters und der Datenmenge hatten weniger alte Beobachtungen einen positiveren Einfluss auf die modellgestützten Vorhersagen als eine höhere Anzahl an Beobachtungen. Die deutlichen Unterschiede der modellgestützten Vorhersagen unterstreichen die Notwendigkeit einer sorgfältigen Modellauswahl und -validierung je nach Einsatzzweck sowie populations- und datenspezifischen Eigenschaften.

In Publikation III galt es, die Herausforderung der Auswahl des richtigen Modells für das individuelle MIPD zu bewältigen. Dazu entwickelten und evaluierten wir zwei automatisierte Multi-Modell-Ansätze. Diese wählen entweder automatisch das Beste (*model selection algorithm*, MSA) oder ein Set von Modellen (*model averaging algorithm*, MAA) aus einer Reihe von Populationsmodellen für einen einzelnen Patienten aus. Die Vorhersageleistung der beiden Algorithmen wurde in einer Simulationsstudie aus sechs unterschiedlichen Populationen sowie einem klinischen Datensatz von 180 Patienten, welche mit Vancomycin behandelt wurden und unter TDM standen, bewertet. In den sechs virtuellen Populationen zeigten der MSA und MAA genauere Vorhersagen (Präzision: 9.9–24.2 %; Richtigkeit: weniger als ±8.2 %) als die einzelnen Populationsmodelle (Präzision: 8.9–51.1 %; Richtigkeit: bis zu 28.9 %). In dem klinischen Datensatz führten der MSA oder MAA zu richtigen und präzisen Vorhersagen (Präzision: 29 % und 30 %; Richtigkeit: -5 % bzw. 0 %). Beide Ansätze wurden in die oben erwähnte MIPD-Software ‚TDMx' implementiert, um dem klinischen Entscheidungsträger die unparteiische und patientenspezifische Auswahl der idealen Modelle zu erleichtern. Zusätzlich wurden der MAA und MSA zur Vorhersage der individuellen Zielparameter der Patienten aus Publikation I und II genutzt und ihre Anwendbarkeit in beiden

Populationen nachgewiesen. Die Vorhersagegenauigkeit lag immer im Bereich des besten identifizierten Populations-PK-Modells oder war sogar besser als dieses.

In Publikation IV wurde der Einfluss der Probenentnahmezeit auf die Vorhersagegenauigkeit des entwickelten MAA und MSA in einer Simulations-Schätzungs-Studie untersucht. Dazu wurden 92 Ein- oder Zwei-Probenentnahmestrategien erstellt, um die individuelle Fläche unter der Konzentrations-Zeit-Kurve (AUC) nach intermittierenden Vancomycin-Infusionen zu schätzen. Die optimalen Einzelprobenzeitpunkte lagen zwischen 2 und 6.5 Stunden nach Infusionsbeginn, wobei die Richtigkeit zwischen -2.9 % und 1.0 % variierte und die Präzision für beide Multi-Modell-Ansätze zwischen 23.3 % und 24.0 % lag. Eine zusätzliche Messung zwischen 4.5 und 6.0 Stunden verbesserte die Vorhersagegenauigkeit (Richtigkeit: -1.7–0.0 %; Präzision: 17.6–18.6 %), obwohl die Unterschiede zwischen den auf zwei Stichproben basierenden Strategien geringer ausfielen. Im Gegensatz zur gegenwärtigen klinischen Praxis, in der meist Talspiegelmessungen zur Auswertung herangezogen werden, sollte die erste Probe idealerweise frühzeitig nach Behandlungsbeginn entnommen werden, während das Entnahmefenster einer zweiten Probe deutlich größer ist. Dies könnte bereits genügend Zeit bieten, um die zweite Dosis zu individualisieren, was bei der Entnahme und Bewertung von Talspiegelmessungen nahezu unmöglich ist.

V. Abstract

The digital era is progressing rapidly, especially in the health-associated context. Excessive amounts of health data, computational advances and constantly increasing insights into diseases require the development and evaluation of novel technologies for integrating the gained knowledge into individualized therapies. While therapeutic drug monitoring (TDM) has become common practise in life-threatening and cost-intensive diseases like haemophilia A or methicillin-resistant *Staphylococcus aureus* (MRSA)-infections, the utility and value of precision medicine has not been fully leveraged yet.[1], [2] So-called pharmacometric approaches have the potential to improve individual therapies through optimizing the efficacy of a drug and minimizing its toxicity. However, this requires (i) the approaches to fit for the intended purpose, (ii) to be carefully evaluated and validated and (iii) to assure the correct use by healthcare professionals.

The aim of the present PhD project is to bring new insights to individualized therapies in two exemplary diseases (haemophilia A and infections treated with vancomycin). By developing and evaluating new and existing pharmacometric approaches it is aspired to mitigate the burden to implement pharmacometric approaches at bedside.

In Publication I, 12 distinct population PK models were evaluated in their performance to predict the time above the factor VIII (FVIII) target by using data from 39 adult haemophilia A patients. The patients received various FVIII products, and five-point PK data measured in two assays were obtained for the external validation. On average, the population models predicted with a positive bias (e.g. bias -3.8 hours to 49.6 hours *a priori*). The model of Abrantes *et al.*[3] was identified to perform best across the population (bias: -3.8 hours *a priori*, -1.0 hours *a posteriori*, 0.6 hours general model fit) and acceptably predicted up to 90 % of the patients. This model was implemented in the open-access model-informed precision dosing (MIPD) software 'TDMx',[4] to allow the community to evaluate patient-individual FVIII dosing.

Apart from the indication haemophilia, the predictive performance of 23 population vancomycin PK models was evaluated in Publication II and based on rich TDM data

(923 samples) from 169 adult patients after receiving continuously infused vancomycin. The study identified the model of Okada *et al.*[5] (bias < -0.1 mg/L) and a pooled-data model from Colin *et al.*[6] (bias < -1.1 mg/L) as most suitable models. Model-based predictions were more accurate when using more recent observations compared to a higher number of observations. The highly variable predictions of the models underline the need of careful model selection and validation depending on the purpose, population- and data-specific properties.

In Publication III, we aimed to overcome the challenge of selecting the correct model for individual MIPD by deriving and evaluating two automated multi-model approaches. The novel approaches either automatically select the best (model selection algorithm, MSA) or a set of models (model averaging algorithm, MAA) for an individual patient amongst a set of candidate models. A simulation study of six distinct populations and a clinical dataset of 180 patients undergoing TDM during vancomycin treatment was used to assess the predictive performance of the two algorithms. Throughout the six virtual populations the MSA and MAA displayed more accurate predictions (imprecision: 9.9–24.2 %; inaccuracy: less than ±8.2 %) than the single population PK models (imprecision: 8.9–51.1 %; inaccuracy: up to 28.9 %). In the clinical dataset, the MSA or MAA resulted in unbiased and precise predictions (imprecision: 29 % and 30 %, inaccuracy: -5 % and 0 %, respectively). Both approaches were implemented into the above mentioned MIPD software 'TDMx' to facilitate the impartial and patient-specific selection of ideal models to the decision maker. Additionally, the MAA and MSA were applied to predict the targets in the individuals introduced in Publication I and II and proved their applicability in these two populations. The predictive performance was always in range of or even better than the best identified population PK model.

In Publication IV, the impact of the sampling time on the predictive performance of the developed MAA and MSA was investigated in a simulation-estimation study. Therefore, 92 one or two sampling strategies were created to estimate the individual area under the concentration-time curve (AUC) after intermittent vancomycin infusions. The optimal single-sample timepoints were identified between 2–6.5 hours post dose, with varying bias values between -2.9 % and 1.0 %, and an imprecision of 23.3–24.0 % for both

multi-model approaches. Adding a second sample between 4.5–6.0 hours improved the predictive performance (-1.7 to 0.0 % bias, 17.6–18.6 % imprecision), although the difference in the strategies based on two samples were minor. Hence, contrarily to current clinical practice where mostly trough samples are obtained, the first sample should optimally be obtained during early treatment phase, while the second sampling window is less strict. This could give sufficient time to already individualize the second dose, which is likely unfeasible using trough sampling.

1 Introduction

1.1 Personalized medicine

In an ideal world personalized medicine would follow the following paradigm: every patient receives exactly the treatment needed. Each drug is administered in its most effective and safest way. The individual outcome is maximised while adverse events and costs are minimized.

Reality proves us far away from that goal. The World Health Organization for example estimated that costs of 42 billion US-dollar per year are purely caused by medication-related errors.[7] Although quality, safety and efficacy need to be assured during every drug approval, economic reasons, considerations about practicability and potentially limited resources mostly led to bulk dosing recommendations for the largest possible groups of patients, like a fixed standard dosing.[8] In this simplest dosing strategy the same fixed dose and dosing interval is assigned to every individual, although this might result in highly variable and potentially suboptimal responses in certain patients.[9] The variability of the responses often bases on multiple factors, which can be classified into differences between individuals (e.g. patient's age, body weight and sex) or within the same individual (e.g. disease progression, organ function and dietary changes) and are termed patient covariates.

Adaptive dosing strategies further incorporate these patient-specific covariates to calculate pre-adjusted dosing regimen. Therefore, it is crucial to know the correlation between the drug effect and the patient-specific covariates (e.g. an increased body weight reduces the desired drug effect, which can be compensated via an increased dose).[10] These correlations are usually quantified in prior studies of certain patient collectives and allow a customized treatment initiation for each collective.

When intending to adjust the dosing strategy during treatment, a feedback mechanism needs to be implemented. By comparing individual measurements (e.g. blood pressure, blood sugar as direct drug effect measurements or plasma concentrations as surrogate markers for the drug effect) with a predefined target, imminent doses can be increased

or decreased to meet the desired drug effect. The combination of feedback and dosing adjustment can be repeated throughout therapy. A detailed discussion of this topic is included in Chapter 1.2 and compared to pharmacometric approaches in Chapter 1.4.

1.2 Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) embodies a form of an 'adaptive dosing strategy with feedback-control' and thus aims for individualized dosing. The overall goal is to maintain individual drug concentrations in biological fluids within specified target ranges to maximize therapeutic benefit, yet avoid toxicity.[11]

Since the first reports on applied TDM in the early 1970s,[12], [13] the therapeutic value of treatment individualization must be thoroughly assessed: Rather than applying TDM universally, certain criteria should be met to justify its application. First, it needs to be assured that the correlation between measured drug concentration and effect is higher than between dose and effect (i.e. blood concentrations are an adequate surrogate for the effect) and there is no clinical marker to directly measure the drug effect.[13] Second, feedback controlled dosing is needed if drugs (i) display a narrow therapeutic window (i.e. a small range between the minimal effective and minimal toxic concentrations), and (ii) result in highly variable exposures or responses in individuals.[14] Third, TDM is also indicated when the risk of intolerable toxic effects are increased and/or the therapeutic success is critical (e.g. in face of death). Lastly, if the patient's response differs from usual expectations due to unforeseen or special exposure-response relations (e.g. the patient belongs to special risk groups, like critically ill), actively applied TDM can assist in refining the individual treatment.[15]

TDM is considered a straightforward process, as measurements can be easily compared with the predefined limits of effective/toxic concentrations (i.e. whether the measured concentration is within target range or not). Thereon adjusted doses or dosing intervals are easy to calculate via the rule of three (i.e. the Dettli rules). Nonetheless, the conventional TDM approach is associated with several disadvantages. Predetermining target concentration ranges is mostly limited to blood/plasma concentrations and

usually established for one way of administration (e.g. intermittent or continuous) and a distinct dosing interval. Evaluating more complex targets, like the area under the concentration-time curve (AUC) or the time above a concentration threshold (TAT), is as unfeasible as interpreting exposure and adjusting doses of drugs exhibiting non-linear pharmacokinetics (PK).[16] Furthermore, the rate of drug input and drug elimination (i.e. the exposure profile) has to be fairly constant over time, meaning steady-state conditions are required after every change of drug amount or interval before TDM will be reasonable.[9] This makes the convential TDM approach rather slow. Last but not least, TDM has been criticized for being a passive monitoring process (i.e. whether the measured concentration is within target range or not) with no clear guidance on achieving individual targets.[15], [17]

Interventions like the target concentration intervention, which defines a distinct target and gives pharmacological-based guidance on how to achieve the same,[18] highlight the common interest on overcoming disadvantages of traditional TDM.

A more sophisticated approach includes pharmacokinetic/pharmacodynamic models to guide dosing and is summarized under the term model-informed precision dosing (MIPD). Before discussing MIPD, the basic elements of PK, PD and pharmacometric modelling are reviewed.

1.3 Pharmacometrics

In the last decades pharmacometrics has evolved to an integral part of clinical pharmacology during drug development, research and therapy.[19] It is the intersection between quantitative pharmacology, mathematics and computational science or as Ette *et al.* pointedly defined the term: “Pharmacometrics is the science of developing and applying mathematical and statistical methods to characterize, understand, and predict a drug’s pharmacokinetic, pharmacodynamic and biomarker-outcomes behavior.”[20] In essence, pharmacometrics rationalizes data-driven decisions in drug development and pharmacotherapy though analysing populations and gaining knowledge in the pharmacokinetic and pharmacodynamics of the drug.

1.3.1 Pharmacokinetics

A fundamental element in pharmacometrics is to provide understanding of a drug's pharmacokinetics (PK). Thus, the term refers to the study of all processes that determine the fate of the drug within a living organism.[21] In this context, a widely employed acronym is 'ADME' and incorporates the absorption (A) of the drug, distribution (D) within the body, the metabolism (M) and excretion (E) – the latter two also known as clearance.[22]

Given the genetic and physiological differences between humans (e.g. age, physiological condition or genetic disposition) and time-dependent alterations within individuals (e.g. disease progression, comedication or organ function), the time-course of a drug and its PK descriptors vary in a group of patients or population. In the field of population pharmacokinetics, clinical samples are collected from multiple patients to describe concentration-time profiles and quantify sources of variability in drug exposure. The main aim of population PK is to associate gained information with patient characteristics and translate this knowledge into mathematical functions.

1.3.2 Pharmacodynamics

If PK is defined as "how does the body affect the drug", pharmacodynamics (PD) can be summarized as "how does the drug affect the body".[23] In essence, PD describes the relationship between drug exposure and beneficial/adverse drug effects. These relationships can be represented in mathematical models and is called PK/PD modelling. Of central interest thereby are the underlying PK/PD mechanisms and the PK impact on the effect variable, which together could provide the fundament of an optimized dosing regimen. As effect variable one could imagine the in-vitro bacterial count in infectious diseases, the time to cure or death, or the physician's assessment aggregated in a score. In coagulation disorders for example, the bleeding frequency or bleeding intensity can be associated with the PK of a clotting factor to derive dosing recommendations.

1.3.3 Pharmacometric modelling

As indicated above pharmacometric modelling is a common tool to derive the drug's PK or PK/PD characteristics and thereupon derive new treatment recommendations. The conceptual framework of this approach, also termed non-linear mixed effects (NLME) modelling, arose in the 1970s by Sheiner *et al.*[24]. Nowadays, it has mostly replaced two more simplistic approaches, which have shown to produce biased results: naïve pooling and the 'two-stage' approach.[25] The naïve pooling calculates the population parameters by fitting all data from the total population at once without accounting for individual differences, which leads to biased population parameters without any estimated variabilities.[26] The 'two-stage' method calculates the individual parameters first and subsequently determines the variability between the individuals. Thus, this method has been shown to result in less biased population parameters but still misspecifies the variabilities and requires the same (high) amount of data from every individual.[27]

In contrast, NLME modelling can simultaneously determine the population, as well as the individual model parameters and quantifies the variability between and within individuals, as well as covariate relationships at once.[24] Furthermore, this process requires less quantities of data compared to the aforementioned approaches and can deal with missing or unbalanced data. Different sources of data can be simultaneously integrated to contribute to different aspects of the model.[28]

Generally, the modelling process underlies four key elements [29], although on-going methodological and computational developments further the set of more complex/refined techniques/applications (Figure 1). First and foremost, the intended use of the model must be defined, along with the pharmaceutical research question. Thereby, pharmacometric models can either be descriptive or predictive. Descriptive models are purely developed to gain knowledge on the drug's PK/PD within the studied population.[30] When the model is used to numerically summarise PK/PD information (e.g. variabilities in the population or covariate relationships), there is no intention to

extrapolate. On the contrary, predictive models, usually build upon descriptive models, are intended to be applied to patients outside the development population.[31] The predictive model behaviour is of greater interest than the exact descriptive parameter values.

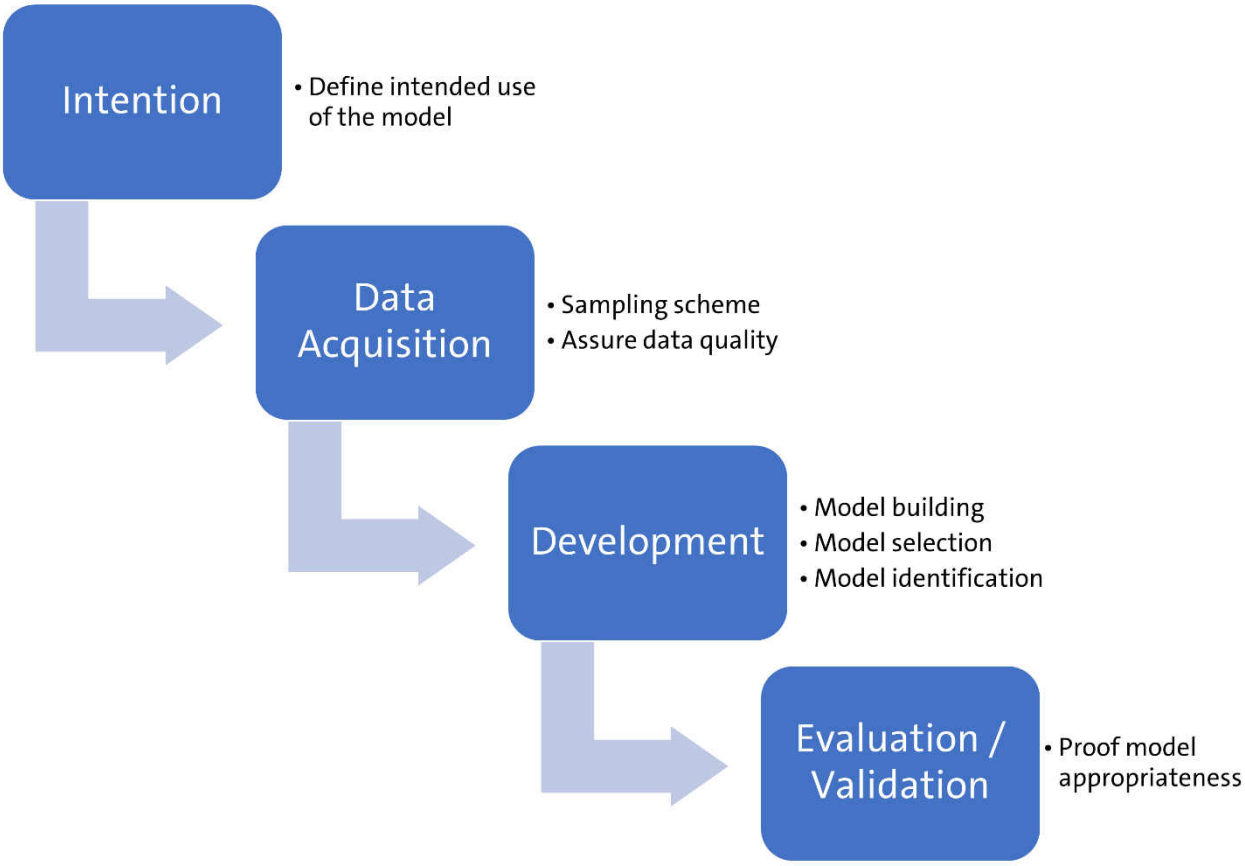

Figure 1: Key elements of the nonlinear mixed effects modelling process

In both cases, the second key element is to acquire the relevant data. Thereby, the quality of data is as important as its appropriateness to potentially answer the research question. Falsely documented or (accidentally) ignored facts (e.g. comedications or organ status) will impair the development of reliable models – the third element of the modelling process.

A NLME model, which 'mixes' or combines fixed effects (e.g. constant covariates or doses of drug) with random effects (e.g. unexplained variability or time-varying covariates) in a set of nonlinear functions,[32] is built upon three components: the structural, the

statistical and the covariate model.[33] While the structural model contains the mathematical structure and describes the central tendencies of the fixed effect parameters, the statistical model accounts for the variation on parameter and observation level by describing the magnitude of the variances (e.g. inter-individual, intra-individual, inter-occasion and residual variability).

In general, the variability of population parameters is assumed to underly a formal statistical distribution (e.g. lognormality) and therefore, NLME models are of parametric nature. An opposing method, the nonparametric approaches, are not mathematically summarising the observation via discrete distributions and typical, fixed parameters. The population trends and their variabilities are rather computed as a set of supporting points, which are associated to the respective individuals and based on their probability to adequately predict the observed data.[34]

The last component of a NLME model, the covariate model, aims to explain parts of the inter- and intra-individual variability through relating individual, measurable patient covariates (e.g. age, body weight) to parameter variances.

During the development of descriptive NLME models a collection of related models with increasing complexity is built to identify the most representative one to answer the initial research question. Therefore, the goodness-of-fit, reliability and stability must be evaluated using credible techniques. Given that the extrapolation within predictive models involves more assumptions on the relationship between prior knowledge and predicted results, these models require a more careful validation to fit the respective purposes.[31] More details of the model evaluation and validation – the fourth key element of the modelling process – will be covered in Chapter 1.3.4.

1.3.4 Model evaluation and validation

Before introducing evaluation techniques used in the present work, a brief distinction between the connotations of evaluation and (external) validation should be made. As a matter of fact, there is no clear consensus on the differences of the terminology of validation and evaluation. Both terms are found interchangeably in the pharmacometric

community.[35] Nonetheless, validation is – in context of this work – focussing on the predictive performance of the models with regard of unseen, future data. In accordance with the FDA guideline, model validation proves the predictability of the model and quantifies the accurateness and reproducibility of the forecast in (new) validation data.[36] In contrast, evaluation is to be used in a broader way and summarises all processes demonstrating whether the proposed application is robustly implemented and whether 'good practise' had been applied to describe the (known) data.[37]

Both terms thereby do not imply the model(s) to be appropriate under any condition but only the evaluated and predefined purpose. In the following a selection of basic evaluation techniques during model development (including selection, evaluation, and validation) will be introduced.

During early stages of model development, the so-called objective function value (OFV) is generally used to discriminate between candidate models. In the NLME framework OFV is often expressed as modification of the extended least squares (ELS) (Eq. 1):

$$OFV = \underbrace{\sum_{i=0}^{n} \frac{\sum_{j=0}^{m}\left(y_j(t_j) - s_j(t_j, \theta, \eta_i)\right)^2}{\sigma^2} + log_e(\sigma^2)}_{\text{ELS}} + \sum_{i=0}^{n} \frac{{\eta_i}^2}{\Omega^2} + constant \qquad \text{Eq. 1}$$

with

- $y_j(t_j)$ being the measurement at time t_j for the ith individual, i.e. the dependent value
- θ being the model parameter vector (constant with respect to time but unknown)
- $s_j(t_j, \theta, \eta_i)$ being the model-predicted value at time t_j, given the model parameter vector θ and including the individual deviations η
- σ^2 being the variance of the residual error
- Ω^2 being the variances of the parameter θ
- η_i being the inter-individual variation term of the ith individual drawn from the variances Ω^2

Thereby, the OFV simultaneously encloses all differences of individual and population parameters as well as between observed and predicted dependent variables (e.g. plasma concentrations). Via this single number differences between competing models can be initially assessed.[38]

Furthermore, goodness-of-fit is usually assessed graphically. Here, prediction versus observations from the total population and/or their (standardized/decorrelated) differences are plotted and visually assessed as for example proposed by Nguyen *et al.*[39] Presuming clean data, the so-called standard diagnostic plots give insight into structural misfits and mismatching residual variability components.

Moreover, these plots can be accompanied by the assessment of (conditional) weighted residuals, which are standardized prediction errors, and simulation-based diagnostics like the visual predictive checks (VPC) or normalized prediction distribution errors. VPC are a graphical comparison of the prediction intervals derived via simulations and the corresponding observations.[40] Normalized prediction distribution errors on the other hand are simulation based computations of the prediction discrepancies which are uncorrelated and normalised.[41] These diagnostics give insight into structural misfits and a visual imprecision of the encoded variability of the predictions.

Another set of techniques aims to evaluate the reliability and stability of a model. Therefore, the uncertainty of all model parameters needs to be assessed, usually in forms of confidence intervals or standard errors. Standard errors of the parameters are approximated via methods like bootstrapping or log likelihood profiling. In a nutshell, bootstrapping is defined as a method of repeatedly generating datasets via resampling of the original data and re-estimating the parameters of the model of interest.[42] The distribution of the re-estimated parameter is subsequently used to display the confidence intervals of the respective parameters. In likelihood profiling, the OFV associated with the surface around each parameter of the final model is graphically displayed.[30]

In case the model is intended to be externally applied for forecasting individual profiles or targets, the predictive performance needs to be assessed and ideally compared to other approaches. For this purpose, several numerical performance indicators, which

should be accompanied by evaluation methods proving model stability and reliability, have been proposed.[43] The mean or median error for example represents the general tendency of the forecast to meet the true values, also known as bias. This metric should be always accompanied by a measure of imprecision. The (root) mean squared error for example enables interpretation of the average spread of the forecasts.

To validate the predictive performance of the models and novel approaches evaluated in the current work (e.g. their ability to accurately forecast) the numerical performance indicators mentioned above were calculated in external datasets that were not used to develop the models. Except in the simulations, the metrics were accompanied by the standard errors of the accuracy metrics to determine uncertainties.

1.4 Model-informed precision dosing

MIPD summarizes computationally guided approaches (including the use of pharmacometric models, machine learning or adaptive model approaches), which aim to draw inference from multiple sourced data on future treatment courses of the patient.[16], [44] The process lies within the broader field of personalized medicine and is increasingly recognised by healthcare professionals, patients and even (former) American presidents, as the latest precision medicine initiative was launched by Barack Obama.[45], [46]

Through implementing pharmacometric models in mobile or web-based software (e.g. InsightRX[47] or TDMx[4]), MIPD supports clinical decision-making and aims to maximize efficacy and minimize toxicity within the individual. It can be seen as an extension to traditional TDM, because it shares the same aim and has similar fulfilling criteria (i.e. narrow therapeutic ranges, imperative of therapeutic success, or high risk of altered PK/PD). Nonetheless, this approach comes with several advantages compared to traditional TDM.

As with classical dosing nomograms or single covariate-based dosing, pharmacometric models can predict a likely dosing regimen to meet the intended target without measuring any drug concentrations (i.e. *a priori*). However, this approach allows to

consider multiple covariates, its correlations and prior knowledge enclosed in the model (e.g. PK structure and variability in similar patients/populations, also termed Bayesian prior) simultaneously and immediately provides a comprehensive representation of the PK parameters together with their probability distributions.[48] Furthermore, with the individual basic parameters at hand, more complex parameters (like the AUC or TAT) can be easily derived.

The power of pharmacometric models becomes apparent when individual drug concentrations are available. The probability distributions of the patient's PK parameters are refined considering the Bayesian prior, dosing, and drug measurement data at once and the most likely set of individual estimates will be generated (i.e. the maximum *a posteriori* (MAP) estimate).[49], [50] Thereby, the drug concentration measurements, of which a single one might already be sufficient, can theoretically be obtained at any time of the dosing interval. Hence, MIPD is not restricted to a fixed dosing regimen and steady-state conditions, although certain timepoints may contribute more to the predictions.[16] Ultimately, MIPD results in maximally precise dosing recommendations, which can be constantly updated as soon as new data becomes available.

Despite its benefits, implementing MIPD in clinical practise still progresses at snail's pace.[51]–[53] One such reason is the necessity to carefully select the underlying model. As Broeker *et al*. demonstrated, varied the predictive performance of 31 published vancomycin PK models drastically, when being used for (Bayesian) forecasting of individual PK profiles.[54]

Further detailed reasons on why MIPD has not yet become reality are discussed in Chapter 4.

1.5 Investigated diseases for application of MIPD

Two different diseases and their corresponding therapies were investigated in this work: haemophilia A as well as (systemic) infections caused by Gram-positive bacteria. Thereby, their contrasting demands on the treatment highlight the potential of MIPD to

enhance treatment across substantially different diseases. While haemophilia A is treated for the entire lifetime, infections caused by Gram-positive bacteria rather require rapid and temporally treatment. More differences regarding their causes, prevalence and treatment targets are described in the following two chapters.

1.5.1 Haemophilia A

Haemophilia A is one of the most common bleeding disorders and affects mostly males due to its x-linked recessive inheritance (incidence 1 in 5 000 males).[55] Although the disease is clinically indistinguishable from haemophilia B (incidence 1 in 30 000), differentiation is necessary due to the divergent cause, that is a deficiency or malfunction of either coagulation factor VIII (FVIII) in haemophilia A or of factor IX in haemophilia B.

Untreated haemophiliacs are usually not expected to reach their adulthood, depending on the severity of the disease. The condition thereby occurs in three forms and is categorized via the intrinsic activity (i.e. endogenous amount of functional FVIII) relative to normal levels. While in mild (6–30 % of normal activity) and moderate (2–5 %) excessive bleeds mostly manifest after major trauma or surgery, patients with severe haemophilia A (≤1 %) encounter 20–30 excessive or even spontaneous bleeds per year.[56]

There is no cure for haemophilia A, but a lifelong and individually optimized replacement of the malfunctioning or missing factor VIII can prolong life to normal expectancies[57] and improve quality of life.[58] This prophylactic treatment involves the periodic administration of exogenous FVIII products to always maintain the patient above 1 % of the normal FVIII level. This has been shown to reduce life-threatening bleedings, recurrent musculoskeletal hemorrhages and its consequent joint disabilities – the main symptoms of haemophilia A.[2], [59]

Since the first description of the disease in the 19th century,[60] its treatment has evolved from blood transfusion to prophylactic replacement therapy using exogenous FVIII derivatives. Nowadays, three classes of FVIII products are available: plasma-

derived, recombinant products and those with extended half-lives. The most common class, the recombinant products, can further be distinguished into full-length, B-domain deleted and other modified products, which differ in tolerability, costs and typical PK (e.g. standard half-life is reported between 8–12 hours and around 20 hours for extended half-lives).[61] But even using the same product the individual response has been demonstrated to greatly vary.[62], [63] Patient characteristics (e.g. age, body weight or von-Willebrand factor) or the underlying assay used to determine FVIII activity only partly explain the PK variability and therefore, make this disease an ideal candidate for personalized medicine using MIPD approaches.

1.5.2 Infectious diseases caused by Gram-positive bacteria

Infections occur in many different forms, from harmless furuncles to life-threatening infections of the lower respiratory tract, cardiovascular system or at intra-abdominal sites, among others. These infections can be extraordinarily dangerous when patients are in vulnerable conditions (e.g. old, immunodeficient or postsurgical patients) or when typically used anti-infective drugs become ineffective due to antimicrobial resistance (AMR) mechanism.

Globally, more than 1.25 million people died in 2019 due to AMR bacterial infections and almost four-times as much died in association with AMR.[64] Thus, infections with drug-resistant bacteria have become a leading cause of death worldwide – even exceeding those caused by HIV/AIDS or malaria (860 000 and 640 000 death, respectively).[65]

The number of human pathogenic bacteria is enormous. Nonetheless, drug resistance in six alone (*E. coli, S. aureus, K. pneumoniae, S. pneumoniae, A. baumannii,* and *P. aeruginosa*) lead to the majority (i.e. 929 000) of the above mentioned deaths.[64] One of the most common pathogen-drug combination is the methicillin-resistant *Staphylococcus aureus* (MRSA). Current European surveillance reports estimate that 15.5 % of the invasive *S. aureus* strains are methicillin resistant. Thereby, the prevalence highly varies from as low as 1.1 % in the northern to almost 50 % in the southern countries of the European Union.[66]

Of those infected with an MRSA strain, conventional antibiotics like beta-lactams, fluoroquinolones or macrolides are not effective anymore.[67] In this case, the glycopeptide antibiotic vancomycin can serve as key alternative.

After being discovered in 1952, vancomycin has been handled as a last resort antibiotic due to its perceived toxicity and better alternatives (e.g. semisynthetic penicillins or cephalothin).[68] Its use dramatically increased from the 1980s on because of the widespread oral administration to treat pseudomembranous enterocolitis, which is today known as one cause of vancomycin-resistant enterococci; and second the rising appearance of MRSA.[69]

Nowadays, vancomycin is one of the most used antibiotics in the hospitals of the United States.[70] It often requires TDM especially in vulnerable patients, given the critical need to rapidly reach adequate antibiotic effects when facing life-threatening conditions (e.g. sepsis or complicated endocarditis). Furthermore, high drug exposures were found to be associated with nephrotoxicity or subsequent stages of acute kidney injuries. [71], [72] Nonetheless, there has been an ongoing dispute on the most appropriate exposure-response relationship of vancomycin.[73][71] While the vancomycin guideline from 2009 recommended to target vancomycin trough concentrations of 15–20 mg/L and therefore, obtain only TDM samples at the lower end of the PK profile, the most recent guideline rather recommends maintaining the patient within an AUC range of 400–650 mg*h/L.[1], [74] To calculate the optimal individual AUC, adequate population PK models and the most informative samples are required.

The glycopeptide vancomycin is bactericidal against Gram-positive bacteria due to inhibition of the cell wall crosslinking and has a low bioavailability.[75] Therefore, doses are either intermittently or continuously infused with both displaying similar safety, microbiological and clinical outcomes.[76] To reach individual targets even faster, MIPD could be applied to forecast future PK profiles and subsequent doses.

2 Objectives

Individualizing therapies is essential in treating life-threatening and cost-intensive diseases to ascertain therapeutic effects and minimize risk of toxicity. Especially when vulnerable or special patients are affected due to their PK alterations (e.g. critically ill, children, multi-morbid), TDM has evolved as an important tool. This is due to the straightforward process of comparing obtained drug measurements with recommended targets and individualizing doses accordingly. Whether the target is to maintain the FVIII concentration of a haemophilic patient above a certain threshold, or whether one targets a distinct antibiotic exposure in MRSA-infected patients using surrogate trough levels – TDM has been advocated for both contrasting diseases discussed in this work.[2], [77]

However, the traditional way of personalized medicine has several disadvantages. Most importantly, TDM is limited to steady-state conditions, and reference ranges of the surrogate are usually obtained for a single dosing strategy (in terms of the way of administration and dosing interval) in a standard patient collective.[78] Furthermore, the variability of exposure-response is usually accounted for using one or two different patient information (e.g. covariates like body weight or kidney function) – especially to calculate the first doses. The complex interpretation of multiple influencing factors simultaneously is likely impossible.

To overcome these drawbacks, TDM can be accompanied by pharmacometric models to further guide dosing at bedside, i.e. MIPD approaches. Unfortunately, systematic evaluation and implementation of MIPD is advancing slowly. Although it is not yet commonly practiced in clinical reality, these models could – implemented in software tools – change the way individual dosing decisions are derived.

Nonetheless, several challenges of MIPD need to be addressed before this process can become common practise. These challenges can be classified into three key elements of MIPD: the model (M), the data/patient (D) and the operator/MIPD-user (O) (Figure 2).

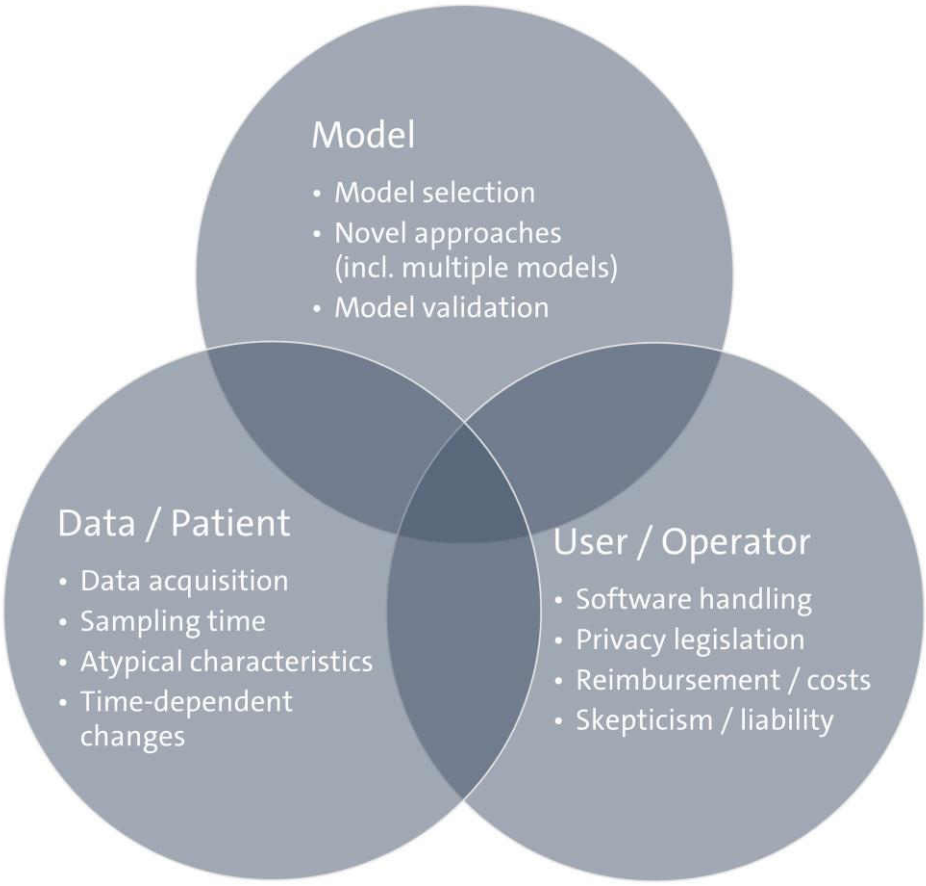

Figure 2: Main challenges of model-informed precision dosing

The objective of this thesis was to evaluate challenges within these elements via the publications included and advocate a wider integration in healthcare. In detail, the aims of the publications were:

Publication I: Systematic evaluation of population pharmacokinetic models for prophylaxis in haemophilia A

- Evaluation of the predictive performance of population PK models to identify suitable models to guide personalized prophylaxis in haemophilia A patients (M)
- Extension of an existing MIPD software developed by Wicha *et al.* [4] to provide a dosing module for haemophilia A treatment (O)
- Assessing assay discrepancies and other influential factors of the patient (D)
- Integration of multiple models in the MIPD approaches developed in Publication III and evaluation of its predictive performance (M, O)

Publication II: Systematic evaluation of population pharmacokinetic models for model-informed antibiosis in Gram-positive infected patients

- Evaluation of the predictive performance of population PK in Gram-positive infected patients receiving continuous vancomycin (M)
- Assessing the impact of aging TDM information (M, D)
- Application and evaluation of the multi-model approaches developed in Publication III (M, O)

Publication III: Development and validation of the model averaging and model selection algorithm

- Development and validation of two novel MIPD approaches, which integrate multiple population PK models at once and aim to automate and objectify the model selection process (M, O)
- Implementation of the multi-model approaches into the MIPD software developed by Wicha *et al.* [4] to be used for vancomycin MIPD (O)

Publication IV: Importance of sampling time and number to forecast the individual drug exposure

- Assessing the impact of sampling time and number of vancomycin plasma concentrations to forecast individual vancomycin exposure in the MAA/MSA (D)
- Comparison of the MIPD approach to a traditional TDM approach (M, D)
- Providing recommendations on sampling time and number to be used in future clinical trials (D, O)

3 Cumulative part

The following cumulative part consists of four peer-reviewed publications, which represent the key results of this thesis. Thereby, the focus was set on various aspects of applied model-informed precision dosing (MIPD) in haemophilia A and MRSA-infections including the identification of optimal models and sampling timepoints, the development of new MIPD approaches as well as the assessment of the impact of aging TDM information.

The articles were published in *Therapeutic Drug Monitoring, International Journal of Antimicrobial Agents, Clinical Pharmacology & Therapeutics* and *Clinical Pharmacology & Therapeutics: Pharmacometrics & Systems Pharmacology*.[79]–[82]

3.1 Publication I

Dosing for Personalized Prophylaxis in Hemophilia A highly varies on the underlying Population Pharmacokinetic Models

David W. Uster, Pratima Chowdary, Anne Riddell, Cecilia Garcia,
Elsa Aradom, Molly Musarara, Sebastian G. Wicha

Therapeutic Drug Monitoring (2022)

Impact Factor: 3.681 (2020)

Synopsis

Providing severe haemophilia A patients with an adequate prophylaxis is essential to prolong their lives and reduce costs due to excessive drug consumption or increased long-term consequences (e.g. joint-damages/disabilities). Thereby, dose individualization is nowadays usually assisted using trough sample-based TDM. A more sophisticated approach is to individualize dosing using population PK models and their predictions of the individual targets.

In Publication I, we aimed to identify the most suitable population PK model to predict the individual time above target using one of multiple FVIII products. Therefore, the predictive performance of twelve published models were compared using sparse data from an external dataset.

The systematic comparison revealed that it seemed beneficial to use models in MIPD which were developed on preferably large and dense data. Nonetheless, simple model selection based on the size of the development data is not enough. Especially, when intending to use a single model for MIPD, sound external validation is necessary.

Furthermore, the use of chromogenic substrate assay (CSA) data for predicting the individual TAT resulted in more accurate predictions than using one-stage assay (OSA) data.

At last, the most promising model (published by Abrantes *et al*.[3]) was implemented in the open-access model-informed precision dosing software 'TDMx' to allow the community to evaluate model-guided individual FVIII dosing. Moreover, we applied the two multi-model approaches developed in Publication III and revealed a similar predictive performance compared to the best population PK model.

ORIGINAL ARTICLE

Dosing for Personalized Prophylaxis in Hemophilia A Highly Varies on the Underlying Population Pharmacokinetic Models

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AU2

Background: Model-informed personalized prophylaxis with factor VIII (FVIII) replacement therapy aimed at higher trough levels is becoming indispensable for patients with severe hemophilia A. This study aimed to identify the most suitable population pharmacokinetic (PK) models for personalized prophylaxis using various FVIII products and 2 clinical assays and to implement the most suitable one in open-access software.

Methods: Twelve published population PK models were systematically compared to predict the time above target (TaT) for a reference dosing occasion. External validation was performed using a 5-point PK data from 39 adult patients with hemophilia A with FVIII measured by chromogenic substrate (CSA) and 1-stage assays (OSAs) using NONMEM under 3 different conditions: a priori (with all FVIII samples blinded), a posteriori (with 1 trough sample), and general model fit (with all FVIII samples including the reference dosing occasion provided).

Results: On average, the baseline covariate models overpredicted TaT (a priori; bias −3.8 hours to 49.6 hours). When additionally including 1 previous trough FVIII sample before the reference dosing occasion (a posteriori), only 50% of the models improved in bias (−1.0 hours to 36.5 hours) and imprecision (22.4 hours and 60.7 hours). Using all the time points (general model fit), the models accurately predicted (individual TaT less than ±12 hours compared with the reference) 62%–90% and 33%–74% of the patients using CSA and OSA data, respectively. Across all scenarios, predictions using CSA data were more accurate than those using the OSA data.

Conclusions: One model performed best across the population (bias: −3.8 hours a priori, −1.0 hours a posteriori, and 0.6 hours *general model fit*) and acceptably predicted 44% (a priori) to 90% (*general model fit*) of the patients. To allow the community-based evaluation of patient–individual FVIII dosing, this model was implemented in the open-access model-informed precision dosing software "TDMx."

Key Words: Bayesian forecast, hemophilia A, individualized medicine, pharmacokinetics, therapeutic drug monitoring

(*Ther Drug Monit* 2022;00:1–9)

BACKGROUND

Hemophilia A is an inherited bleeding disorder caused by deficient clotting factor VIII (FVIII).[1] Since the first accurate description of this hereditary disease in the early 19th century,[2] the treatment for hemophilia A has evolved from blood transfusion to prophylactic replacement therapy using recombinant FVIII derivatives. Nowadays, periodic administration of exogenous FVIII aims to always maintain the FVIII level in patients with severe hemophilia above 1% of the normal level to potentially prevent life-threatening bleeding, recurrent joint hemorrhages, and its consequent joint disabilities.[3,4]

Ensuring an adequate plasma level depends not only on the dose but also on the FVIII pharmacokinetics (PK) in an individual patient.[5] PK parameters describing the distribution and clearance of FVIII commonly exhibit substantial interindividual variability leading to false dose recommendations if inappropriately accounted for.[6,7] Some interindividual variability can be explained by the patient characteristics such as age or body weight; however, dose individualization based on these covariates only addresses a part of this variability.[8–10]

Another approach, commonly referred to as Bayesian forecasting or model-informed precision dosing (MIPD), aims to further reduce the imprecision in dosing calculations by combining individual patient's information, including samples with measured FVIII levels (FVIII:C) using limited sampling strategy, patient covariates, and prior PK information of

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.drug-monitoring.com).
D. W. Uster and S. G. Wicha performed the analyses and wrote the manuscript; S. G. Wicha designed the study; P. Chowdary developed the idea, designed the data collection, and critically reviewed the manuscript; and A. Riddell, C. Garcia, E. Aradom, and M. Musarara collected the clinical data and critically revised the manuscript. All the authors have approved the manuscript.
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a collective group in the form of a population PK model. These models simultaneously characterize the drug-concentration time courses in individuals as well as the whole population and usually consist of 3 elements: mathematical equations (including PK parameters) complemented by covariate relationships between PK parameters and patient characteristics as well as a statistical component accounting for parameter deviations within an individual (unexplained residual variability) and across individuals (interindividual variability).

Because personalized prophylaxis has been demonstrated to be superior to standard prophylaxis for costs and clinical outcomes,[11,12] the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis has published their rationale and guideline to adopt population PK approaches for the patient-tailored treatment of hemophilia.[13,14]

However, the major challenge remains the selection of a population PK model that can be used in MIPD software tools. Most population PK models are commonly developed for a specific (sub) population but are not intended for use in MIPD. Although there are approaches to compare available population PK tools[15] or (modified) population PK models in a single tool,[16] none of them have incorporated Bayesian forecasting using real-life clinical assay data to evaluate the predictive performance of various FVIII products. Furthermore, the ongoing controversy regarding assay discrepancies raises the issue of whether the chromogenic substrate assay (CSA) or the 1-stage assay (OSA) should be primarily used in clinical practice to guide dosing decisions.[17–21]

This study aimed to (1) systematically compare published heterogenous population PK models, developed for various FVIII products, as well as compare 2 previously developed multimodel approaches, which either automatically select the most suitable population PK model from a set of candidate models per individual or average the predictions of the population PK models according to their individual model fit;[22] (2) identify models most suitable for MIPD by using a clinical data set, including various FVIII products and PK profiles over 48 hours with 2 assays; and (3) implement the most suitable model in the web-based, open-access MIPD software "TDMx."

TABLE 1. Demographics and Clinical Characteristics of Patients Included in the Study

Characteristics	Value [range]	Missing
Patients	Male, n = 39	
Severity		
Moderate	2	—
Severe	37	—
Age, yrs (median)	28 [18–69]	—
Body weight, kg (median)	73 [46–121]	4
Body height, cm (median)	173 [148–193]	6
Von Willebrand factor, % (median)	111 [48–249]	3
Blood type		13
O+ (O−)	8 (−)	
A+ (A−)	12 (−)	
B+ (B−)	4 (1)	
AB+ (AB−)	1 (−)	
FVIII product*		
Full-length recombinant (FLrFVIII)		
2nd Generation, Octocog alfa (Helixate and Kogenate)	3	
3rd Generation, Octocog alfa (Advate)	17	
B-domain deleted (BDDrFVIII)		
2nd Generation, Moroctocog alfa (ReFacto)	18	
3rd Generation, Turoctocog alfa (NovoEight)	2	
Extended half-life, Efmoroctocog alfa (Elocta)	1	
Dosage, IU	1000–4000	
Observations per assay		
Chromogenic substrate assay (CSA)	229	
Total BLQ (trough)	23 (15)	
One-stage assay (OSA)	229	
Total BLQ (trough)	14 (12)	

*Patients may belong to more than 1 group.

BDDrFVIII, B-domain deleted recombinant factor VIII product; BLQ, data below the lower limit of quantification (<1 IU/dL); CSA, chromogenic substrate assay; FLrFVIII, full-length recombinant factor VIII product; N.D., not defined; OSA, one-stage assay.

MATERIALS AND METHODS

Clinical Data for the Model Evaluation

The clinical PK data sets acquired from the Katharine Dormandy Haemophilia and Thrombosis Centre (London, UK) were part of an ethically approved study (Rec Number: 15/LO/1868). PK samples were collected after obtaining written informed consent and a 48-hour washout period between October 2018 and December 2019. Patients received doses ranging between 20 and 50 IU/kg of their body weight (presented in Table 1), and samples were collected at 6 time points: baseline preinfusion and postinfusion at 10 minutes, 3 hours, 8 hours, 24 hours, and 48 hours as described by Stass.[23] Furthermore, the samples were analyzed by CSA and OSA (see **Text**, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A557, which contains details of the 2 assays used). Data below the quantification limit of 1 IU/dL (10% in CSA and 6% in OSA) were encoded as half of the lower quantification limit and were mostly predose levels.

Population Pharmacokinetic Models—Description and Comparison

A literature search through PubMed identified 12 publications describing population PK models of various FVIII products developed using diverse populations.[5,24–34] "Hemophilia A," "pharmacokinetics," and "population" were used as the search terms. The described models were encoded and processed using NONMEM software (version 7.4.3; ICON, Dublin, Ireland).

AU1

To assess the population PK models structurally, the PK profile of a standard patient was simulated model-wise (see **Text**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A558, which contains information of the simulated standard patient), and subsequently, the time above the target (TaT) of 2 IU/dL in steady-state conditions was compared among the models estimations.

In addition, the models were compared with 2 recently developed multimodel approaches, namely the model selection (MSA) and model averaging algorithm (MAA). The MSA automatically selects the most suitable model for an individual patient from a set of candidate models (a distinct number of population PK models identified as performing best in this study), and the MAA averages the predictions of all these candidate models weighted proportionally to their individual patient-specific model fit.[22] In detail, the model fit was compared through the maximum likelihood (*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.

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

Evaluation of the Predictive Performance

Three different scenarios were evaluated, which differed in the quantity of FVIII:C (either measured with CSA or OSA), provided to each model to forecast the TaT in a densely sampled "reference" dosing interval. The scenarios were as follows.

A priori, the baseline covariate models were used to forecast the reference TaT (using only patient covariates such as body weight, age, and drug type).

A posteriori, the baseline covariate models were additionally supplied with a predose FVIII trough level to forecast the TaT for the subsequent future dosing interval. Notably, the "future" PK profiles were blinded to the model. This scenario mimics the bedside process during therapeutic drug monitoring, where the aim was to forecast future PK profile using the available information.

General model fit, where all available FVIII:C values from either assay were supplied to the baseline models. The Bayesian maximum a posteriori estimates were generated with parameters and variabilities encoded as reported in the respective publication (as in the scenarios above, NONMEM MAXEVAL = 0 was used); however, in addition, FVIII:C from the reference dosing interval was also provided. Hence, this scenario does not represent forecasting but rather a retrospective evaluation to determine the maximum ability of the models to fit all available data.

In all these scenarios, the individually predicted TaT was compared with the TaT predictions of a reference model that was developed based on the study data and was assumed to reflect the true TaT in the reference dosing interval (details of the development of the reference model: see **Text**, **Supplemental Digital Content 3**, http://links.lww.com/TDM/A559, which explains the development and structure of the reference model, and see **Figure**, **Supplemental Digital Content 4**, http://links.lww.com/TDM/A560, which demonstrates the reference model fit in the 39 individuals).

Further evaluation included goodness-of-fit plots, displaying the population predicted versus observed FVIII:C and prediction-corrected visual predictive checks (pcVPCs) created using R (version 4.0.2., R Foundation for Statistical Computing, Vienna, Austria), and Perl-speaks-NONMEM (version 4.9.0, Nordgren et al, Uppsala, Sweden). The pcVPC, stratified by assay and FVIII product, was created using 1000 simulation data sets, as described by Bergstrand et al.[35]

As performance indicators, bias, which represents the accuracy (Equation 2), and root mean square error (RMSE; Equation 3), representing imprecision, were calculated using the mean difference between the predicted and true TaT, with *n* being the number of individuals.[36]

$$\text{Bias} = \frac{1}{n}\times \sum_1^i (\text{predicted}_i - \text{reference}_i) \quad (2)$$

$$\text{RMSE} = \sqrt{\frac{1}{n}\times \sum_1^i \left((\text{predicted}_i - \text{reference}_i)^2\right)} \quad (3)$$

The performance of the models was considered clinically acceptable if the bias across the population was between −12 and +12 hours, with the 95% confidence intervals of the calculated bias including 0.

Dosing Software "TDMx"

To translate the results obtained in this study into clinical practice, we encoded the best-performing model in the open-access online MIPD software TDMx (www.TDMx.eu).[37] The software supports probabilistic a priori based dosing simulations and Bayesian dosing using the a posteriori predicted PK.

RESULTS

Clinical Data for the Model Evaluation

In total, 44 patients (460 samples) who received a B-domain deleted (BDDrFVIII) or a full-length product (FLrFVIII) were enrolled in this study. Four patients with no information on the date or amount of the previous dosing, and one suspected with a genetic defect that might have caused assay discrepancies, were excluded from this study. The characteristics of these 39 patients are presented in Table 1. Two samples from the same individual were suspected to be low in quantity compared with the preceding and subsequent samples of the same patient analyzed by both the assays and were excluded.

Concentration dependency of the assay results was observed for both the BDDrFVIII and FLrFVIII products. Compared with the OSA, CSA reported 13% higher levels at higher concentrations (>20 IU/dL) and vice versa (mean = −25%) at lower concentrations.

Population Pharmacokinetic Models—Description and Comparison

The 12 population PK models differed in their model structure, the inclusion of covariates, and statistical model component. The 10 two-compartment models and 2 one-compartment models were developed based on human plasma FVIII data measured using CSA (n = 4), OSA (n = 7), or both assays (n = 1). All models accounted for body composition in the form of body weight (n = 8) or fat-free mass (n = 4), while 7 accounted for the patient's age, and 6 implemented a baseline FVIII:C. If more than one FVIII product was used to develop the model (n = 3), the models corrected either the bioavailability or the clearance and central volume of distribution depending on the product. Other covariates (vWF and disease severity) were model-specific (see **Table, Supplemental Digital Content 5**, http://links.lww.com/TDM/A561, which illustrates details of the evaluated population PK models). The statistical component comprised at least 1 interindividual variability term on the clearance, except for the model of Abrantes et al,[24] and on the central volume of distribution. Three models included interoccasion variability between 10 and 41% on the clearance or volume of distribution, an additional intraindividual variability of the respective PK parameter across observed dosing occasions.[38] Regarding the unexplained residual variability (the variability of the measured FVIII:C around the individually predicted PK profile), all but the model of Karafouldiou et al[34] used a combined (n = 6) or additive error submodel (n = 1) with an additive error component above the general target FVIII:C of 1 IU/dL.

The models were compared with a simulated PK profile of a standard patient (body weight, 75 kg; height, 1.7 m; age, 35 years; vWF level, 110%; and receiving 3000 IU of a BDDrFVIII or FLrFVIII product every 3 days), where the outputs varied substantially among the evaluated models. The predicted peak of FVIII:C ranged from 62 IU/dL to 125 IU/dL and was found to be the lowest with the 1-compartment model as reported by Karafoulidou et al[32] and the largest with the model reported by Chelle et al[29] (Fig. 1A) after simulation. As anticipated, the extended half-life (EHLrFVIII) models displayed a milder decline in the profile than the normal half-life models. F1

Within the same model, the PK profiles and resulting TaT for BDDrFVIII and FLrFVIII were identical in both assays, except for the profiles simulated by the models of Abrantes et al,[24] Hazendonk et al,[31] and McEneny-King et al.[33] After BDDrFVIII administration, simulation using the model of Abrantes et al revealed a TaT that was 3.5 hours shorter in the OSA than in CSA, owing to the inclusion of product-dependent bioavailability in the model. With the other 2 models, the TaT using the BDDrFVIII was 8.1 hours (Hazendonk[31]) or 7.1 hours (McEneny-King[33]) shorter than using FLrFVIII, independent of the assay. Given that BDDrFVIII to FLrFVIII differences are mostly found in OSA, which had been solely used to develop the 2 models, both were modified to handle BDDrFVIII, similar to

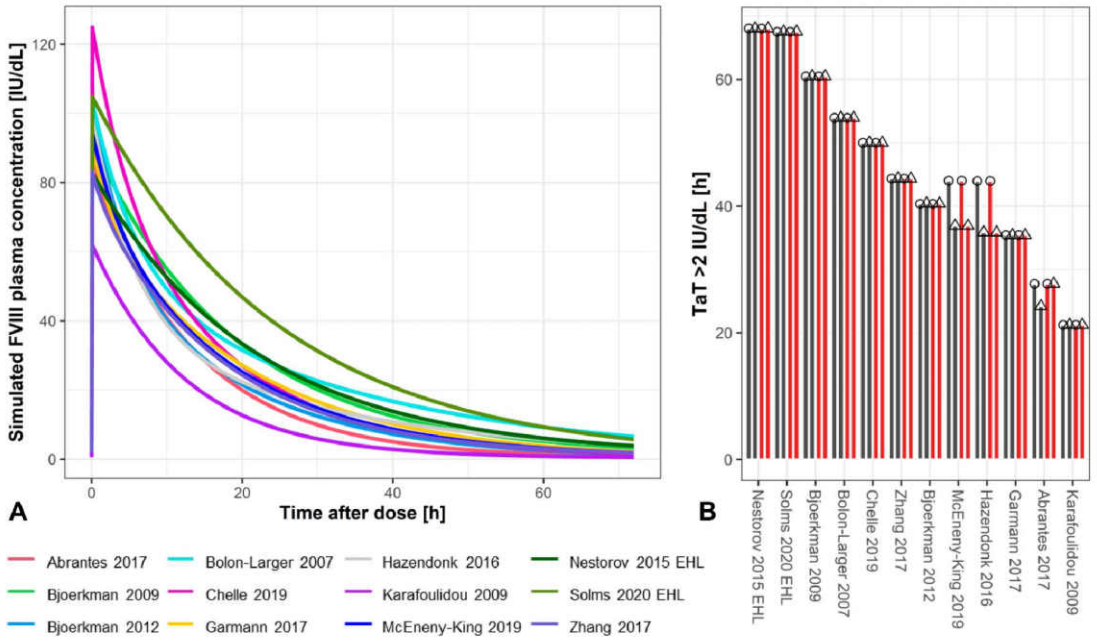

FIGURE 1. A, Simulated FVIII pharmacokinetic profiles at steady state using a chromogenic assay and (B) simulated time above target (TaT) of 2 IU/dL in a standard patient (body weight 75 kg, height 1.7 m, age 35 years, and vWF level of 110%) receiving 3000 IU of either a B-domain deleted (triangles) or full-length recombinant (circles) product every 3 days and measured with the chromogenic (red) and 1-stage assay (gray), respectively, using 12 population pharmacokinetic models of FVIII. When compared with all the models, Abrantes 2017,[24] McEneneny-King 2019,[33] and Hazendonk 2016[31] accounted for the differences in B-domain versus full-length recombinant products.

FLrFVIII, when evaluating the predictive performance of CSA data.

The simulated TaT ranged from 21.2 hours to 60.5 hours and was largest in the EHLrFVIII models (67.5–68.0 hours, Fig. 1B). However, even without considering the EHLrFVIII models, the simulated TaT varied by a factor of 3; the shortest TaT was simulated by the model of Karafoulidou et al[32] and the longest by the model of Björkman et al from 2009.[27]

Evaluation of the Predictive Performance

The individual TaT values were predicted between 27.0 and 168.0 hours, using the baseline covariate models (a priori), and were highly dependent on the model. In comparison with the true TaT obtained from the reference model and all the CSA data (see **Text**, **Supplemental Digital Content 3**, http://links.lww.com/TDM/A559, which explains the development and structure of the reference model), the a priori predictions differed from −80.1 hours to +149.9 hours (−85.1 hours to +149.9 hours in OSA), with 2 patterns being identified (Fig. 2, a priori). The models either overpredicted F2 the TaT independent of the true TaT (eg, models of Björkman, Bolon-Larger, Hazendonk, and Karafoulidou) or overpredicted the TaT in patients with a true TaT smaller than 2 days, while underpredicting patients with a true TaT > 3 days (eg, models of Abrantes, Björkman developed in 2012, Chelle, and McEneney-King). This was reflected in the prediction-corrected visual predictive checks (see **Figure**, **Supplemental Digital Content 6**, http://links.lww.com/TDM/A562, which allows graphical comparison of the prediction intervals of each population PK model), the goodness-of-fit plots (see **Figure**, **Supplemental Digital Content 7**, http://links.lww.com/TDM/A563, which demonstrates the goodness-of-fit of the population PK models), and a mostly positive bias of −3.8 to 49.6 hours (−6.7 to 49.6 hours OSA) and an RMSE of 20.1–61.4 hours (20.1–61.4 hours OSA) across the models. Only the models of Abrantes[24] and Björkman (developed in 2012)[5] fulfilled the acceptance

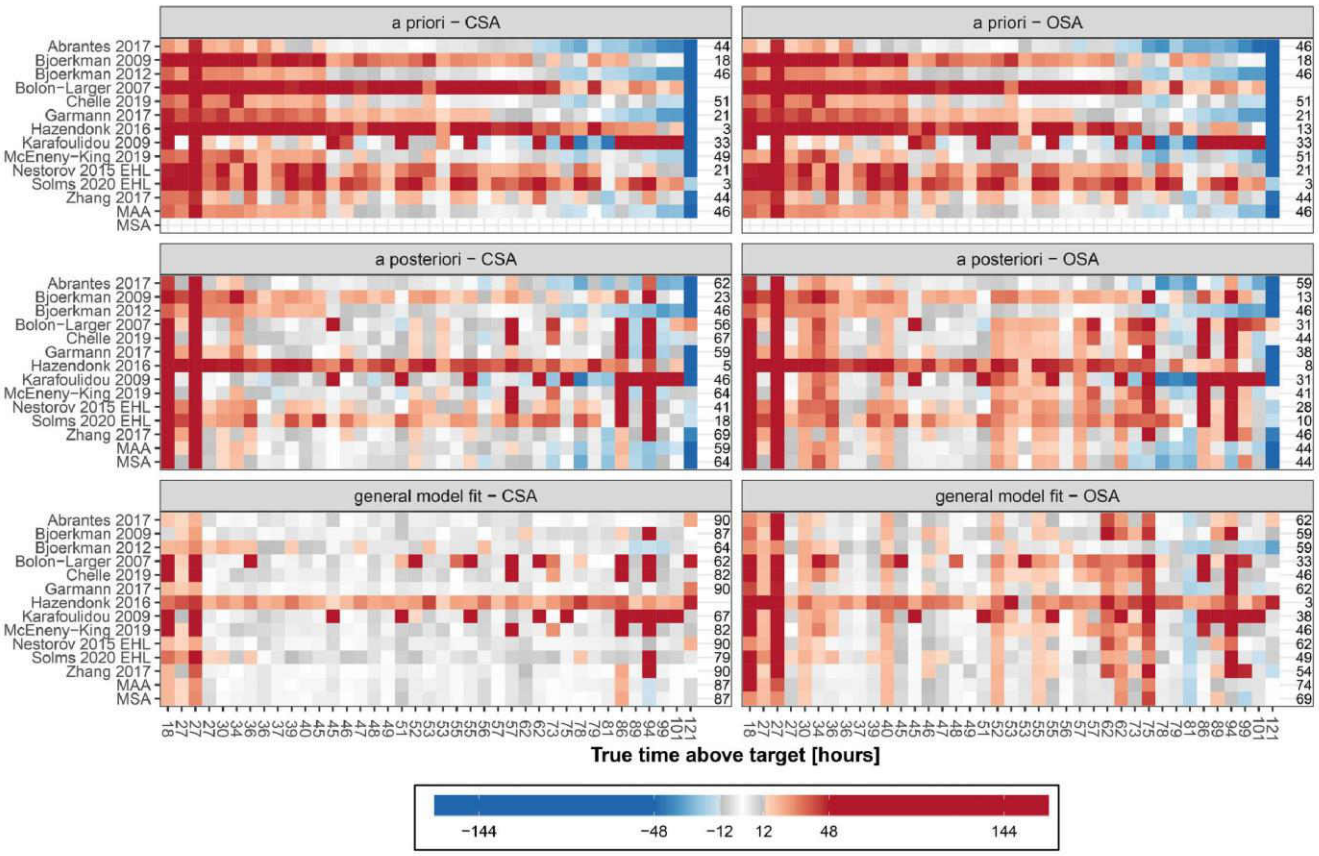

FIGURE 2. Difference of the individually predicted time above target (TaT) of 2 IU/dL to the true TaT (ie, time obtained from the internal reference model and all CSA samples) per model. Each column represents 1 patient with the individual, true TaT displayed on the x-axis. A deviation of less than 12 hours to the true TaT was stained in shades of gray, producing white toward an unbiased prediction. Positive deviations are light red in between 12 and 48 hours and dark red >48 hours; negative deviations are blue in the same scheme. To the right of each panel, the percentage of individual predictions differing less than 12 hours to the true TaT is displayed. The scenarios are a priori prediction using the baseline covariate models, Bayesian forecasting using the FVIII:C trough directly prior dosing (a posteriori), and (*general model fit*) Bayesian estimation using all available samples. No data for MSA in the scenario a priori. CSA, chromogenic substrate assay; MAA, model averaging algorithm; MSA, model selection algorithm.

criteria (bias $< \pm 12$ hours and its 95% confidence interval including 0) with a bias of −3.8 hours (OSA, −6.7 hours) and 3.3 hours (OSA, 3.3 hours), respectively (Fig. 3).

Although the inclusion of the predose trough level in the a posteriori forecast resulted in overall lower bias values between −1.0 and 36.5 hours (−0.5 to 34.7 hours OSA) with an RMSE between 22.4 and 60.7 hours (23.0–62.3 hours OSA), the performance metrics compared with a priori improved in only 50% of the models. The remaining models did not improve significantly (n = 2) or displayed a higher imprecision (n = 4). The models of Abrantes and Björkman (developed in 2012) performed best of all the models, and the percentage of the population with a predicted TaT close to the true TaT (ie, the difference in the predicted to true individual TaT < 12 hours) increased from 44% to 62% in the model of Abrantes and remained at 46% in the model of Björkman developed in 2012 (Fig. 2).

If all CSA data were supplied (ie, *general model fit*), the models, excluding that of Hazendonk, predicted TaT differing less than ±12 hours from the true TaT in 62%–90% of the patients (Fig. 2), while the predictions using OSA data remained worse (33%–74%). The bias ranged from 0.6 to 31.4 hours (RMSE: 7.1–58.3 hours) using CSA data and ranged from 2.6 hours to 37.6 hours (RMSE: 13.9–59.7 hours) using OSA data. The predictions were clinically acceptable with the models of Abrantes,[24] Garmann,[30] and Nestorov[34] using CSA data and Björkman (developed in 2012)[5] using OSA data. Overall, the predictions were usually closer to the true TaT when CSA data were used and were best in the model of Abrantes (bias 0.6 hours).

The candidate models of the multimodel approaches were identified as the 5 models that displayed the best performance metrics (the models of Abrantes, Björkman developed in 2012, Chelle, Garmann, and Zhang).[5,24,26,29,30] These models were then used together, and the best performing model for each patient was selected automatically. In all scenarios, the bias of the 2 algorithms was always below 7.3 hours with a 95% confidence interval including 0 (except in the *general model fit* using OSA data) while the RMSE was between 7.7 hours and 30.5 hours (Fig. 3 and for details see **Figure**, **Supplemental Digital Content 8**, http://links.lww.com/TDM/A564, which demonstrates the accuracy and the imprecision of the predicted time above target of the model averaging algorithm and model selection algorithm and the single models used in both). The MSA selected the models of Abrantes and Zhang in 12–17 and 12–19 patients, respectively (see **Figure**, **Supplemental Digital Content 9**, http://links.lww.com/TDM/A565, which demonstrates the composition of the model selection algorithm within the population). Both algorithms were always in the range of the best single models and resulted in comparable individual TaT predictions, whereas the MAA was slightly better.

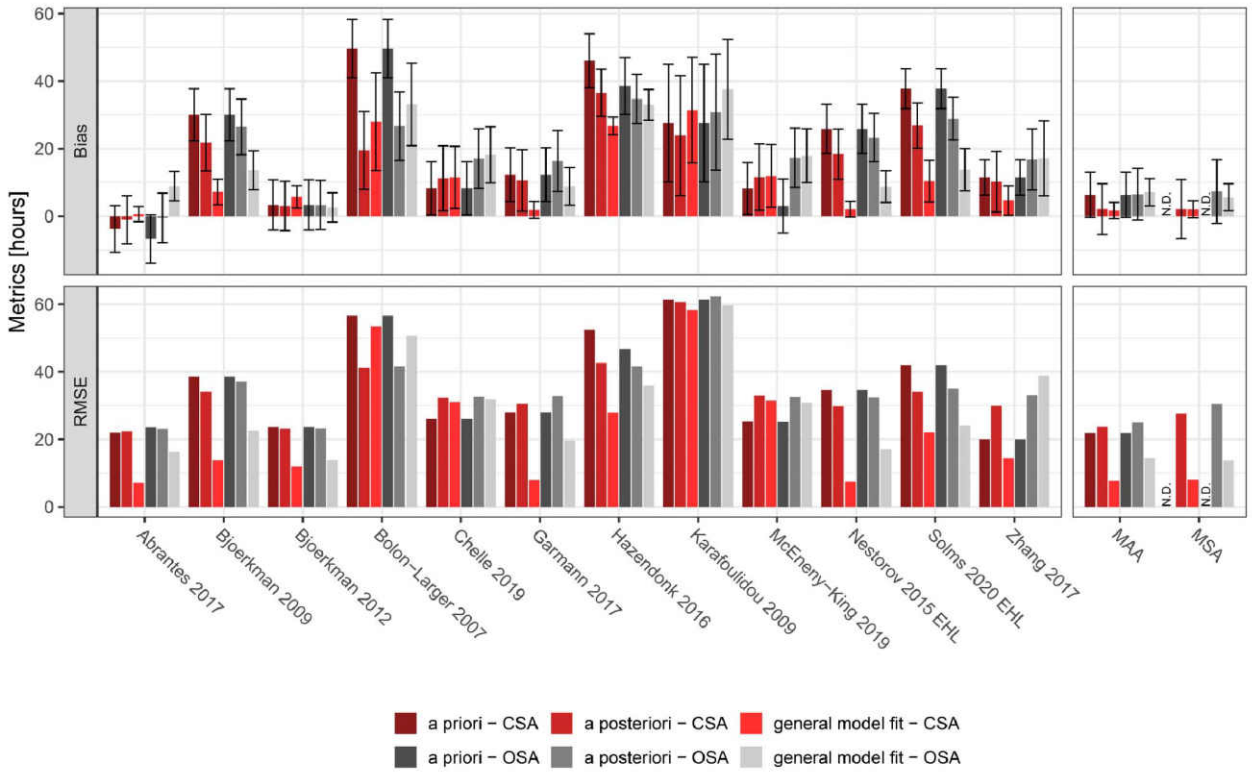

FIGURE 3. Accuracy (bias) and the imprecision (root mean square error, RMSE) of the predicted time above target (TaT) in comparison with the true TaT (ie, time obtained from the internal reference model and all CSA samples) per model and separated by the assay used (chromogenic substrate assay—red and 1-stage assay—gray). The 3 hues represent the forecasting scenarios. Whiskers cover the 95% confidence interval of the bias calculated by using the standard error; N.D., not defined.

Dosing Software "TDMX"

We encoded the best-identified model of Abrantes[24] in TDMx (www.TDMx.eu) and cross-validated it against NONMEM, the gold-standard software for population PK modeling. The model predictions were virtually identical for the population predicted, individually predicted FVIII:C, and the predicted time above the target (see **Figure**, **Supplemental Digital Content 10**, http://links.lww.com/TDM/A566, which demonstrates the agreement of the individual predictions using the model from Abrantes et al in either NONMEM or the MIPD software "TDMx"). The PK profile of a representative patient (24 years, 73 kg body weight, and receiving 2000 IU and 3000 IU Advate) is shown in Figure 4.

DISCUSSION

Our study revealed that the evaluated population PK models highly varied in their structure, parameters, and inclusion of covariates and their corresponding predictions. Independent of true TaT and its length, the models tended to be positively biased. We argue that this misfit has diverse and often multilayered reasons. First, the evaluated models were mostly developed to characterize the PK of FVIII in specific populations, but not for MIPD during therapeutic drug monitoring in more diverse patient groups and using different assay types. For example, the model of Hazendonk was developed to guide dosing during perioperative treatment using 1 of 7 FVIII products. However, the higher target and higher residual unexplained variability seemed to make this model unsuitable for use in the setting of prophylactic treatment, as noted by the authors themselves.[31]

Second, certain model structures result in systematic overpredictions. The evaluated 1-compartmental model,[32] as well as the only model with proportionally implemented interindividual variability,[28] led to substantial overpredictions. Higher TaT was also predicted using the EHLrFVIII models, which in this case seems reasonable, given that the half-life of EHLrFVIII is at least 66% higher.[39] The commonly implemented characteristics, such as age and body mass, were especially useful during the a priori predictions as confirmed by other authors,[40–42] while covariates, such as race or study identifier,[24,31] were not obtained or not applicable in this study.

Third, the size of the data set available during the original model development seemed to affect the predictions, whereas the number of included FVIII drug types did not correlate with the performance. The models with the smallest number of individuals[27,28,32] displayed worse predictive performance and were based on 1 to 8 different FVIII products (see **Figure**, **Supplemental Digital Content 11**, http://links.lww.com/TDM/A567, which demonstrates the predictive performance of the models in relation to the number of patients included during model development). By contrast, the models with the largest data sets[5,24,33] performed the best in bias and RMSE.

In general, the TaT at the patient level was well reflected by the performance metrics but revealed a few nuances, especially in the a posteriori forecasting and *general model fit* (Fig. 2). In the 2 models fulfilling the acceptance criteria in 5 of the 6 scenarios, the TaT predictions (*general model fit*) deviated by more than 12 hours from the true TaT in 14 patients,[5] whereas the similar deviations were observed only in 4 patients in the model of Abrantes[24] (Fig. 2).

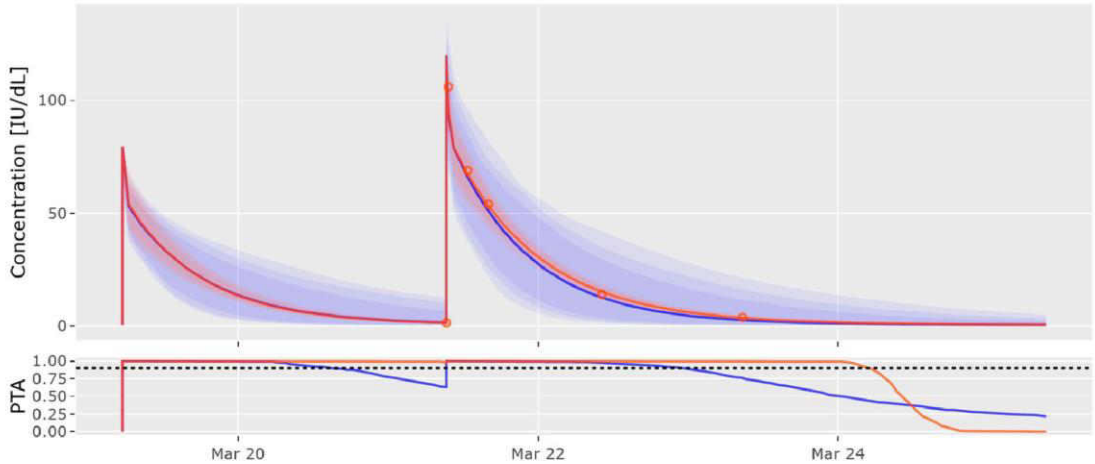

FIGURE 4. Graphical output of the MIPD software TDMx (www.TDMx.eu) with the estimated PK profile (upper panel) and the probability of target attainment (PTA) using a target FVIII concentration of 2 IU/dL (lower panel). The patient (severe hemophilia A, 24 years, 73 kg body weight, and 173-cm body height) was dosed twice with a full-length recombinant product (2000 IU and 3000 IU Advate; Takeda Manufacturing Austria AG, Vienna, Austria). Six FVIII samples (circles between 106 and 3.8 IU/dL) were obtained using the chromogenic assay. The blue line represents the population (a priori) prediction obtained from the baseline covariate models in the upper panel and the therewith calculated PTA in the lower panel, while the orange line represents the individual predictions additionally using the obtained samples in the upper and the respective PTA in the lower panel. The shaded area represents the prediction intervals calculated by using stochastic "Monte-Carlo" simulation (sampled from the matrix detailing the interindividual variability of the PK parameters; n = 500).

Nonetheless, the same 4 patients seemed difficult to be predicted in other well-performing models (eg, Garmann,[30] Nestorov,[34] and Zhang[26]). This might be caused by the influences not being accounted for (eg, genetic defects) or perhaps even sample (time) irregularities that impair the individual model fit.[43] Although the performance metrics of the model of Björkman (developed in 2012)[5] were seemingly consistent with the model of Abrantes,[24] the latter should be preferred in individual forecasting. The few mispredicted TaTs in the latter model tended to be shorter than the true TaT, which might result in a higher FVIII consumption, but not in an increased risk of undertreatment. Furthermore, the performance metrics were misleading in the case of the model of Björkman (developed in 2012) as overpredictions and underpredictions occurred symmetrically across the patients, implying a false high accuracy.

To evaluate the predictive performance, TaT was chosen in favor of pure comparisons of predicted versus observed concentrations, given its clinical relevance and easy interpretation. Prophylactic treatment aims to prevent spontaneous bleeding by ensuring that FVIII trough levels in patients are above 1 IU/dL (in the same range as a patient with moderate hemophilia A).[44] Nonetheless, the targeted threshold was set to 2 IU/dL for 2 main reasons. (1) To ensure a certain time buffer where the patient remains above the intended threshold and (2) to reduce the influence of the samples, which is at the lower limit of quantification. The acceptance criteria of the model performance were set to $\pm$12 hours because prophylactic treatment is dosed at day-to-day intervals, and the risk of changing the decision to dose on a subsequent day might be minimized with a bias of less than half a day.

With the multimodel approaches (MAA and MSA),[22] we aimed to combine the collective knowledge of multiple FVIII population PK studies using a different approach than that intended by the generic population PK model developed by McEneny-King et al.[33] The authors used an approach to pool data from heterogeneous sources, which has also been successfully applied in other fields.[45,46] However, our automatic averaging/selection from the set of models performed superior to the generic model throughout the scenarios (Fig. 3). This might be due to the ability of the multimodel approaches to describe atypical patients, which do not match the rest of the studied population. Nonetheless, the algorithms did not outperform the best single model[24] but were ranked second. Given that the single models tended to display a positive bias, the algorithms mainly had 1 direction to approach the individual PK curve. Future studies comparing the performance of "pooled-data" versus "pooled-model" approaches and different sets of heterogeneous models would be of interest.

A few limitations of this study need to be mentioned. The data set contained less than 40 individuals receiving 1 of 6 FVIII drugs. Such heterogeneous data might not be sufficient to develop a new model yet might serve as an external validation set according to FDA criteria because its size was—with 2 exceptions—always more than 15%[47] of the size of the original model development data. Nonetheless, we recommend further external validation to extrapolate our findings to pediatric populations, patients receiving EHLrFVIII products, and moderate to mild hemophilia A patients. Furthermore, it is questionable whether only 1 trough sample, directly preceding the next dose, is sufficient during MIPD, especially because the clinically intended target threshold is close to the lower limit of quantification. Nonetheless, as previously reported, limited PK information is better than none[48]; this minimized trough sampling scheme used in this study can be easily used to transition from simple trough-based dose adjustments to model-guided precision dosing.

CONCLUSIONS

Throughout the model analysis, predictions using CSA data were more accurate than those using OSA data. This fact and the substantial assay errors of up to 35% for OSA[49,50] and phenotype-corresponding discrepancies between the 2 assays[20,21] indicate that the CSA should be preferred in model-informed precision dose calculations. Our systematic model comparison identified that Abrantes model[24] performs best in the adult population included in this study under the tested scenarios. The implementation of this model in an open-access MIPD software (TDMx) might provide another step forward to improve individualized treatment of patients with hemophilia A using BDDrFVIII and FLrFVIII products.

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3.2 Publication II

Model-Informed Precision Dosing of Vancomycin via Continuous Infusion: A Clinical Fit-For-Purpose Evaluation of Published PK Models

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Synopsis

When treating severe infections with last resort antibiotics like vancomycin, the patient is usually balancing on a fine line between life and death. Subtherapeutic exposure levels are as dangerous as supratherapeutic levels, given its risk to develop AMR and lack of bacterial eradication or drug-induced adverse effects, respectively. Hence, tailoring individual vancomycin dosing according to the individual target (i.e. the AUC over MIC) is crucial to improve treatment outcome. The individual AUC can be determined using population PK models implemented in MIPD software. Yet, this requires externally validated models suitable for the intended purpose.

We hypothesize that the selection of the model is dependent on the population of interest and the mode of drug administration. Therefore, we systematically compare 23 models in forecasting vancomycin drug exposure with different levels of individual data (e.g. covariates only or covariates plus a single TDM measurement).

In Publication II, we identified the two-compartmental models of Okada *et al.*[5] and Colin *et al.*[6] as most suitable for non-intensive care unit patients to forecast individual exposures after continuous vancomycin infusion. In fact, different models were identified as compared to previous systematic model comparisons for hospitalized patients receiving intermittent vancomycin infusion.[54], [83]

Thus, caution is required when transferring these results to other populations and reveal the need of more sophisticated approaches as for example introduced in Publication III.

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Model-informed precision dosing of vancomycin via continuous infusion: a clinical fit-for-purpose evaluation of published PK models

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ABSTRACT

Background: Model-informed precision dosing is an innovative approach used to guide bedside vancomycin dosing. The use of Bayesian software requires suitable and externally validated population pharmacokinetic (popPK) models.
Objectives: This study aimed to identify suitable popPK models for a priori prediction and a posteriori forecasting of vancomycin in continuous infusion. Additionally, model averaging (MAA) and model selection approach (MSA) were compared with the identified popPK models.
Methods: Clinical pharmacokinetic data were retrospectively collected from patients receiving continuous vancomycin therapy and admitted to a general ward of three large Belgian hospitals. The predictive performance of the popPK models, identified in a systematic literature search, as well as the MAA/MSA were evaluated for the a priori and a posteriori scenarios using bias, root mean square errors, normalised prediction distribution errors and visual predictive checks.
Results: The predictive performance of 23 popPK models was evaluated based on clinical data from 169 patients and 923 therapeutic drug monitoring samples. Overall, the best predictive performance was found using the Okada et al. model (bias < –0.1 mg/L) followed by the Colin et al. model. The MAA/MSA predicted with a constantly high precision and low inaccuracy and were clinically acceptable in the Bayesian forecasting.
Conclusion: This study identified the two-compartmental models of Okada et al. and Colin et al. as most suitable for non-ICU patients to forecast individual exposure profiles after continuous vancomycin infusion. The MAA/MSA performed equally as well as the individual popPK models; therefore, both approaches could be used in clinical practice to guide dosing decisions.

1. Introduction

Vancomycin, a glycopeptide antibiotic, is one of the most commonly used broad-spectrum antibiotics for treatment of severe systemic infections caused by Gram-positive bacteria such as *Streptococcus* spp., *Enterococcus* spp. and *Staphylococcus* spp., including methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. The efficacy of vancomycin has been correlated with the pharmacokinetics/pharmacodynamics (PK/PD) index of the area under the concentration-time curve (AUC) divided by the MIC of the suspected pathogen (AUC/MIC) [2].

Single-point concentrations are currently monitored as a surrogate parameter for the target AUC/MIC. Trough concentrations of 15–20 mg/L for serious infections due to MRSA have previously been recommended for intermittent dosing, and concentrations of 20–25 mg/L during assumed steady-state conditions for continuous dosing regimens [2]. However, recent studies have demonstrated that the use of a single-point concentration may not be an optimal approach for predicting overall drug exposure [3]. The most accurate way to guide vancomycin dosing should be through AUC-guided dosing and monitoring. According to the revised consen-

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sus guideline on therapeutic drug monitoring (TDM) of vancomycin in patients with MRSA infections, AUC values should be maintained between 400–600 mg.h/L to maximise efficacy (assuming an MIC of 1 mg/L) and minimise the likelihood of nephrotoxicity [2]. Bayesian forecasting software programs, based on a population pharmacokinetic model (popPK model), might be useful for AUC-based dosing. This approach, also known as model-informed precision dosing, can be used in clinical practice to improve the efficacy of antibiotic treatment [4]. Bayesian forecasting software can either be used a priori (i.e., without TDM) to determine the most optimal starting dose of vancomycin, or a posteriori (i.e., in combination with one or more observed TDM measurements) to perform dose optimisation based on the specific PK profile of an individual patient [5].

The use of Bayesian software requires a suitable popPK model that characterises vancomycin exposure in the intended patient population and information on patient-specific covariates known to impact PK parameters (e.g., age, gender, weight and kidney function) [6]. Ideally, a popPK model is externally validated to determine its predictive performance before it is used in the clinic to guide vancomycin dosing [1]. This requirement was reinforced by a recent systematic model evaluation study using clinical data from intermittent infusion, where the investigated models displayed a heterogenous predictive performance [7]. As many institutions are moving towards continuous vancomycin infusion [8], this study aimed to identify suitable popPK models for a non-intensive care unit (non-ICU) patient population treated with vancomycin in continuous infusion. Additionally, a model averaging approach (MAA) and model selection approach (MSA) were evaluated to determine its performance for a priori prediction and a posteriori forecasting compared with the identified popPK models.

2. Material and Methods

2.1. Ethics

The research was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Ghent University Hospital (EC/2019/1670), AZ Sint-Jan Brugge (2505) and OLV Aalst (2019/109).

2.2. Clinical data

Clinical PK data were retrospectively collected from patients under continuous vancomycin therapy and admitted to a general (internal or surgical) non-ICU ward of one academic and two non-academic large Belgian hospitals (Ghent University Hospital, AZ Sint-Jan Brugge and OLV Aalst) during the period of January 2017 to December 2019. Patients were excluded if they underwent dialysis or extracorporeal membrane oxygenation. In detail, the following data were documented from patients undergoing TDM: the time and amount of vancomycin TDM measurements; the respective doses and rates; patient age, gender, weight and height; and serum creatinine concentration. Data below the lower limit of quantification (4 mg/L; $n = 1$) were excluded. Treatment with vancomycin was started with a loading dose (median 20.7 mg/kg, range 13.4–26.5 mg/kg), irrespective of the patient's renal function, immediately followed by a continuous infusion (dependent on renal function). Maintenance doses were adjusted according to local hospital TDM guidelines to achieve a target steady-state concentration range of 20–25 mg/L. In case of severe infection or risk of compromised tissue penetration, target concentrations up to 30 mg/L were used.

2.3. Selection of the population PK models

A systematic literature search in PubMed was performed to identify popPK models of vancomycin in adults using the following MeSH terms: 'pharmaco-kinetics', 'vancomycin' and 'population model'. Models were selected for evaluation if the following three criteria were met: (i) the model was published between January 2010 and March 2019; (ii) the PK model was based on data from at least 25 individuals; and (iii) a parametric approach for model building was applied.

2.4. Evaluation of the models

All models were encoded and processed in NONMEM® (Version 7.4.3; ICON plc, Dublin, Ireland). The models were systematically compared in their structure, population used to develop the model, predictive performance using patient demographics and individual dosing information, and different quantities of pre-existing vancomycin TDM measurements.

In the a priori scenario, predictions were based on the typical population estimates of the model and all available patient covariate and dosing information without consideration of the individual TDM measurements.

To quantify how time since TDM measurement and number of TDM measurements impact the performance of the models, three patient-individual a posteriori forecasting scenarios were tested. In these scenarios, an occasion was defined as the period between two infusion rate changes with at least one vancomycin measurement being available. The TDM measurement from the most recent, an older occasion or both occasions were used to forecast the observed TDM measurement of a third (i.e., future) occasion. The third occasion was chosen because fewer than 50 patients had more than three occasions recorded.

In the scenario 'general model fit', all available TDM measurements from each patient were used to reveal the maximum performance of models. The residuals of the predicted to the observed vancomycin concentrations were compared for all TDM results. If a covariate was not present in the dataset, the typical population value was imputed (i.e., standard level of albumin was assumed in the Alqahtani [9] and Revilla [10] models; and of cystatin C in the Chung et al. [11] and Tanaka et al. [12] models), while categorical covariates were assumed to be absent (i.e., no patient was assumed to be neutropenic (Bury et al. [13], clearance would otherwise decrease by 25%), diabetic (Mangin et al. [14], intercompartmental clearance would otherwise decrease by 70%), under co-administration of furosemide (Medellin-Garibay et al. [15], clearance would otherwise decrease by 31%)). This followed the clinical assumption that a covariate of relevance would have been documented in case of presence.

The predictive performance was quantified by the bias (Eq. 1) as a measure of accuracy and the root mean square error (RMSE, Eq. 2) to quantify the precision of the model prediction under the scenarios outlined above.

$$Bias = \frac{1}{n} \times \sum_{1}^{i} (predicted_i - observed_i) \quad (1)$$

$$RMSE = \sqrt{\frac{1}{n} \times \sum_{1}^{i} \left((predicted_i - observed_i)^2 \right)} \quad (2)$$

with n being the number of total concentrations in the evaluated scenario. The 95% CIs were calculated to statistically compare the models as proposed by Beal et al. [16].

Given the currently accepted vancomycin target concentrations during continuous infusion (i.e., steady state concentration of 20–25 mg/L, if MIC $\leq$ 1 mg/L) [17], a bias of $<$ 2.5 mg/L was defined

Table 1
Demographic and clinical characteristics and therapeutic drug monitoring (TDM) data of the study population (n = 169 patients).

Characteristic	Median (range)
Age, years	63 (17–93)
Weight, kg	70 (39.1–140)
Height, cm	168 (127–196)
Baseline serum creatinine concentration, mg/dL	0.75 (0.28–2.74)
	N patients/samples (%)
Patients with 1 treatment episode	157
Patients with 2 treatment episodes	11
Patients with 3 treatment episodes	1
Gender	
Male	86 (50.9)
Female	83 (49.1)
Patients with haematological malignancies	55 (32.5)
TDM samples	923
Treatment episodes with 1 sample	25 (13.8)
Treatment episodes with 2–5 samples	92 (50.8)
Treatment episodes with > 5 samples	64 (35.4)
Samples within 24 h after start treatment	90 (9.8)
Samples between 24–48 h after start of treatment	141 (15.3)
Samples between 48–72 h after start of treatment	113 (12.2)
Samples between 72–96 h after start of treatment	98 (10.6)
Samples between 96–120 h after start of treatment	81 (8.8)
Samples > 120 h of treatment	400 (43.3)

as clinically acceptable, if the confidence interval included 0. Additionally, the precision value should be as low as possible.

The models were further evaluated using normalised prediction distribution errors (NPDE) and prediction corrected visual predictive checks to evaluate the typical population predictions and identify structural misspecifications [18,19]. All data evaluation was computed using R® (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria).

2.5. Model averaging and model selection algorithms

The models were compared with two algorithms – MSA and MAA – which have recently been developed and implemented in a web-accessible Bayesian forecasting tool named TDMx [20]. The algorithm either automatically selects the most suitable model for an individual patient among a set of candidate models (MSA), or averages the predictions of all candidate models proportionally weighted to their retrospective model fit (MAA) [21]. The set was based on six models being developed in distinct populations [10,14,15,22–24].

3. Results

3.1. Clinical data

A total of 923 TDM measurements were retrospectively collected from 169 hospitalised patients who received continuous vancomycin: 50.8% of patients had 2–5 vancomycin observations, while 13.8% were documented with one single observation (Table 1). Vancomycin concentrations were measured with intra-run and between-run accuracy < 10.5 CV% for all concentration ranges, using the immunoassays Architect I 2000sr, Abott at Ghent University Hospital, Cobas c702, Roche Diagnostics at General Hospital Sint-Jan Brugge-Oostende AV and Cobas Proc503 at General hospital OLV Aalst. Demographic and clinical characteristics and TDM data of the study population can be found in Table 1.

3.2. Population PK models

The 23 identified population PK models differed in their underlying patient population, number of patients included for model building, and in their structure (Supplementary Table) [9–15,23–38]. All but the Udy model [35] had a renal function estimator in their covariate model on clearance (19 models included estimated creatinine clearance, three serum creatinine concentration), 17 models included body weight as covariate on central volume of distribution and seven included patient age on either parameter. Continuous infusion PK data were used to develop seven of the 23 models [10,14,24,28,31,35,38], while the others were purely based on intermittent infused vancomycin data.

3.3. Evaluation of the models

The performance of the models predicting individual plasma concentrations based on the covariates and dosing information only (a priori) resulted in bias values between –10.4 and 16.8 mg/L, while the RMSE ranged 7.0–22.3 mg/L (Figure 1). Three models (Bae et al. [37], Colin et al. [38] and Okada et al. [32]) fulfilled the acceptance criteria (bias < ± 2.5 mg and 95% CI included 0) in this scenario (bias < –0.2 mg/L and RMSE of 6.5 mg/L, 6.8 mg/L and 6.8 mg/L, respectively; Supplementary Figure 1). The a priori performance was also reflected by the prediction corrected visual predictive checks (Supplementary Figure 2). The best visual predictive checks were displayed by the models from Bae et al., Colin et al., Dolton et al., Medellin-Garibay et al., Okada et al. and Purwonugroho et al. (Figure 2) [15,26,32,33,37,38]. Despite the general trend of the data being adequately simulated in the above-mentioned models, the magnitude of variability was simulated too high in the Bae et al. and Purwonugroho et al. models [33,37].

In the a posteriori forecasting scenarios, the inclusion of TDM measurements generally led to improved accuracy and precision in comparison with the predictions from the a priori scenario. Across all models, the bias (and RMSE) varied from –6.1 to 11.3 mg/L (RMSE: 4.5–18.1 mg/L) using data from one and between –4.5 and 7.9 mg/L (RMSE: 4.6–14.9 mg/L) using data from two pre-existing occasions, respectively. In general, the inclusion of more recent samples (median time between samples from the most recent occasion to the first sample from the forecasted occasion: 44.1 hours, interquartile range 24.0–72.6 hours) in relation to the forecasted concentration was more beneficial than the inclusion of a higher number of samples (median time between samples from the first two occasions and first sample of forecasted occasion: 49.8hours, interquartile range 44.4–96.2 hours). This finding was reflected in a higher precision (RMSE one occasion versus two occasions versus most recent occasion: 5.6 mg/L, 4.5 mg/L, 4.4 mg/L, respectively) with bias being comparable (median bias [range]: –0.3 mg/L [–6.1 to 11.0 mg/L], –0.2 mg/L [–4.6 to 11.3 mg/L], –0.4 mg/L [–4.5 to 7.3 mg/L], respectively).

Estimating the individual PK parameters based on all recorded data (i.e., general model-fit) the bias in comparison with the a priori predictions improved between 1.2-fold and 135-fold (to values between –1.4 and 5.8 mg/L) with RMSE values < 5 mg/L in all but the Usman [36] model. Bias exceeded ± 1.5 mg/L in none of the other models, but the corresponding 95% CI included 0 in eight of them. The lowest bias and imprecision in the a priori and general model-fit scenarios were displayed by the Okada et al., Colin et al. and Bae et al. models [32,37,38]. Small nuances in the normalised prediction distribution errors (Figure 3 and Supplementary Figure 3) were found to not be statistically significant when comparing the 95% CIs of the RMSE, as proposed by Beal et al. [16] (i.e., the CIs of the models overlapped in the respective scenarios; Supplementary Figure 1). All three models were two-compartmental models and accounted for at least renal function on clearance (via estimated or measured creatinine clearance or serum creatinine concentration) and body weight on volume of distribution. While the clearance and the total volume of distribution in a standard patient was comparable for these three models (2.8–4.28 L/h, 90.7–107.2

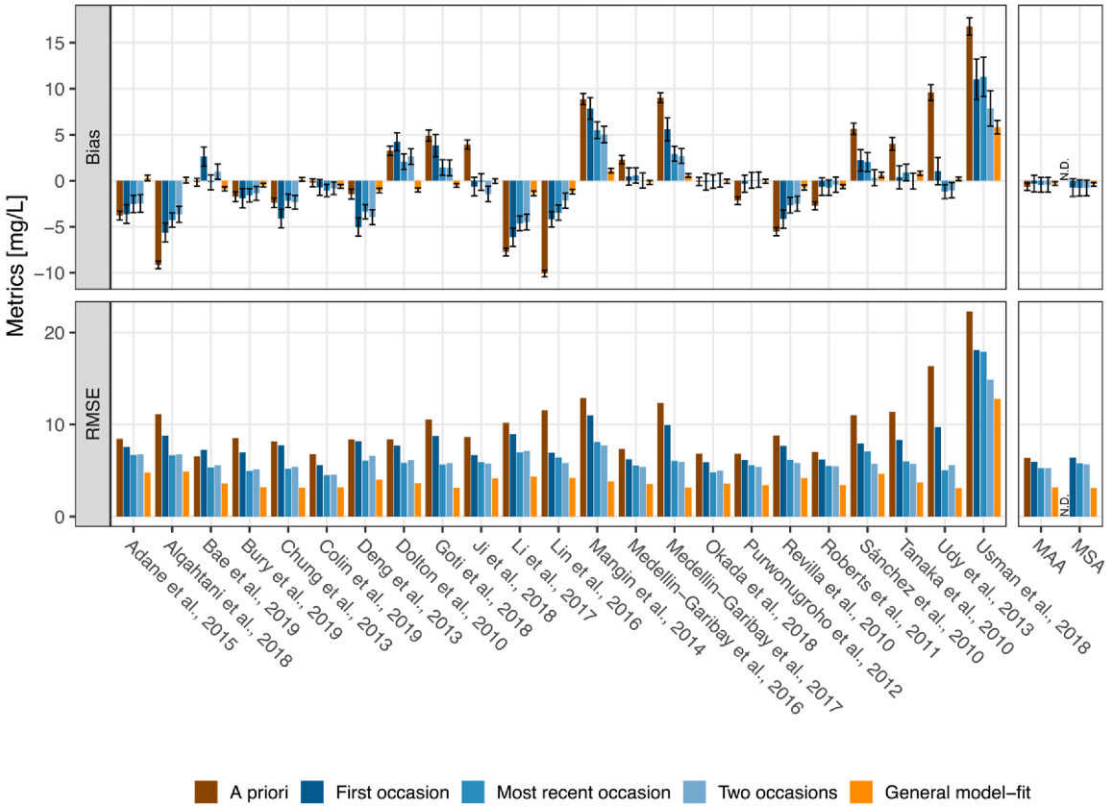

Figure 1. Bias and root mean square error (RMSE) of the predictions from the individual population PK models (left panels) and the two multi-model algorithms on the right (i.e., model averaging (MAA) and model selection (MSA)) per scenario. Either all available observations were predicted using covariate dosing information with (general model-fit, orange) or without (a priori, brown) supplying individual vancomycin observations. The blue bars represent the metrics in a posteriori forecasting using observations from one occasion (i.e., the first or most recent) or two occasions to forecast the hidden vancomycin concentration from the subsequent occasion. Error bars represent the 95% CI based on the standard error. N.D. = not defined

L, respectively), the intercompartmental clearance varied six-fold (1.95–11.7 L/h) (Supplementary Table).

The best models identified via the prediction corrected visual predictive checks also performed best in the a posteriori forecasting (except for the Bae et al. model [37]). Overall, the best predictive performance was displayed by the model from Okada et al. [32], which had no bias (i.e., < −0.1 mg/L) in any scenario paired with an imprecision being constantly low (i.e., second best in a posteriori forecasting) and was followed by the model from Colin et al. [38]. The Colin et al. model [38] predicted the most precisely and displayed a bias of below −1.1 mg/L in all scenarios. Due to the high precision, the narrow 95% CI of the bias missed 0 in the forecasting scenarios based on the most recent occasion and two occasions.

The multi-model approaches MAA and MSA predicted with a constantly high precision and low inaccuracy (Supplementary Figure 4). Comparing both algorithms amongst each other, neither was statistically superior to the other, given the 95% CI of the bias and RMSE overlapped in all scenarios (Supplementary Figure 1). Nonetheless, the precision of the MAA was better than 21 of the 23 models across all scenarios and < 15% higher than the RMSE of the two best single models. The MAA and MSA were clinically acceptable in the a posteriori forecasting and their performance metrics were in the same range of the Okada et al. model [32].

4. Discussion

It is believed that this is the first study in which an external evaluation of popPK models was performed based on vancomycin PK data from continuous infusion. The models from Okada et al. [32] and Colin et al. [38] showed the best predictive performance. Both models predicted vancomycin plasma concentrations with a clinically acceptable bias and imprecision in the a priori setting and all a posteriori scenarios. Model performance metrics generally improved under a posteriori forecasting compared with a priori. This is consistent with several other recent studies in which accuracy and precision of the model predictions improved by including measured vancomycin concentrations in addition to dosing and covariate information [7,39,40]. Within the a posteriori scenario, model performance metrics based on the most recent vancomycin concentration were superior to the metrics based on a higher number of samples. This may be related to the long duration of vancomycin treatment, which means that older data were used during model validation.

Accuracy of model predictions depends on a number of factors, of which the similarity in patient characteristics between the model building dataset and external evaluation dataset is key, amongst similarities in measured concentration range and timing of samples, and similarities in type of bioassays for vancomycin (and covariates). Interestingly, the models from Okada et al. [32] and Colin et al. [38] considerably differ in both patient population and study design. The Colin et al. model [38] is a pooled popPK model based on a large amount of patient data (n = 2554) from 14 different studies. It includes data of vancomycin, administered by continuous and intermittent infusion, from a large variety of patients from premature neonates to healthy volunteers to critically ill patients. As also stated by Broeker et al. [7], these results show the usefulness of a large database of heterogeneous

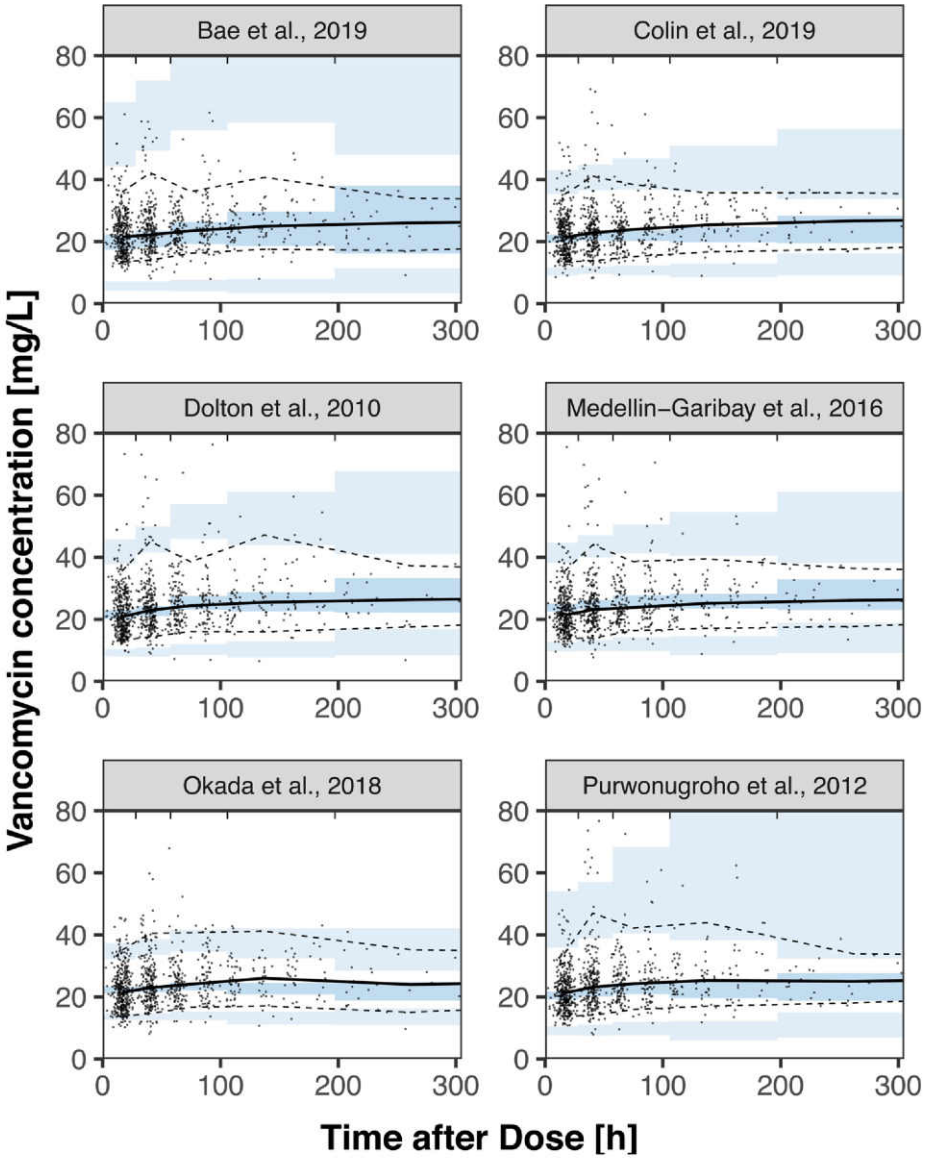

Figure 2. Prediction corrected visual predictive checks of the best six models. The black solid and dashed line represents the median of the observed data (black dots) and its 5^{th}/95^{th} quantiles, respectively. The blue, shaded areas represent the 90% CI of the 5^{th}, 95^{th} (light) and 50^{th} (dark) quantiles of the simulations (n = 1000).

patients to develop a predictive model that adequately describes the PKs of vancomycin in a general and stable patient population. On the contrary, the Okada et al. model [32] was developed in 95 Asian patients undergoing allogeneic haematopoietic stem-cell transplantation. It could only be speculated why this model performed with high prediction accuracy. Augmented renal clearance of vancomycin has previously been reported in haemo-oncology patients [41]. However, in the Okada et al. study, the estimates for vancomycin clearance did not differ from reported clearance values in other populations [26]. This reasoning is also in accordance with the current stratified analysis, in which no difference in model performance could be detected for patients with or without haematological malignancies (Supplementary Figure 5). It was hypothesised that this similarity in patient PK behaviour is amongst the reasons why this model performed well in the current (more heterogeneous) patient population. It is believed that race has never been described as a clinically significant covariate on vancomycin disposition.

Although data of continuous vancomycin infusion was used in the current study, the Okada et al. model [32] was developed using data of vancomycin administered during intermittent infusion. Furthermore, of the three models with lowest bias and imprecision, only the Colin et al. model [38] was developed using a mix of vancomycin data collected in patients on continuous infusion and receiving intermittent dosing. Models purely based on data from continuous infusion were not found to be better than the other models. With the exception of Colin et al., these models performed rather at the lower end – especially a priori. This can also be observed for the two models from Medellin-Garibay et al. [15,31]: although they developed a model based on data from continuous infusion in 2017 [31], the 2016 model [15] based on data from intermittent infusion performed better. These results are similar to the study by Guo et al. [39], in which the model by Roberts et al. [42], developed with vancomycin data collected during continuous infusion, sufficiently performed with data collected during intermittent dosing. This finding indicates that the mode of administration on

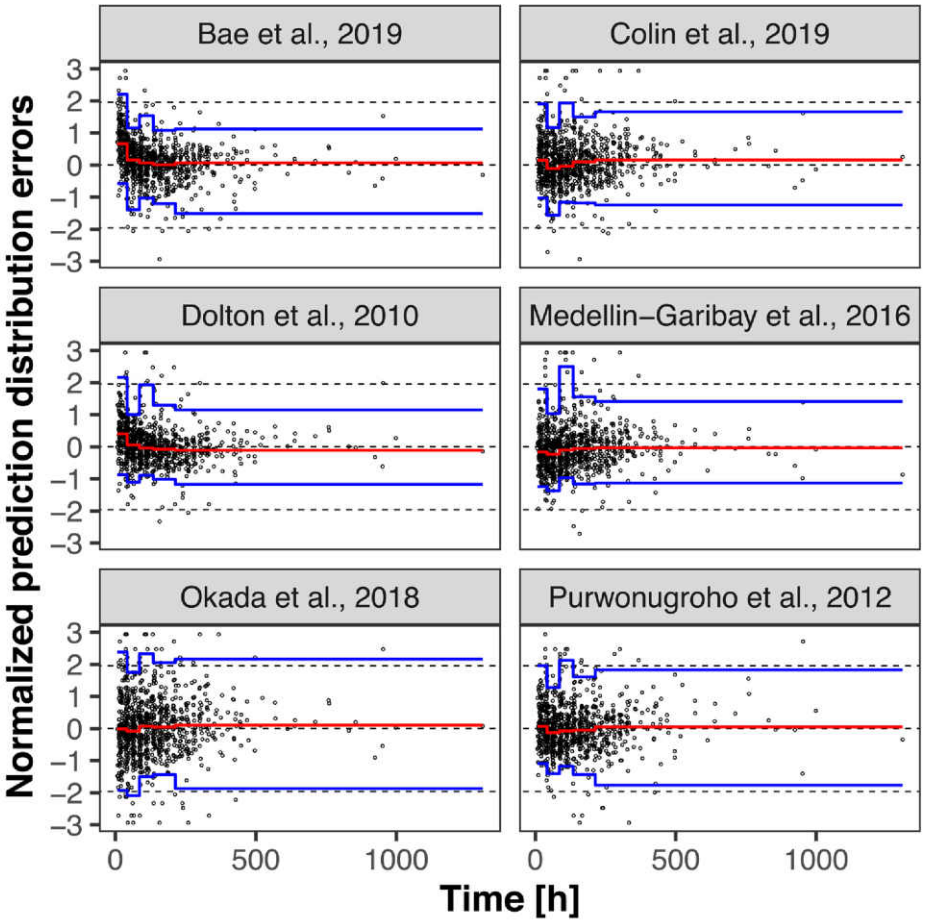

Figure 3. Normalised prediction distribution errors of the best six PK models based on the forecasting metrics. If the model adequately described the data, NPDEs display a normal distribution. Therefore, the NPDEs using all available observations were calculated (black dots). The blue and red lines represent 2.5th, 97.5th and 50th quantiles of the NPDEs over the treatment time, respectively, and should ideally overlap with the dotted lines (i.e., the approximate values for the 2.5th, 50th and 97.5th quantiles of the standard normal distributions).

which the model is based is not the main selection criterion for model-informed precision dosing of vancomycin. However, as also stated by Guo et al. [39], model predictive performance can still be affected by mode of administration and should always be evaluated. Broeker et al. [7] performed a similar evaluation of various popPK models using PK data following intermittent infused vancomycin. In this study, the model from Goti et al. [27] was considered the most suitable model to support model-based dosing. Similar to the model from Colin et al. [38], it is a model based on a large patient database (n = 1812). Remarkably, the model from Goti et al. [27] did not perform well in this study. The predictions by Goti et al. [27] show an overall high imprecision and overprediction of high plasma concentrations. Besides differences in mode of administration, variation in assay methods for vancomycin and serum creatinine could provide an explanation for this discrepancy with the Broeker et al. study results [7]. Since detailed study information on bio-analysis of both components was lacking and the current study included a pooled PK model, these study characteristics could not be evaluated in the current study. Therefore, it is essential to either externally validate popPK models or at least rely on a set of models (i.e., MAA/MSA) before using them in Bayesian forecasting.

Model performance was evaluated by using both numerical and graphical performance diagnostics. The choice of the criteria used for model validation is subjective and can vary among different studies. This study defined the clinical acceptability threshold for bias as 2.5 mg/L, which is derived from practical considerations when vancomycin is administered in continuous infusion. Given the recommended local targets of vancomycin concentrations during continuous infusion in patients with MRSA infections (i.e., 20–25 mg/L), a difference between the model-predicted and observed concentrations of ca. 10% would not result in a dose adjustment when the actual concentration is 22.5 mg/L. Bias was therefore considered most clinically relevant when it exceeded 2.5 mg/L.

The dataset used in this study was based on clinical data from a non-ICU adult patient population. Results are therefore only applicable to this general patient population and not transferrable to a specific patient population such as ICU patients or those on haemodialysis. The imputation of the less common covariates (e.g. neutropenia status for the Bury et al. model [13]) could improve predictive performance in a special (e.g. neutropenic) subpopulation and should be externally evaluated in further studies. Another limitation of this study was the manner of data collection from patient registers. A retrospective data collection can cause bias by random error, even if the data were inspected before model validation. Finally, the literature review, performed in March 2019, implied that several new models after this date were not included in this study.

In conclusion, this study identified the Okada et al. model [32], followed by the Colin et al. model [38] as most suitable for a non-

ICU patient population treated with vancomycin by continuous infusion. The multi-model approaches performed as equally well as the two popPK models. Given that a superior performance of either one was not observed, the implementation of a single popPK model might be slightly easier. Nonetheless, both approaches could be used in clinical practice to determine initial vancomycin dosing regimens and to guide dosing decisions according to measured vancomycin concentrations – especially if already implemented in accessible web-tools (e.g., TDMx). Model performance improved by using the most recent plasma concentration measurements compared with using more plasma concentration measurements. Future prospective research is needed to determine whether these identified PK models can generate accurate dosing recommendations to achieve target exposure.

Declarations

Funding: The authors have no funding to declare.

Competing Interests: The non-commercial web-tool TDMx has been created and is maintained by SGW. He has no financial benefit from this analysis.

Ethical Approval: The study was approved by the Ethics Committee of the Ghent University Hospital (EC/2019/1670), AZ Sint-Jan Brugge (2505) and OLV Aalst (2019/109).

Sequence Information: Not applicable.

Author Contributions: AH and DWU contributed equally to the manuscript. AH and PADC drafted the study protocol, performed the study and obtained the data. DWU and SGW performed the pharmacometric analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2022.106579.

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3.3 Publication III

A Model Averaging/Selection Approach Improves the Predictive Performance of Model-Informed Precision Dosing: Vancomycin as a Case Study

David W. Uster, Sophie L. Stocker, Jane E. Carland, Jonathan Brett, Deborah J.E. Marriott, Richard O. Day, Sebastian G. Wicha

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Synopsis

Variability in drug-response relationships between or even within individuals may lead to insufficient clinical effects and/or significant adverse effects. Especially in severe infections a rapidly induced, maximally precise antibiosis is vital to save lives. Forecasting drug exposures using pharmacometric models can improve individual target attainment when compared to TDM. However, yielding the maximal outcome of this MIPD requires the 'correct' model to be used for the individual, respectively.

In Publication III, we derived and evaluated a model selection algorithm (MSA) and a model averaging algorithm (MAA) using Gram-positive infected patients receiving vancomycin treatment as a case example. These algorithms automate model selection and find the best model or combination of models for each patient.

The concept of using multiple models at once was proven in a simulation study of six distinct populations, as well as in a clinical dataset of 180 patients undergoing TDM. Both algorithms outperformed the model of Goti *et al*.[84] (previously being identified best for Bayesian forecasting of a heterogenous population[54]) in terms of bias and precision.

While six distinct models included in the multi-model approaches resulted in the best predictive performance, the exclusion of up to three models resulted in minor decreases of the performance.

We concluded that the objective selection of a model/set of models is critical to cover atypical patients otherwise being mis-specified. Both algorithms were implemented into the MIPD-software 'TDMx' to lower the burden of adequate model selection and validation for MIPD.

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A Model Averaging/Selection Approach Improves the Predictive Performance of Model-Informed Precision Dosing: Vancomycin as a Case Study

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Many important drugs exhibit substantial variability in pharmacokinetics and pharmacodynamics leading to a loss of the desired clinical outcomes or significant adverse effects. Forecasting drug exposures using pharmacometric models can improve individual target attainment when compared with conventional therapeutic drug monitoring (TDM). However, selecting the "correct" model for this model-informed precision dosing (MIPD) is challenging. We derived and evaluated a model selection algorithm (MSA) and a model averaging algorithm (MAA), which automates model selection and finds the best model or combination of models for each patient using vancomycin as a case study, and implemented both algorithms in the MIPD software "TDMx." The predictive performance (based on accuracy and precision) of the two algorithms was assessed in (i) a simulation study of six distinct populations and (ii) a clinical dataset of 180 patients undergoing TDM during vancomycin treatment and compared with the performance obtained using a single model. Throughout the six virtual populations the MSA and MAA (imprecision: 9.9–24.2%, inaccuracy: less than ± 8.2%) displayed more accurate predictions than the single models (imprecision: 8.9–51.1%; inaccuracy: up to 28.9%). In the clinical dataset, the predictive performance of the single models applying at least one plasma concentration varied substantially (imprecision: 28–62%, inaccuracy: −16 to 25%), whereas the MSA or MAA utilizing these models simultaneously resulted in unbiased and precise predictions (imprecision: 29% and 30%, inaccuracy: −5% and 0%, respectively). MSA and MAA approaches implemented in TDMx might thereby lower the burden of fit-for-purpose validation of individual models and streamline MIPD.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Bayesian forecasting using population pharmacokinetic models is increasingly recognized as a useful tool to inform optimal dose selection, particularly for drugs used to treat infectious diseases.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The selection of the most accurate model to inform optimal dosing remains challenging, particularly for use in heterogenous and complex patient populations and novel, pragmatic approaches to guide model selection are required.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The use of an automated model averaging/selection approach allows for model structure uncertainty, while retaining at least the performance level of the most appropriate model in the algorithm for the individual patient. Implemented in the open-access software TDMx makes the approach easily accessible.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The developed algorithms may increase the accuracy of precision dose calculations associated with a better response as well as lowering the burden of fit-for-purpose validation of pharmacometric models for model-informed precision dosing.

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Pharmacometric models, if implemented in model-informed precision dosing (MIPD) software, can support dose individualization through forecasting future drug responses. The process, also referred to as Bayesian forecasting, usually includes the computational combination of patient information, individual plasma concentrations, and prior information in the form of population pharmacokinetic (PopPK) models to generate individual estimates. The estimated responses, in turn, can be used to assess whether (future) pharmacokinetic (PK)/pharmacodynamic targets can be attained with or without dose adaptations.

High-impact examples of applied MIPD[1–4] demonstrate the usefulness of treating individuals instead of populations.[5] Nonetheless, MIPD as a crucial pillar of precision medicine has not yet become integrated into clinical practice on a large scale.[6] A number of barriers toward the implementation of MIPD have been identified, including the lack of clinically oriented training in MIPD, the lack of acceptance of more complex dosing strategies (by prescribers),[7] unclear reimbursement, or the lack of pharmaceutical industry support.[8] Another challenge associated with MIPD is the selection of an appropriate pharmacometric model and the related fit-for-purpose validation required.[9]

The model selection process is challenging as PopPK models are usually developed and validated to provide quantitative insight into the PKs of a specific population, but their forecasting performance in diverse real-world populations undergoing therapeutic drug monitoring (TDM) is rarely evaluated. Selecting the "incorrect" model can potentially result in inappropriate dose recommendations and therefore lead to patient harm and/or suboptimal treatment outcomes and repeatedly validating models in different populations is arduous and costly.[9–12]

The objective of this study was to mitigate the challenge of the clinical application of MIPD by developing and evaluating a model selection algorithm (MSA) and a model averaging algorithm (MAA), which automates the model selection process for use in Bayesian forecasting. Both algorithms were compared with individual pharmacometric models in comprehensive simulation studies as well as in a heterogenous real-world clinical TDM dataset of patients administered vancomycin and subsequently implemented in the web-based MIPD software TDMx.[13] Vancomycin was exemplarily chosen because the latest international consensus guideline for TDM of vancomycin recommends using area under the curve (AUC) guided dosing through MIPD[14] and therefore suitable PopPK models are urgently required.

METHODS

Single-model approach

Contemporary Bayesian forecasting software commonly utilizes the single-model approach to inform dose selection.[15] Six published vancomycin PopPK models, developed in distinct patient populations, including extremely obese, critically ill, hospitalized, and those with sepsis, trauma, and post-heart surgery[16–21] were encoded in NONMEM (version 7.4.3; ICON plc, Dublin, Ireland). A detailed overview of the model properties can be found in **Table S1**. As an external reference, the two-compartment model of Goti *et al.*,[22] which was recently determined as the most accurate for vancomycin Bayesian forecasting was used.[10] Furthermore, to compare the predictive performance of the MSA and MAA to a best case of a single model Bayesian forecast, we re-estimated the parameters of the Goti model[22] using our clinical dataset (**Table S1**).

Multimodel approach

Two automated multimodel approaches were developed with the same six candidate PopPK models to be used simultaneously for forecasting individual PK profiles of either simulated or real-world patients (see below). Both algorithms comprised three essential steps (**Figure 1**): (1) the PK parameter estimation, (2) the automated comparison of the model fits, and (3) the adjustment of the forecasted concentration-time profiles.

Model selection algorithm. First, the individual PK parameters were estimated with each of the six PopPK models on observed data. Second, the forecasted (i.e., predicted) concentration-time data was automatically weighted using the weighting schemes described below. Third, the MSA selected the best fitting model via the obtained weightings and the competing models were discarded.

Model averaging algorithm. In the MAA, the available concentration-time data was used to average the model predictions under consideration balancing the predictions of each model using different weighting schemes that reflect individual goodness of fit. Similar to the MSA, the PK parameters of the individual patients were estimated with each PopPK model and individual weightings assigned. Then, in contrast to the MSA, the MAA averaged the model-predicted vancomycin concentrations at each forecasted time point using the set of PopPK models jointly with the data-derived weighting scheme. Furthermore, to investigate the vancomycin-specific target, the MAA also averaged the forecasted AUC.

Weighting schemes. The second step of the MSA/MAA requires a criterion to quantify the individual model fits with respect to the candidate models. Therefore, three different weighting schemes that summarize different model fit metrics were investigated: the objective function value (OFV), an adjusted Akaike information criterion (AIC) or the squared prediction errors (SSEs). Subsequently, the most suitable weighting scheme was implemented in the multimodel approaches.

The first weighting scheme compared the maximum likelihood (LL) obtained through the OFV of the ith model relative to the set of n models as follows:

$$W_{\mathrm{OFV}_i} = \frac{\mathrm{LL}_i}{\sum_1^n \mathrm{LL}_n} = \frac{e^{(-0.5\times \mathrm{OFV}_i)}}{\sum_1^n e^{(-0.5\times \mathrm{OFV}_n)}} \quad (1)$$

The second weighting scheme (W_{AIC}) consisted of an adjusted AIC with two main parts, adopting the approach proposed by Aoki *et al.*[23]: the LL and a penalizing term. In contrast to conventional AIC,[24] solely the number of random-effect parameters that quantify the magnitude of explained variability (i.e., interindividual variability (IIV)), were included in the penalizing term k (Eq. 2).

$$W_{\mathrm{AIC}_i} = \frac{e^{(\ln(\mathrm{LL})_i - k)}}{\sum_1^n e^{(\ln\ (\mathrm{LL})_n - k)}} \quad (2)$$

The third weighting scheme utilized the SSEs, which, in contrast to Eqs. 1 and 2, excludes the influence of the model structure on the predictions (Eq. 3). Here, *true* represents the measured and *pred* means the predicted value of the jth observation, respectively.

$$W_{\mathrm{SSE}_i} = \frac{e^{(-0.5\times \mathrm{SSE}_i)}}{\sum_1^n e^{(-0.5\times \mathrm{SSE}_n)}} = \frac{e^{\left(-0.5\times \sum\left(\mathrm{true}_j - \mathrm{pred}_j\right)\right)}}{\sum_1^n e^{\left(-0.5\times \sum\left(\mathrm{true}_j - \mathrm{pred}_j\right)\right)}} \quad (3)$$

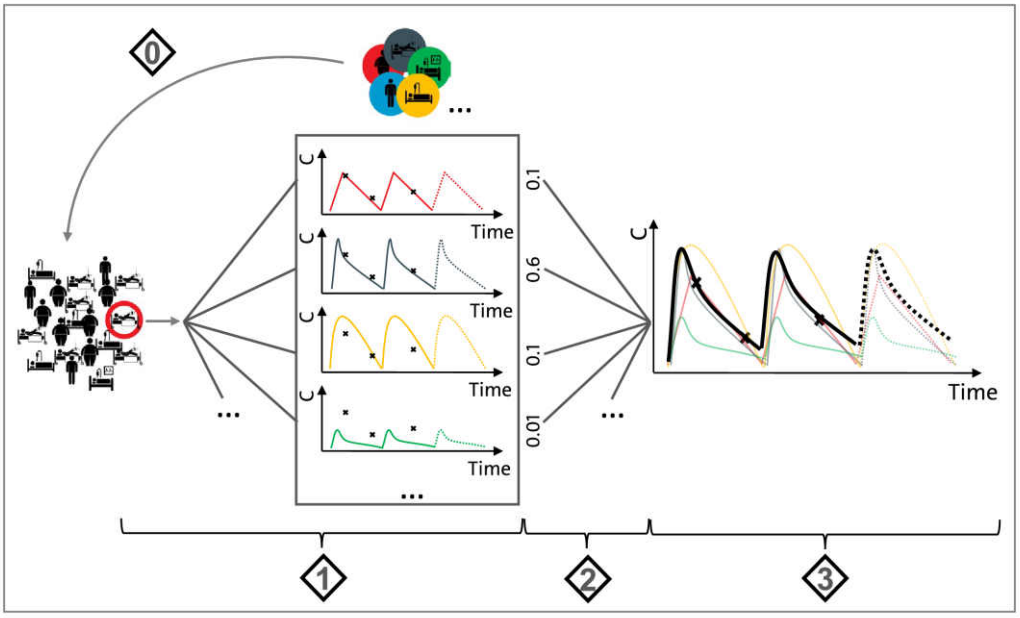

Figure 1 Model averaging scheme applied to a patient from a heterogenous or unknown population (red circle) with information on dosing, plasma concentrations (black cross), and the relevant covariates to forecast a future pharmacokinetic (PK) profile (dotted line). The algorithm comprises three steps: (1) Estimation of the PK profiles with a certain number of selected models. (2) Automated comparison of the individual model fit via a predefined criterion (e.g., the objective function value) and calculation of individual weights (e.g., W_{OFV}). The better the fit of the model, the higher the weighting. (3) Adjustments of the predictions by the respective weighting and building a weighted average (black line) with the best fitting model given the highest influence (model averaging algorithm) or being selected, while others are discarded (model selection algorithm). (0) is not part of the algorithm, but explains the simulation study graphically. Colored icons – models developed in distinct populations; colored lines – estimated PK profile of the chosen patient using the models, respectively. [Colour figure can be viewed at wileyonlinelibrary.com]

Robustness of the algorithm. In order to evaluate how many candidate models per multimodel approach were required for accurate predictions, we sequentially excluded the model(s) with the best performance metrics and estimated the vancomycin PK profiles of patients in the clinical dataset (see below) using the MSA and MAA with the weighting scheme W_{OFV}. The predictive performance of the algorithms with the smaller set of models was compared via the forecasting performance metrics (Eqs. 4 and 5).

Simulation study

A virtual population of 1,000 patients with randomly acquired covariates receiving the same vancomycin dose every 12 hours was created. The covariates were either sampled from a normal (age, body mass index, and body height), log normal (serum creatinine), or a binomial distribution (sex) to mimic a real adult population. Parameter details and correlations can be found in **Table S2**. With each of the six models, PK data were simulated, including a peak and a trough plasma concentration from three dosing intervals and the AUC between 24 and 36 hours (i.e., true AUC). Subsequently, the PK data obtained from the 6,000 simulated patients (1,000 per model) were evaluated using the single-model approach as well as the two multimodel approaches.

Clinical data

The predictive performance of the algorithms was evaluated in previously published heterogeneous clinical datasets.[10,25] Data from hospitalized and critically ill patients (n = 374) with 1,967 routine vancomycin TDM samples between January 2010 and August 2019 were retrospectively collected. This dataset includes 180 patients for whom plasma vancomycin concentrations were available for 3 dosing occasions (samples = 741). Patient demographics and clinical data are summarized in **Table S3**. The studies were approved by the St. Vincent's Hospital Human Research Ethics Committee in Sydney (2019/ETH09850, 2019/ETH02942 and 2019/ETH03054). Vancomycin concentrations were determined by standard immunoassay (EMIT 2000, Siemens Healthineers). Eleven datapoints (0.6% of all plasma concentrations) were below the limit of quantification of 2 mg/dL and were excluded. The age, bodyweight, and height were available in every patient. If specific continuous covariates were not available, either the median of the dataset or the median of the model population was imputed. If categorical covariates were missing, the data were assumed to be in the negative category (e.g., not receiving concomitant furosemide).

Forecasting performance metrics

The predictive performance of the MSA and MAA were compared with the single-model approach using the six PopPK models as well as to the "reference" PopPK model.[22] Predictive performance was assessed via the differences between the predicted and observed plasma vancomycin concentrations (clinical data) or the simulated and predicted AUC. Three different scenarios (outlined below) were used to predict plasma concentrations and the AUC in the third observed dosing occasion (ODO), where observed plasma vancomycin concentrations were "hidden" from the models or algorithms. The third ODO was chosen, as in the clinical dataset information from at least two previous dosing intervals were available in the majority (52%) of the patients. The ODOs were defined as not necessarily consecutive dosing intervals for which one or more observed vancomycin concentration(s) were available.

The first and second scenarios mimicked the bedside process of achieving a clinical target. First, predictions were made using solely the patient covariates (*a priori*). Second, the vancomycin concentrations from one or two previous ODOs were used in addition to the covariate information to forecast the PK profiles in the third (hidden) ODO. The third scenario

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was used to retrospectively determine the general fit of the models/algorithms to the data by including the third ODO. Relative root mean square error (rRMSE, Eq. 4) and relative bias (rBias, Eq. 5) were used to determine (im-)precision and (in-)accuracy of the forecasted parameters, respectively.[26] The metrics were calculated relative to the observed plasma concentrations in the clinical dataset and the predicted AUC relative to the true AUC obtained in the simulations.

$$rRMSE = \sqrt{\frac{1}{n} \times \sum_{1}^{i} \left(\frac{(\text{predicted}_i - \text{true}_i)^2}{\text{true}_i^2} \right)} \times 100 \quad (4)$$

$$rBias = \frac{1}{n} \times \sum_{1}^{i} \left(\frac{(\text{predicted}_i - \text{true}_i)}{\text{true}_i} \right) \times 100 \quad (5)$$

The performance of the models was considered clinically acceptable if the rBias was between −20% and 20%, with the 95% confidence intervals (CI) including zero.[25] Additionally, the precision metric (rRMSE) should be as small as possible.

The simulations and all data fitting processes were done in NONMEM in conjunction with PsN (version 4.9.0).[27] The "tidyverse" package (version 1.3.0)[28] in R (version 3.6.1)[29] was used to develop the algorithms as well as to assess the results graphically and mathematically.

MIPD software for vancomycin

For translation of the herein presented results into clinical practice, we developed a vancomycin dosing module in the open-access MIPD software TDMx.[13] The software module contains the single models as well as the MSA and MAA algorithms and allows for AUC-based dose calculations of vancomycin. The software can be accessed under http://www.tdmx.eu/.

RESULTS

Evaluation of the weighting schemes

Three weighting schemes (i.e., W_{OFV}, W_{AIC}, and W_{SSE}) were evaluated. Whereas the weighting scheme W_{OFV} consisted solely of the likelihood, obtained through the NONMEM calculated OFV, the W_{AIC} further accounted for model complexity through penalizing IIV. Due to the low number of observations per patient in the Bayesian estimation of the PK parameters (e.g., maximum four observations in the simulation study), the penalizing term dominated the resulting W_{AIC}, and therefore shifted the influence of the more complex models toward the less penalized ones (**Figure 2** vs. **Figure S1**). In comparison to W_{OFV}, the model, including the highest number of IIV terms (Thomson[21]), was less often selected in the forecasting of hospitalized patients (simulated by the Thomson model[21]) using W_{AIC} (one occasion: 63.9% vs. 0.3% and two occasions 71.3% vs. 8.9%). Simultaneously, the Adane[16] and Revilla[19] models were increasingly selected (< 13% to > 28%). Despite this shift in the distribution of the weights, the performance metrics of the MSA and MAA using the W_{OFV} were just slightly superior over the W_{AIC} (e.g., MSA one occasion rBias/rRMSE 0.6%/18.6% vs. 1.8%/19.4%; **Figure S2**). The W_{OFV} was slightly preferable to W_{SSE} with an rRMSE being 0.9% and an rBias 0% smaller on average. Therefore, the W_{OFV} was used in the following analyses.

Simulation study

Across all six simulated populations, the proportion of patients, for which the selected model corresponded with the model used to simulate the data, ranged from 21.1% in the Medellín-Garibay model[18] to 63.9% in the Thomson model[21] when using data from one ODO (**Figure 2**, one occasion). Although the PK parameters of the other patients were estimated with the algorithm assigning the highest weight to the other five models (i.e., a "wrong" model), the MSA led to similar metrics as the best single-model approach in the respective (sub-)population (**Figures S3 and S4**).

Overall, the metrics of the MAA and MSA were in good alignment throughout the 6,000 simulated patients with slightly higher imprecision and inaccuracy in the MAA approach (mean

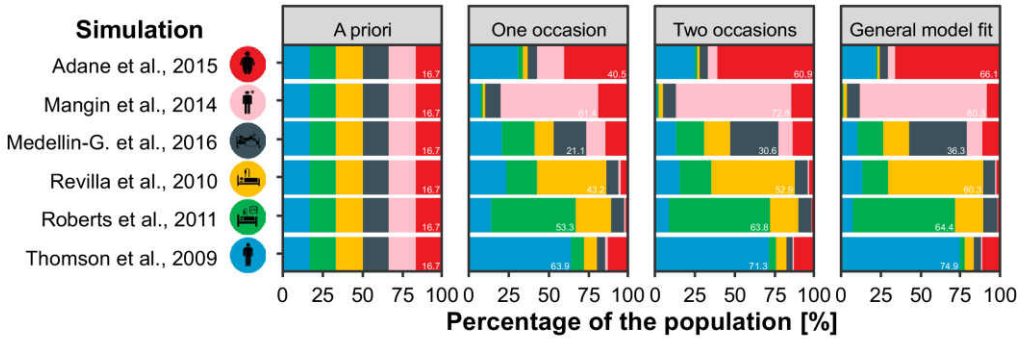

Figure 2 Influence of the models in the multimodel approaches using the weighting scheme W_{OFV} and stratified by the simulated populations (*y-axis*). Each patient was stained in the color of the particular model which obtained the highest weight in the algorithm. *(A priori)* prediction using the patient covariates only; Bayesian forecasting using plasma vancomycin concentrations from (One occasion) the second (i.e., most recent) observed dosing occasion and (Two occasions) the first and second observed dosing occasion; (General model fit) Bayesian estimation using plasma vancomycin concentrations from all three dosing intervals. White numbers – numerical value of the biggest portion in the subpopulation and scenario, respectively. In each simulation, the pharmacokinetic parameters of majority of the individuals were predicted solely by (for model selection algorithm) or mostly influenced by (for model averaging algorithm) the same model used in the underlying simulation. This pattern increased when more data was supplied and indicates that the algorithm detected the underlying true simulation model (i.e., the optimal model for each individual patient). [Colour figure can be viewed at wileyonlinelibrary.com]

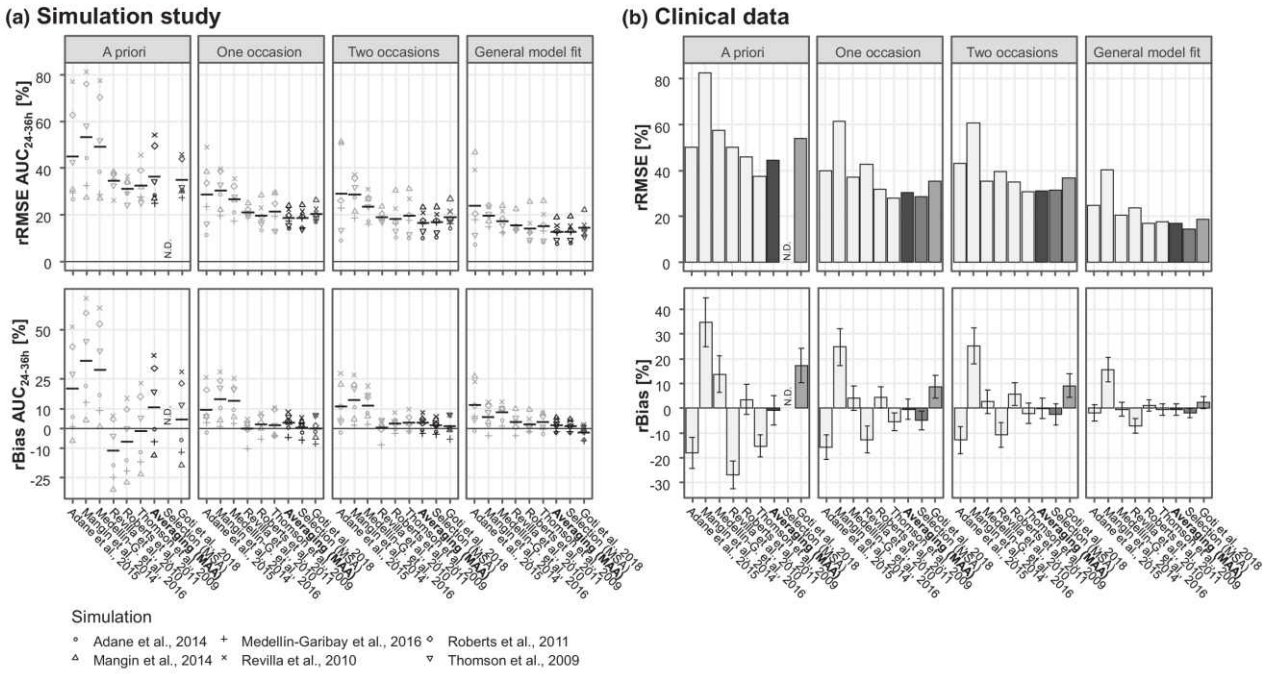

Figure 3 The relative root mean square error (rRMSE) and relative bias (rBias) when predicting either the area under the curve (AUC) or concentration-time data in the third dosing occasion, which is blinded to the models/algorithms from in various settings: *A priori* prediction using the patient covariates only; Bayesian forecasting using plasma vancomycin concentrations from (One occasion) the second (i.e., most recent) observed dosing occasion, and (Two occasions) the first and second observed dosing occasions; (General model fit) Bayesian estimation using plasma vancomycin concentrations from all three dosing occasions. (**a**) Simulation study; the predicted vs. the simulated AUC between 24 hours and 36 hours calculated in the whole 6,000 simulated patients (horizontal line) and the (sub-)populations (shapes), respectively, and (**b**) clinical data; the predicted vs. the vancomycin concentrations in the third observed dosing occasion obtained in the clinical studies. The ordinate is displaying the six single model approaches (light grey), the model averaging algorithm (black), the model selection algorithm (dark grey), and the external model (grey) per scenario. Whiskers cover the 95 % confidence interval of the relative bias calculated via the standard error. N.D., not defined.

absolute difference rRMSE 0.1% and rBias: 1.7% in the forecasting; **Figure 3a**). In comparison with the single-model performance throughout the 6,000 heterogenous virtual patients, the MSA displayed the most precise predictions ranging from an rRMSE of 18.6% (18.8% MAA) in the forecasting using one occasion to 12.9% (12.8% MAA) in the general model fit vs. the single model approaches with an imprecision of 19.3–30.3% in the forecasting or 14.1–23.8% in the general model fit. The rBias of the MAA and MSA was always less than ± 9% and < 15% using the single models, except in the *a priori* setting, which is by default an average of the model predictions with equal weightings (MAA) or not defined (MSA). In comparison to the *a priori* forecast, the inclusion of concentrations from one ODO led to an improvement of the precision and accuracy of the MAA by a factor of two and four, respectively. Additional concentrations from a second ODO improved predictions only marginally.

In each simulated population, the predictions of the MSA and MAA outperformed most of the single-model approaches with an rBias between −5.9% and 8.2% and an rRMSE always < 24.2% in the forecasting and general model fit, whereas the single models varied between −10.3% and 28.9% (rBias) and an rRMSE of up to 51.1% (**Figure 3a**–shapes). The single-model approach was only slightly

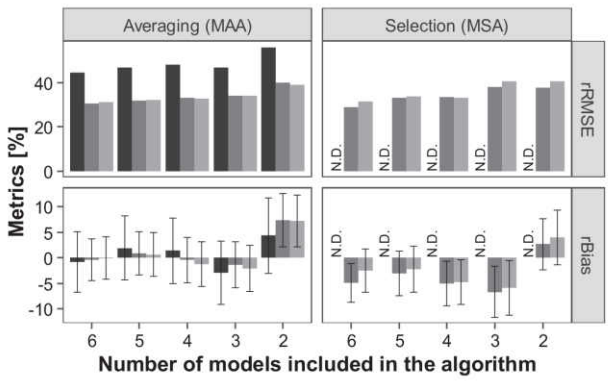

Figure 4 Robustness of the model averaging algorithm (MAA; left) and the model selection algorithm (MSA; right) displayed via the relative root mean square error (rRMSE) and relative bias (rBias) of the clinical data. The successively excluded models are: Thomson, Roberts, Medellín-G., Adane (from left to right), remaining: Mangin, Revilla. (black) *a priori* prediction using the patient covariates only; Bayesian forecasting using plasma vancomycin concentrations from the second (i.e., most recent) dosing occasion (dark grey), and the first and second dosing occasions (light grey). Whiskers cover the 95% confidence interval of the rBias calculated via the standard error. N.D., not defined.

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more precise, when it was used to forecast the PK within the respective population the model was developed for (**Figures S3 and S4**).

In comparison to the "reference" model of Goti,[22] the MSA and MAA were more precise (rRMSE) while being similarly accurate (rBias < ± 10%). The rRMSE using the Goti model[22] ranged from 20.3% to 19.0% (one and two occasions), whereas the precision of the multimodel approaches ranged from 18.8% to 16.8%.

Clinical data

Forecasting performance. The MSA and MAA were applied to the clinical dataset and confirmed the simulation study findings. Although the forecasting performance of the single models varied substantially (rBias: −16 to 25%, rRMSE: 28–62%), the MAA using these models simultaneously resulted in unbiased and precise predictions using data from one (rBias: 0%, rRMSE: 30%) and two previous ODOs (rBias 0%, rRMSE: 31%; **Figure 3b**), matching the simulation study results that additional concentrations only marginally improved the predictions. The rRMSE of the MAA was always in the range of the best single model (absolute deviation to Thomson model[21]: *a priori*: 7.2%, forecasting: 2.7%/0.5%, and general model fit: −0.7%).

Although both MSA and MAA displayed an rRMSE in the forecasting between 29% and 32%, the MAA was slightly more accurate (rBias one occasion/two occasions −0.4%/−0.1% MAA vs. −5.0%/−2.5% MSA). Although the 95% CI of the two algorithms were overlapping in large parts, only the 95% CI of the rBias in the MAA included 0 in all settings. The MAA, unlike all single-models, met the clinical acceptance criteria in every scenario. The approaches performed better than the recently evaluated best model of Goti[10] (rBias one occasion/two occasions: 8.6%/9.1%, rRMSE: 35% and 37%). Even if

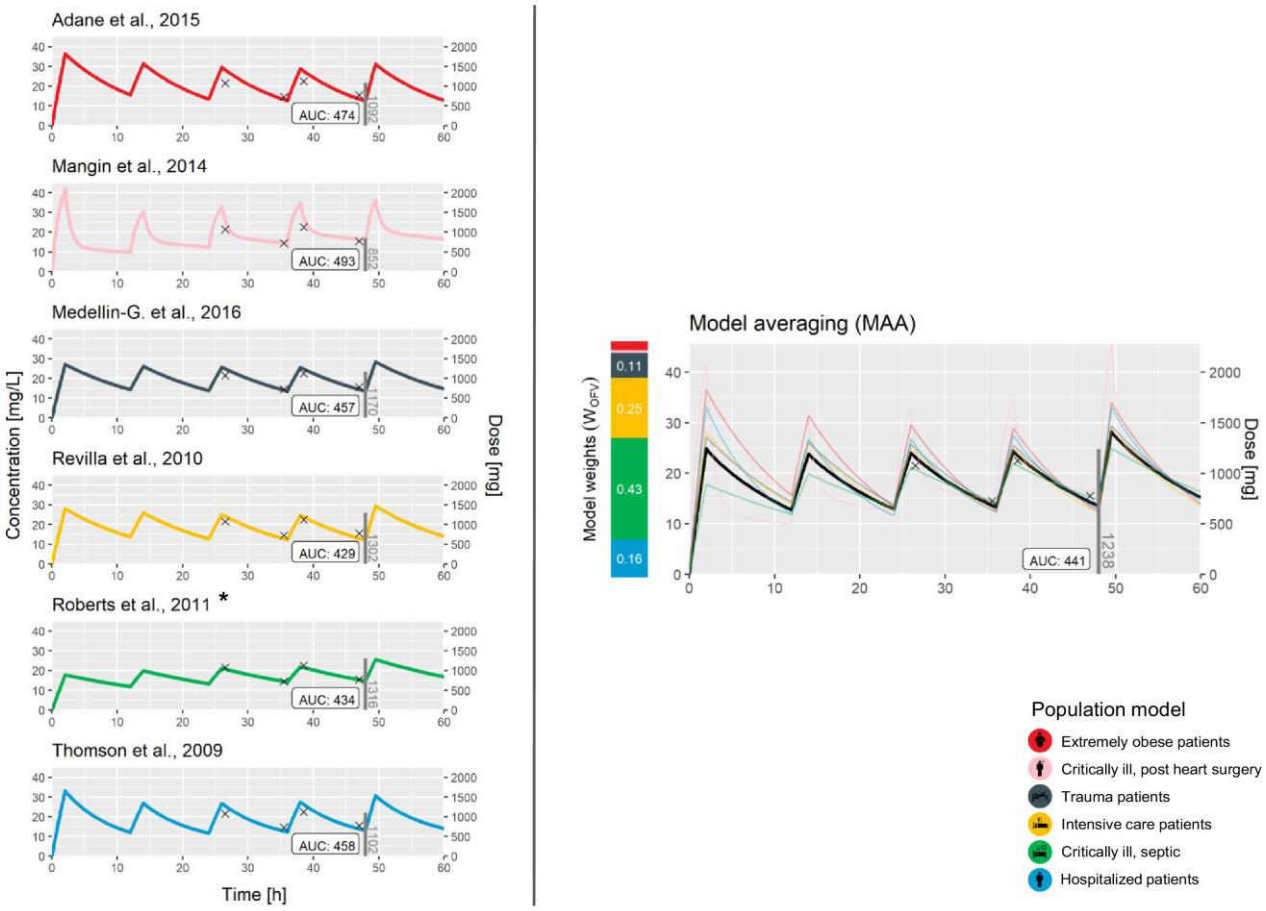

Figure 5 Calculation of an optimal vancomycin dosing on day 3 in a critically ill example patient (male, 70 kg, 1.75 m, 56 years, serum creatinine: 80 µmol/L) to attain the target area under the curve $(AUC)_{24h}$/minimal inhibitory concentration (MIC) ratio of 500 with the model-informed precision dosing software TDMx. The patient received 1,000 mg vancomycin twice daily, following a loading dose of 2,000 mg and 2 peak and 2 trough vancomycin plasma concentrations were measured between 23 and 14 mg/L. With the single-models (left), model fit was heterogeneous and the determined AUC_{24h}/MIC ratio varied from 429 to 493. The single model-derived dose recommendations varied between 852 mg and 1,316 mg (grey). The model selection algorithm (MSA) selected the Roberts model as indicated by the highest weight (*). The model averaging algorithm (MAA; black line, right panel) predicted an AUC_{24h}/MIC ratio of 441 prior dose adjustment, and the subsequent dose recommendations was 1,238 mg. The MAA was mainly influenced by the Roberts and Revilla model, both derived in the critically ill population, as indicated by the model weights (barplot). Both the MSA and the MAA calculated a plausible dose adjustment being in line with the most accurate single model. [Colour figure can be viewed at wileyonlinelibrary.com]

the parameters of the best reference model[22] were re-estimated based on our clinical dataset and the predictive performance of the adjusted model improved, the two algorithms were similar to, or performed better than, the single model (**Figure S5**).

Robustness of the algorithm. In order to evaluate how many models were needed in the MSA and MAA, we successively excluded the model with the best weighting and assessed the performance of the algorithms consisting of six to two models. The predictive performance of the MAA was "stable" even when only three instead of six models were used, where the rRMSE increased from 30.4% to 34.2% in the forecasting (44.4–46.6% *a priori*) and the rBias varied between −2.1% and 0.7% (−2.9 to 1.9% *a priori*; **Figure 4**). The 95% CI of the rBias included 0 in all scenarios and never exceeded ± 7.4%. When using two models in the MAA, the rRMSE increased by 5.7% in the forecasting (9.2% *a priori*) with a rBias of 7.3% (4.3% *a priori*). The exclusion of up to four models in the MSA resulted in greater imprecision (rRMSE 28.7% to 40.4%) and a rBias between −6.7% to 3.9% (**Figure 4**). In comparison to the MAA, the forecasting of the MSA was less accurate (mean rBias MSA −2.9%; MAA 1.0%) and less precise with a larger rRMSE in 8 of 10 settings.

MIPD software for vancomycin

The vancomycin module in TDMx was cross-validated against NONMEM (version 7.4.3) indicating virtually identical results of the model predictions as well as objective function values (**Figures S6 and S7**).

A patient case example using the single-model approaches as well as MSA and MAA is presented in **Figure 5**. Single models did not only provide a very heterogenous fit to the example patient, but also derived dose recommendations to attain an AUC_{24h} over minimal inhibitory concentration ratio of 500 were highly variable ranging from 852–1,316 mg, whereas the MSA and MAA predicted an optimal dose of 1,316 and 1,238 mg, respectively.

DISCUSSION

For vancomycin—one of the most commonly used antibiotics in clinical practice[30]—more than 30 PopPK models have been developed in diverse patient populations.[10] However, to choose and validate a model for an individual patient might not always be within the skill-set of the decision maker. We therefore provide two new multimodel approaches using automated model selection/averaging in Bayesian forecasting, with a better forecasting performance than a single PopPK model. When implemented in MIPD software, the clinical decision maker does not need to rely on one predetermined model but can automatically allow the algorithms to find the most suitable predictions for an individual patient. Thereby the precision dosing process will be streamlined and the burden of local model validation lowered. Moreover, by implementing the MSA and MAA into the web-based MIPD software TDMx,[13] the developed algorithms are readily available to the scientific and clinical community.

The MSA/MAA required predictions to be adequately weighted. Therefore, three different weighting schemes were compared and the most suitable identified. The weightings derived from the W_{OFV}, which represent a balance between those from the W_{AIC} and W_{SSE}, provided superior weightings, although there was little difference in the predictive performance among the three schemes.

Although single pharmacometric models are usually evaluated in a specific population prior to their publication, extrapolating from a single model might not guarantee suitable predictions of concentration-time profiles in another, potentially very different, patient population. Even if the underlying population were known, the patient could still display atypical PK parameters. This implies that more flexibility is required when predicting PK parameters in clinical settings with patients from heterogenous populations. We demonstrated that the multimodel approaches provided this essential flexibility to forecast "future" vancomycin PK profiles of a heterogeneous population more accurately than using a single model.

Several factors could contribute to the superior performance of MSA and MAA over the single-model approach. First, predicting PK parameters with a single model ignores uncertainty in the structural model that could affect the predictive performance.[23,31] Specifically, a single model might not reflect the most suitable compartmental structure or parameterization. Furthermore, individuals differ in their physiology and therefore in their drug disposition. Extremely obese patients, for example, display a typical volume of distribution of vancomycin of 0.5 L/kg, one third of the value in patients with sepsis, whereas the clearance is comparable.[16,20] In contrast, the clearance of vancomycin determined in trauma patients is significantly lower than in extremely obese and more similar to the clearance in critically ill patients undergoing heart surgery.[17,18] These alterations in key PK parameters are especially relevant in critically ill patients[32] and highlight the importance of dosing decisions to be informed through careful selection of a pharmacometric model in MIPD. To ensure generalizability of the study findings the PopPK models selected to evaluate MSA and MAA were developed in diverse populations (i.e., extreme obese, critically ill, and hospitalized patients, among others). Second, a single model might include misinterpreted covariates (e.g., for burn status)[33] or lack covariates, which are critical in particular patients (e.g., correction for age, body weight, and kidney function).[34] However, the concurrent use of various models will include a larger range of covariates. Third, single models developed in small, homogenous cohorts of patients while displaying good internal predictivity, might not display external predictivity due to selection bias in the covariate submodel[35] and underestimated parameter uncertainty in studies with small patient numbers.[36] Finally, single models may have been developed based upon routine clinical data, which often exhibits uncertainty in documented dosing and sampling time. Uncertain sampling inflates the residual error of the models and thus can lead to a worse individual fit using the model in a sparsely sampled TDM setting due to a lower "trust" in the observed values and a higher impact of the Bayesian prior during Bayesian forecasting.[37]

When implementing MSA or MAA it might be challenging to select the candidate models to be included in the algorithms. To

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this end, we evaluated the robustness of the MSA and MAA in this case study by successively excluding the best models (**Figure 4**). This stepwise exclusion of the candidate models resulted only in a minor decrease in the predictive performance of the MSA and MAA until only four and three models remained, respectively. Even with the two models that performed worst in the single model approach, a considerably improved forecasting performance could be observed when used in MSA, and even better in MAA (**Figure 4**). Whether this behavior is generalizable and whether a similar approach could be used to identify the best set of models would need to be evaluated in further MIPD settings beyond vancomycin, but this indicates that the algorithms in the evaluated case study are not dependent on a distinct single, well-performing model. This robustness makes the MAA and MSA an attractive approach also in settings where only a few PopPK models are available. Hence, MSA and MAA can use all relevant collective knowledge simultaneously to inform precision dosing calculations. Further, this process is automatable and enables the re-allocation of resources which would otherwise be required for the time-consuming task of identifying and validating the most suitable model for MIPD. Although Bayesian averaging in patient care[38] and drug development[23,39] has been discussed before, we, for the first time, systematically developed and evaluated such an approach in the context of MIPD.

Other popular approaches in MIPD are nonparametric in nature. The developed MSA and MAA combine the flexibility of nonparametric approaches[40] with the rigor of a parametric framework, without needing to know the nonparametric distribution (i.e., support points) of the population, which are rarely published. A comparison between MSA/MAA and nonparametric approaches with regard to handling outliers might be worth pursuing in future studies. Moreover, all PopPK models were coded from publications whereas nonparametric models require the derived sets of support points/raw data, which are rarely publicly available.

Some limitations of this study are acknowledged. The MSA and MAA require TDM data to weigh the predictions and find the best model during the course of therapy. For the first dose calculation (i.e., the *a priori* setting), a manual selection of the model is still required. Furthermore, none of the investigated vancomycin population models included interoccasion variability (IOV), a term quantifying PK variability between dosing occasions within the same individual. Although the inclusion of IOV during model development has been shown to be beneficial,[41] this variability can be challenging to handle in MIPD using the single-model approach.[42] Hence, investigation of MSA/MAA approaches with IOV should be evaluated in future studies.

Although the time required to complete the MSA and MAA per individual (mean 7.0 seconds with SD < 0.6 seconds using two samples and a set of six models) in the TDMx-based Bayesian forecasting was acceptable, calculating the uncertainty in the PK-profile predictions is only feasible with the MSA post-autoselection. Simulating the uncertainty with each model of the MAA set (e.g., using the Monte Carlo method) and averaging the obtained CI based on the weighting is highly time-consuming, and more research is required to provide assurance that the calculated CI will be statistically correct.

Moreover, in order to fully benefit from MIPD tools in critical therapies, the transferability of the present case study with vancomycin to other drugs in or outside the field of infectious diseases should be investigated.

In conclusion, the present study comprehensively evaluated model averaging and selection algorithms in MIPD using vancomycin as a case study. The algorithms overcome one of the major difficulties associated with the implementation of MIPD into clinical practice—selection of the most appropriate PopPK model for an individual patient. The developed algorithms can provide a more reliable Bayesian forecast when compared with using a single model.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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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. D.W.U. and S.G.W. designed the research. D.W.U., S.G.W., S.L.S., J.E.C., J.B., D.J.E.M., and R.O.D. performed the research. D.W.U. and S.G.W. analyzed the data.

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ERRATUM

Erratum: A Model Averaging/Selection Approach Improves the Predictive Performance of Model-Informed Precision Dosing: Vancomycin as a Case Study

David W. Uster, Sophie L. Stocker, Jane E. Carland, Jonathan Brett, Deborah J.E. Marriott, Richard O. Day, and Sebastian G. Wicha, *Clin. Pharmacol. Ther.*, **109,** 175–183 (2021), https://doi.org/10.1002/cpt.2065. First published online: September 29, 2020

In the published version of the above article, there is an error in Eq. 3, the sum of (true – pred) should be squared, but it is displayed incorrectly as follows.

$$W_{\mathrm{SSE}_i} = \frac{e^{(-0.5\times \mathrm{SSE}_i)}}{\sum_1^n e^{(-0.5\times \mathrm{SSE}_n)}} = \frac{e^{(-0.5\times \Sigma(\mathrm{true}_j - \mathrm{pred}_j))}}{\sum_1^n e^{(-0.5\times \Sigma(\mathrm{true}_j - \mathrm{pred}_j))}}$$

The correct equation should be:

$$W_{\mathrm{SSE}_i} = \frac{e^{(-0.5\times \mathrm{SSE}_i)}}{\sum_1^n e^{(-0.5\times \mathrm{SSE}_n)}} = \frac{e^{(-0.5\times \Sigma(\mathrm{true}_j - \mathrm{pred}_j)^2)}}{\sum_1^n e^{(-0.5\times \Sigma(\mathrm{true}_j - \mathrm{pred}_j)^2)}}$$

This error occurred during the typesetting process and we apologize for the error.

doi:10.1002/cpt.2353

3.4 Publication IV

Optimized Sampling to Estimate Vancomycin Drug Exposure: Comparison of Pharmacometric and Equation-Based Approaches in a Simulation-Estimation Study

David W. Uster, Sebastian G. Wicha

Clinical Pharmacology & Therapeutics: Pharmacometrics & Systems Pharmacology (2022)

Impact Factor: 4.054 (2020)

Synopsis

The latest MRSA-treatment guideline recommends to individualize vancomycin dosing based on the individual AUC determined with MIPD software.[1] Thereby, two measurements (i.e. a peak and a trough sample) are considered gold standard to determine the individual AUC, but single-sample strategies might be more economic.

In Publication IV, we systematically evaluated optimal sampling times for AUC-determination of vancomycin using automated one or two sample strategies with the MAA and MSA. Both algorithms were compared to a conventional equation-based approach (EQA) in a simulation-estimation study of 6 000 heterogenous virtual patients.

In contrast to current clinical practice that focuses on trough samples, a single sample obtained between 2–6.5 hours post dose resulted in unbiased and precise predictions using the MAA and MSA. An additional sample between 4.5–6.0 hours improved the predictive performance, but the differences between all two-sampling strategies were minor. In contrast, the EQA always required two samples, steady-state conditions and was positively biased.

The MAA/MSA preferred samples to be drawn early in the profile and accurately predicted the AUC even after the first dose. This emphasizes the potential of the MAA/MSA to already individualize the second dose precisely, which is likely unfeasible using trough sampling.

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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 heterogenous 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

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.

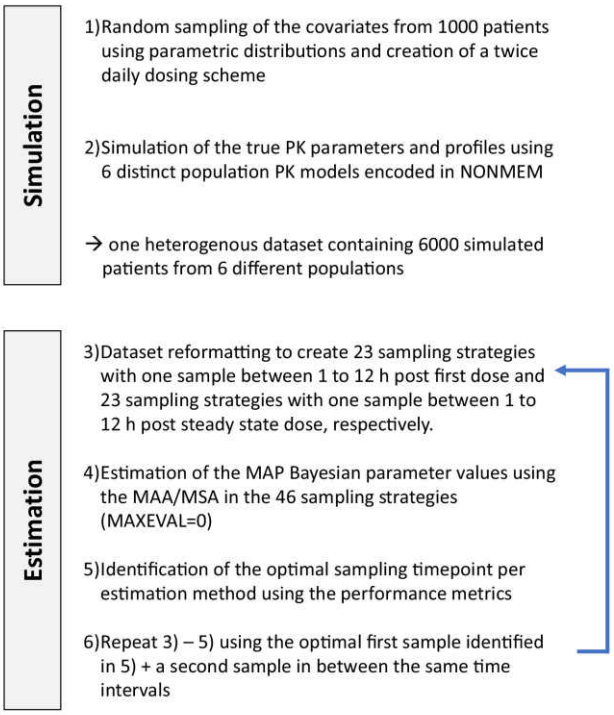

FIGURE 1 Workflow of the simulation-estimation study consisting of six main steps. MAA, model averaging algorithm; MAP, maximum a posteriori prediction; MAXEVAL=0, NONMEM-specific MAP estimation with fixed population parameters; MSA, model selection algorithm; PK, pharmacokinetics

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. model[22]; 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. model[27] (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 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.

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)

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:

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

$$\text{MdPE} = median\left(\{rPE_0 \ldots rPE_i\}\right) \quad (5)$$

$$\text{IQR} = quartile_3\left(\{rPE_0 \ldots rPE_i\}\right) - quartile_1\left(\{rPE_0 \ldots rPE_i\}\right) \quad (6)$$

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).

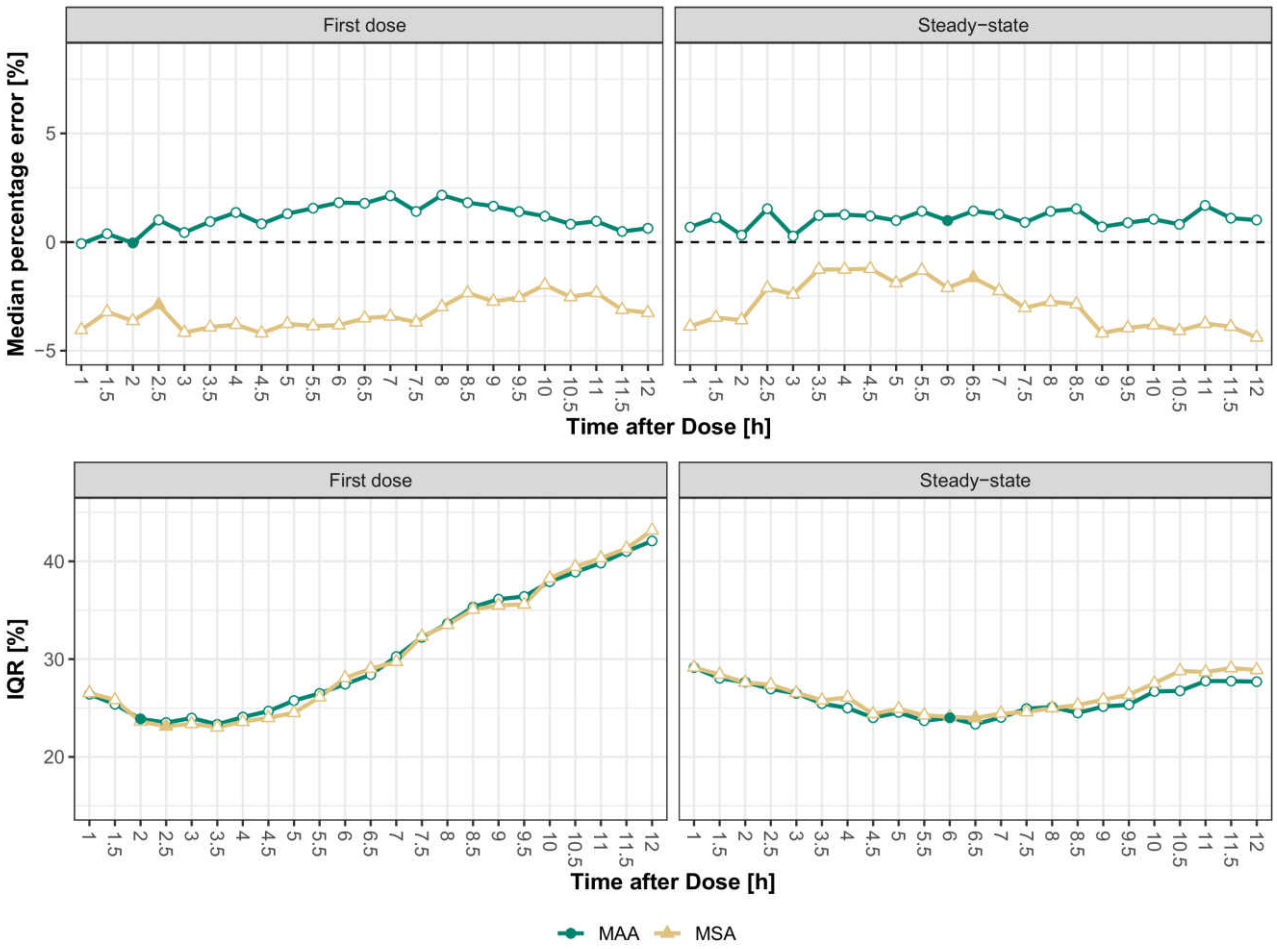

FIGURE 2 Performance metrics of the multimodel approaches using the single-sample strategies in the total population (n = 5925). The median percentage error and the interquartile range (IQR) of the relative prediction errors of the area under the concentration-time curve represent accuracy and imprecision, 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

	First sample, h	Second sample, h	Single-sampling strategy[a]		Two-sampling strategy[b]		"Peak-trough" strategy[c]	
			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.

[a]Performance metrics using the "first sample" timepoint.

[b]Performance metrics using the "first sample" and "second sample" timepoints.

[c]Performance metrics using a sample at 1 h and at 11.5 h after the start of infusion.

[d]With two fixed sampling times at 3 and 11.5 h after the start of infusion.

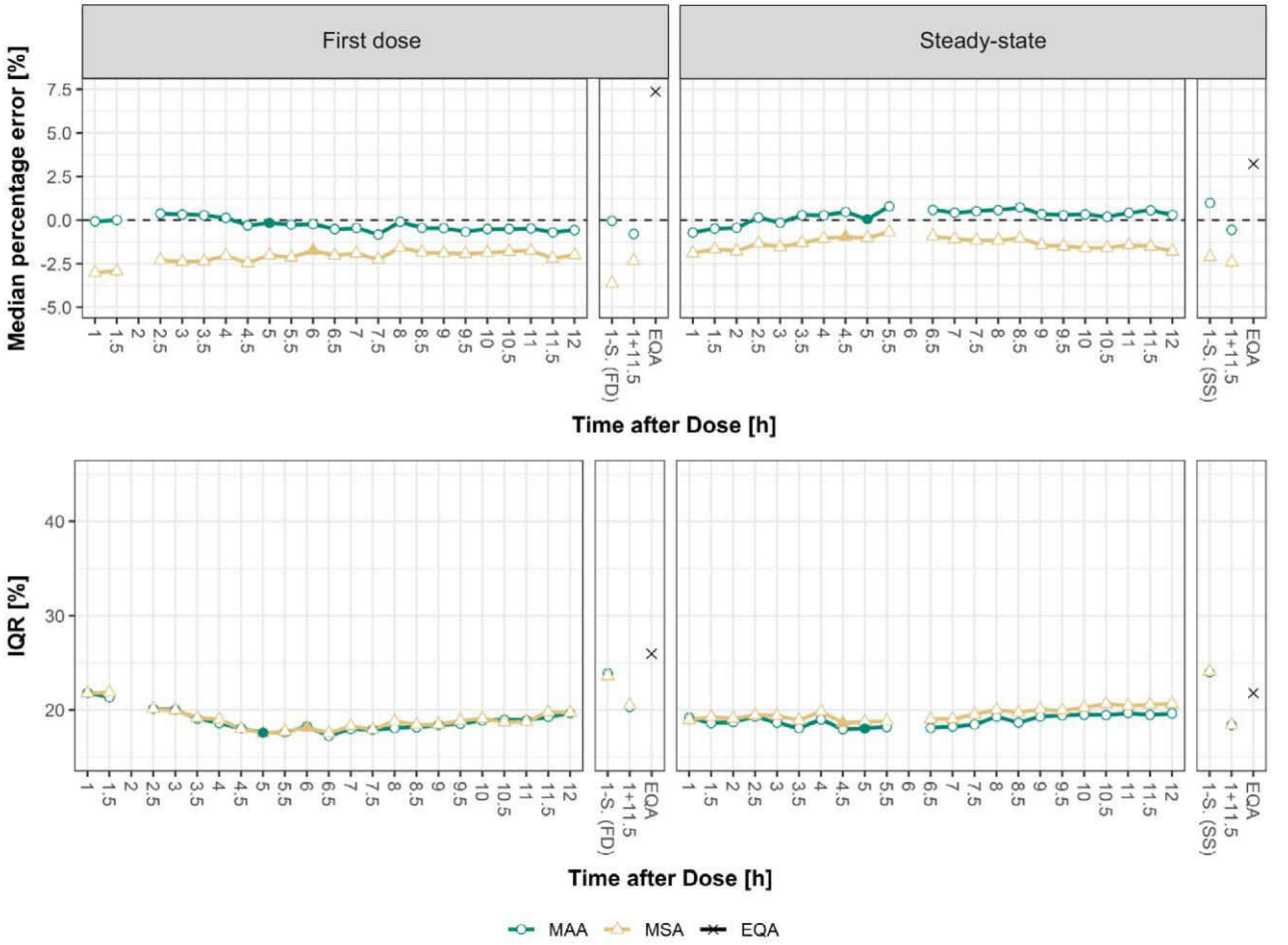

FIGURE 3 Performance metrics of the multimodel approaches using the optimized first sample and a second sample drawn in between 1–12 h after the start of infusion. Time after dose indicates the timepoint of the second sample drawn in the 5925 patients either in the first dosing interval (i.e., first 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. model[27] (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 deemphasized 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 individualized 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 w 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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4 Discussion

The following provides a comprehensive, overarching discussion of the four articles included in this work. The structure is based on the three key challenges of MIPD (Figure 2), starting with the model-specific factors – including the identification, selection, and comparison of suitable population PK models and novel approaches for MIPD. The patient and data-related challenges as well as the advocation of MIPD to the user/operator are elucidated afterwards given the necessity to introduce the results of the model identification and the developed approaches first.

4.1 Basis of model-informed precision dosing: the pharmacometric model

The main fundament of every MIPD approach clearly is the underlying model. Thereby, it is essential to choose the most appropriate one and assure adequate use within the respective MIPD approach.

4.1.1 Model selection in long-term prophylactic replacement- versus temporary anti-infective treatments

Both investigated diseases are substantially different with regard to their targets, drug's PK, treatment options and consequences in over-/underdosing. Prophylaxis in haemophilia A usually requires life-long treatment with one of the multiple, non-bioequivalent FVIII products to maintain intrinsic FVIII levels above a minimal threshold. On the contrary, the temporary antibiotic treatment with vancomycin needs to be rapidly introduced and targets a distinct drug exposure (i.e. an AUC/MIC ratio of 400-600). Additionally, antibiotic overdosing with its increased risk of severe adverse effects (like acute kidney failure) is as life-threatening as underdosing, which risks treatment failure.

Despite these differences, TDM is recommended in both pharmacotherapies.[1], [2], [85] A prospective study including 46 children with severe haemophilia A found that plasma concentration-guided prophylaxis improved quality of life in more than 50 % of the

children, while the remaining ones did not require treatment optimization.[86] Similarly, a retrospective study on trough-guided vancomycin dosing of 150 patients revealed that more than 50 % of the individuals were initially treated suboptimally. While TDM enabled the prescribers to identify these issues, multiple dose adjustments were necessary for target attainment and more than 10 % of the individuals never reached the target.[87]

A more promising way to improve individual treatments is computer-guided AUC monitoring and precision dosing using population PK models. In Chapter 1.4 the various theoretical advantages compared to TDM were introduced (i.e. the inclusion of multiple covariates simultaneously, ability to predict maximally precise dosing schemes with sparse data, no need of steady-state conditions and handling of non-linear PK). Furthermore, some preliminary studies already highlight the potential benefit of MIPD through, for example, faster target attainment compared to trough-based dosing of vancomycin and reduced risk of adverse events.[88]–[92] However, these studies are mostly small-scaled, retrospectively conducted and do not exhaustively address challenges of MIPD. Given the range of already published population PK models, a major challenge remains with the selection of the most accurate model to inform optimal dosing of FVIII products or vancomycin in heterogenous or complex patient populations. Our model comparisons in Publication I and II demonstrated the highly variable predictive performance of the population PK models. The bias in the 12 investigated FVIII population PK models, for example, ranged from -3.8 hours to 49.6 hours, indicating a trend towards overpredicting individual targets. Across the two diseases, it seemed beneficial to use a population PK model, which (i) was developed in as large as possible cohorts (e.g. 754 haemophilia A patients in the study of Abrantes *et al*.[3] or 2 554 vancomycin treated patients in the study of Colin *et al*.[6]) and (ii) was built on a rather heterogenous patients collective (e.g. in the model of McEneny-King *et al*.[93] or Colin *et al*.[6]).

Interestingly, we identified the model of Okada *et al*.[5] to be best, when predicting individual AUC in Gram-positive infected patients under continuous vancomycin therapy. The population PK model was neither the same as found in previous model

comparisons (i.e. Goti *et al*.[84]),[54], [83] nor developed in a population fully matching our study collective of hospitalized patients with and without haematological malignancies.

Hence, simply matching the candidate model to the target population or selecting the model with the largest database does not guarantee the best performance. Novel approaches are necessary to establish MIPD as sound option for personalizing treatment.

4.1.2 Novel approaches in model-informed precision dosing

In Publication III, the development and evaluation of two new MIPD approaches were introduced with the aim to (i) overcome model selection bias and (ii) to accurately forecast the vancomycin exposure in individuals from a heterogenous population. The two multi-model approaches either automatically select the best (MSA) or a set of models (MAA) for an individual patient amongst a set of candidate models. In a nutshell, these algorithms are (i) estimating the individual PK parameters based on observed data with a set of population PK models, (ii) individually weighting the forecasted data of the different candidate models separately, and (iii) either averaging the predictions at each forecasted timepoint using the set of models jointly (MAA) or selecting the predictions of the best fitting, i.e. highest weighted, model (MSA).

The MAA/MSA were applied to forecast the drug-specific target of individuals from clinical datasets of haemophilia A patients (Publication I), hospitalized patients receiving continuous vancomycin (Publication II) and hospitalized patients receiving intermittent vancomycin infusions (Publication III). Publication I and II revealed a similar performance of the MAA/MSA as compared to the best population PK model identified in the model comparisons, respectively. In Publication III, both approaches predicted individual vancomycin plasma concentrations less biased and more precise than using a previously identified model being recommended for MIPD in hospitalized patients.[54] Interestingly, the included set of vancomycin PK models did not contain the best performing model, but a selection of six models developed in preferable different

populations (e.g. critically ill, extremely obese or trauma patients). In fact, the predictive performance of the six models, separately, varied from substantial underprediction using the model developed in critically ill (from Revilla *et al*.[94]) to similar overpredictions using a model for patients post heart surgery (Mangin *et al*.[95]). Nonetheless, implemented in the MAA/MSA the performances of the population PK models added up. We hypothesize this to be caused by the ability of the MAA/MSA to rely on information from multiple population. The MAA/MSA were more flexible in terms of the parameter distributions to draw from. Thus, both were able to describe atypical patients not matching the rest of the studied population.

When applying the multi-model approaches to forecast the time-above target in real haemophilia A patients, the set contained the top five performing models identified in the model comparison of Publication I. Here, the MAA/MSA approximated the performance of the population PK model identified best (from Abrantes *et al*.[3]) but did not surpass the same. Given that the population PK models included in the MAA/MSA mostly displayed a positive bias, the algorithms had mainly one way to approach the individual PK profiles. It seems, therefore, important to include models developed in preferably different populations rather than only including 'very good' performing models into such multi-model algorithms.

The robustness testing in Publication III revealed that the MAA/MSA could compensate for bad performing models until the MAA/MSA consisted of only three population PK models. The reason why also individually bad performing models do work when being part of the MAA/MSA, may lie within the automatic weighting function. Bad performing models received a low weight in the MAA or MSA due to a relatively higher penalizing term. Thus, the respective models contributed only marginally to the model prediction.

In this thesis, four different weighting functions were assessed and revealed the OFV to be best (i.e. the likelihood, which accounts for deviations of the individual MAP parameters from the model-specific population parameters as well as the differences between observed and individual predicted vancomycin concentrations).[81], [96] The other three weightings resulted in only small differences. The Akaike criterion,[97] for example, was overly penalizing more complex models when supplying only a few

samples, while the summed squared residuals were neglecting the prior information included in the model structure and hence, might overfit the data. The extended least squares weighting, best described as the interim between OFV and summed squared residuals, revealed the smallest differences to the OFV weighting.

4.1.3 Comparing existing approaches of personalized medicine to the model averaging-/ model selection algorithm

The MAA/MSA developed in Publication III is a new way to computationally guide dosing individualization. With the emergence of pharmacometrics and steadily progressing technological resources, further approaches have been invented. The following provides a comprehensive assessment of the various approaches compared to the MAA and MSA.

Equation-based approach

At the latest after the revised MRSA treatment guideline has been published, vancomycin dosing and monitoring has shifted from trough-based- to AUC-guided dosing using Bayesian approaches.[1] However, the pharmacometric know-how and resources required to integrate these state-of-the-art approaches into clinical practise has urged researchers to develop alternatives. Pai *et al.* adapted an approach previously proposed for aminoglycosides and daptomycin.[98], [99] Here, the individual vancomycin AUC is analytically approximated based on simple first-order PK formulas and two vancomycin plasma concentrations.[48] The major advantages of this EQA are its simplicity, which does not demand thorough pharmacometric knowledge. In 2019, a prospective randomized clinical trial involving 65 MRSA-infected patients implies that the EQA improved vancomycin-associated cure in comparison to trough-based TDM.[100] Complementary conclusions were drawn in a larger retrospective studies from Olney *et al.* [101] and Turner *et al.*[102]. The estimated AUC values using the EQA or a Bayesian two-concentration method resulted in congruent clinical decisions (i.e. dosing adjustment required/not necessary) in more than 75 % of the study population.

Nevertheless, the EQA – in contrast to MAA/MSA – always requires steady-state conditions and two concentrations. The peak and trough sample must be obtained after the early distribution phase. Hence, the EQA (i) is neglecting the bi-exponential decline of vancomycin, (ii) is limited to a fixed dosing interval and (iii) only enables adjustments in the later stages of the therapy. Especially in antibiotic therapies, it is essential to achieve optimal drug exposure as early as possible to ensure a rapidly effective antibiosis.[103] Furthermore, the snapshot of the AUC provided by the EQA cannot incorporate dynamic changes of the patient (e.g. decline of the renal function), while a Bayesian approach is able to adapt via the incorporated covariates.

Pooled-data model

For vancomycin, more than 30 population PK models are available in the literature. While these heterogenous studies provide valuable insights into specific patients or treatment regimens, most of them are limited to describe the special subpopulation or clinical intervention. As discussed in Publication III the difficulties lie within the 'correct' selection of the model, whose study conditions' best match the clinical conditions of the patient.

Even if a formally matching model is found, a modest number of individuals included during model development could jeopardize the predictive performance of the model due to population sampling errors and other random incidences.[54], [79], [80]

In the last decade, the idea of meta-analysis on data-level emerged.[104] Its aim is to apply the gained but separated knowledge of the drug's PK in distinct populations without the need of pre-selecting a distinct model. Thereby, the observations from contributing population PK studies are gathered and evaluated across the broad populations. This leads to so-called pooled or next-generation models developed for a general predictive purpose in a broad range of patient types and based on large data. Colin *et al*. developed such a pooled vancomycin PK model based on data from 14 different studies (2 554 patients), including continuous and intermittent, neonates to aged, healthy to critically ill patients.[6] Similarly, McEneney-King *et al*. pooled data

from eight studies (310 patients) to develop a generic population PK model for Bayesian forecasting of at least seven FVIII products.[93] In our external validation of the predictive model performance (Publication I and II) both models successfully demonstrated their potential to forecast individual PK profiles and performed at least in the same range of the MAA/MSA. Yet, the pooled-data approach always requires access to the raw data and additional efforts to design a new model prior use in MIPD. The MAA and MSA instead require the data-derived model files, which often can be recoded from the original publication. Additionally, pooling the data bares the risk of neglecting (minor) subgroups or not accounting for specific conditions, while the MAA/MSA can easily be complemented by specific 'niche' models. Although these niche models separately may not necessarily be better for MIPD in a whole population,[105] MAA/MSA still might benefit on individual levels. Future studies comparing the performance of 'pooled-data' vs. 'pooled-model' approaches and different sets of heterogenous models would be of interest to further verify the extended use of MAA/MSA.

Continuous learning approach

A model may be selected (i) after the performance has been deemed acceptable in settings mimicking the intended clinical purpose as close as possible and (ii) based on matches of the study group and targeted individuals (e.g. physical condition, body composition or disease status). Nevertheless, naively implementing the selection into MIPD-software and rigidly applying it in clinical routine from there on, bears the risk of overrating the model's potential. Assuming that the model is totally unbiased in every patient, is as incautious as presuming the new parameter distributions always display the same magnitude as observed in the model development population.[106] The main reasons are time-varying changes related to the MIPD-applying institution (e.g. assay changes, changes in staff or their operation methods) and time-dependent changes within the patients physiology, PK and PD, which are not explainable with the model.

Consecutively, older data of the individual patient may be less informative to predict its future PK profile or target.

One way to improve an impaired model performance is to flatten model priors relative to individual observations.[107] The anchor points of the model (i.e. the Bayesian priors) are objectively downweighed in favour of more recent individual plasma measurements.

Additionally, the (TDM) data collected during MIPD of multiple patients could be used to update the model structure and parameters periodically. Although these continuous learning (COLE) approaches have been introduced in dosing of vancomycin,[105] modelling of paclitaxel-induced neutropenia[108] and haemophilia prophylaxis,[109] there is still a need for large data-based (and ideally prospective) evaluation of COLE prior a systematic comparison to the MAA/MSA. Yet on conceptual level, three pitfalls are conceivable with COLE.

First, TDM data is often prone to documentation errors. When using flawed data to continuously update a model one risks to sustainably harm its performance,[110] while in MAA/MSA the model parameters are not altered. Hence, only the very single patient is affected, though time-dependent changes may still be covered by automated and individual shifts in the weighting function of the MAA/MSA.

Second, COLE requires a substantial quantity of data (ideally >200 patients) in the very hospital that aims to implement such an updating tool,[105] while the MAA/MSA may work with the first patient.

Third, the updated parameters need to be communicated comprehensively and the predictive performance of the COLE approach must be periodically reassessed to rapidly detect over-/underadaption. Otherwise, opacity or lacking validation may mask overfitting and consecutively threatens the therapeutic success.[109]

Adaptive maximum a posteriori estimation

A strategy to account for time-varying changes in the individual is to encode an additional variability term on distinct parameters, named inter-occasion variability

(IOV). This variability term aims to characterize seemingly random changes in PK or PD of the individual. However, the morphology of IOV issues a major challenge when being used in predictive- rather than descriptive models. The IOV is randomly drawn from period to period and based on the data from that respective time. Given future data has not yet been collected, the individual IOV may not simply be extrapolated to that future. Wicha *et al.*[111] and a thereupon constructed simulation study[112] investigated multiple ways to handle IOV in MIPD and recommended to downweigh historical drug concentration measurements or ideally include IOV to generate the MAP estimates but exclude the IOV for forecasting future doses, respectively.

An approach even more flexible was proposed by Guo *et al.*[113] The authors detected in a retrospective TDM-based study that the estimated clearance of 408 vancomycin-treated patients on an intensive care unit is decreasing over time. To account for time-dependent shifts, they developed an iterative adaption of the individual model parameters. In detail, the individual MAP estimates based on a distinct set of historical TDM measurements become the new prior after new drug measurement data has been obtained. Adapting the model prior for each MAP iteration improved the predictive performance of the underlying model in comparison to the classical MAP estimation.

Nonetheless, shifting the model parameters over time bears the risk of overfitting similar to the above introduced approach of flattening the prior.[107] Since the new MAP estimate can be drawn from the same distribution (i.e. magnitude) as in the preceding iteration, the prior can shift completely untied. Even a single erroneous measurement may cause dramatically misguided parameters. In contrast, MAA and MSA rather add another variability term on model-level, but do not risk changing into misguided models during the MIPD process. Especially the handling of IOV in different multi-model approaches should be investigated in further studies.

4.2 Data acquisition and patient-specific factors

Optimal sampling time

Acquiring data is time-consuming and error-prone, given it is carried out by humans. Although there often is a consensus about what to collect for dosing individualization, it may be questionable when exactly to collect the information – especially in sparse sampling strategies. Nowadays, trough samples are commonly used for TDM, but differently timed or even multiple samples are required depending on the method used to individualize dosing and intended target. For example, the EQA (see 4.1.3) always depends upon one peak and one trough level obtained in the same dosing interval and at steady-state to approximate the individual AUC.[48] Thereby, this log-linear regression needs a strictly followed sampling scheme and is only reliable in case of stable PK. For pharmacometric approaches, the estimation is less sensitive to the sampling time compared with conventional approaches.[114] However, optimized sampling may still advance individual therapies as long as the exact sampling time is accurately documented.[89], [114]–[116]

In Publication IV, we hypothesized that certain time windows may contain more information than for example a trough sample (usually obtained during vancomycin TDM) to forecast the individual AUC. In fact, the optimal single-sample timepoints were identified around 2 hours after the first dose and around 6 hours, when being at steady-state conditions. These early sampling time windows allow for dose adjustments within the first dosing interval – presuming rapid bioanalytic of the vancomycin plasma concentration is available. This, in turn, might give sufficient time to already individualize the second dose, which is impossible with the currently used trough sampling strategy. These rapid and precise dose adjustments are of double value, given that every delay of antibiotic treatment in septic patients is associated with a 7.6 % higher death rate.[117] Additionally, our simulation-estimation study showed that the timing of the second sample was less impacting the predictive performance, provided the first sample was optimally timed.

Albeit our results were purely based on simulations, these were in line with a prospective study comparing AUC-guided versus trough-based vancomycin dosing and emphasize that pre-trough measurements should be preferred in MIPD of vancomycin.[89] To further validate these findings, our results could directly indicate the ideal and reduced sampling intervals in prospective studies to lessen the burden on the participants.

Drug quantification of clinical samples

The timing of the sampling is impacting the predictive performance of the pharmacometric models, whether with a focus on optimal time windows within the dosing interval or in relation to the forecast (e.g. given that more historical data reduced predictive performance [54], [113]). Nonetheless, additional data-related factors should be considered during MIPD.

One such factor is the assay used to quantify the drug within the clinical sample. For diagnosing and treating haemophilia A, two assays are widely used: the one-stage clotting assay (OSA) and the chromogenic substrate assay (CSA). The assays indirectly measure the FVIII activity either based on the turbidity induced through FVIII activated clotting (in OSA) or the spectrometric analysis of a chromogenic substrate released from a FVIII-dependent reagent.[118] Although both assays are accepted for FVIII quantification, there is an ongoing controversy about which one to prefer for clinical monitoring.[118]–[121] While the OSA is inexpensive, easy to automate and rapid, the CSA is more sensitive at lower FVIII levels, more reproducible across laboratories/FVIII products and may be more precise. [122] In Publication I, we evaluated the predictive performance of published population PK models as well as the MAA/MSA using the two assays, respectively, and found that predictions using the CSA data were more accurate than those using OSA.

Vancomycin samples are commonly quantified using chemiluminescence and enzyme immunoassays, but turbidity- and fluorescence assays have also been proposed.[123]

Although all assays independently of the monitored disease can determine the drug concentration below a certain threshold with an acceptable random variation, a major challenge for MIPD lies within handling samples below this lower limit of quantification (LLOQ).[124] Common assays for vancomycin and FVIII report a LLOQ between 1 and 5 mg/L and 1 IU/dL, respectively.[125], [126] If the LLOQ is close to the targeted (surrogate) concentration (e.g. in haemophilia A the target is defined as time above 1 IU/dL), the information provided by these samples is limited. Similarly, the predictive model loses power, if the residual error component exceeds the value of the LLOQ. When optimizing sampling times for MIPD, these factors should be additionally considered.

Impact of different populations

Furthermore, patients are usually classifiable into specific populations (e.g. critically ill, obese or patients with certain co-morbidities). Organ functions or physiological conditions that deviate from 'normal' expectations, thereby, alter the PK of the drug.[127] For example, haemophilic children display larger volumes of distribution compared to normal weighted adults. Although an increased volume of distribution prolongs the half-life of a drug, FVIII products are eliminated faster in children compared to adults due to their also higher clearance.[128] Another example are critically ill patients being treated with vancomycin. These intensively monitored patients usually display substantial and even nonlinear PK changes, such as increased volume of distributions and time-varying elimination rates.[78], [129]

If these PK alterations are not appropriately accounted for, predictions using a single population PK model in MIPD may be hampered. In contrast, the MAA/MSA is able to cover a wider range of populations, through the inclusion of particularly different models. Even if a patient does not subjectively fit into a specific group or may display atypical parameters, the MAA/MSA are able to select the objectively best fitting model.[81]

4.3 The MIPD user/operator and implementation into clinical practise

In Publication I and III, we demonstrated the implementation of (i) a population PK model suitable for haemophilia A prophylaxis and (ii) the multi-model approaches MAA/MSA for vancomycin dose adjustments into the MIPD software TDMx.[4] Although mainly an educational tool, we aimed to integrate the idea of novel MIPD approaches into usable tools to bring them closer to clinical care. Yet, to deem a software suitable for MIPD, certain requirements on the tool are made. Besides the discussed topics of selection and validation of the underlying model(s) (4.1) and assuring quality of the data (4.2), four main aspects are relevant.

- Firstly, as with any software, its usage strongly depends on the user's experience. The end-user specific interface needs to be intuitive and unambiguous but at the same time must provide enough information and transparency to easily comprehend the outcome.[130] Time-consuming activity during routine practise must be avoided, for example through integration into existing electronic prescribing systems.[131] The software should provide a set of convenient features next to the precision dosing-functionality (e.g. structured data export functions, interactive plots and parameter overviews or generation of suitable reports). The more complex the software becomes, the more important becomes user support (e.g. via clinical manuals, online support or discussion forums) as well as adequate training to enhance the user's experience.[132], [133]
- Secondly, data is the currency of the world wide web. Especially when it comes to health-related information, abuse of this valuable asset must be prevented. Thereby, it is easiest to comply with current standards in data security and privacy legislation, if the user is in full control of his data and no confidential information will be saved on (or externally accessible from) servers foreign to the user/his institution (e.g. as with TDMx). Given that this hampers the possibility of continuous learning approaches or the assembling of large databases, other developers aim to comply with data security standards and privacy policies through fulfilling the European Union General Data Protection Regulation (EU

GDPR[134]) or equivalents (e.g. InsightRX[135] or WAPPS-Hemo[136]). This includes secured access via personal logins, encrypted databases, as well as confidential and anonymized data collection.

- The third aspect influencing suitability of the MIPD software is based on costs introduced during development and application. Although it is desirable, from a scientific perspective, to already provide MIPD software with drug approval, the increase in costs and regulatory difficulties discourage pharmaceutic industries of its development. For example, engineering a companion tool during drug development (i.e. a dynamic label) could support dosing decisions already in earlier study phases and allows for more heterogenous inclusion of study participants. However, it requires more funds due to increased need of validation, more frequent monitoring, potentially increased physician time and higher numbers of trial participants.[52]

  Additionally, regulatory obstacles occur due to the unsolved problem of responsibilities when MIPD is a prerequisite for drug approval.[137] In case of (dosing) failure, it may not be clear who is responsible: the prescriber, who based his decision on MIPD software, or the provider of the MIPD-software. Hence, regulatory guidance to validate software (as from the EU[138] and FDA[139]) is just the first step.

  Moreover, widespread utilization of MIPD during clinical routine must prove a positive cost to benefit ratio. Given that evidence of cost savings through MIPD over current best practice is relatively sparse, benefits have yet to be shown unequivocally in large prospective studies.[89], [140] Otherwise, MIPD approaches will unlikely be a serious competitor to classical dosing strategies in hospitals.
- Fourth, practising physicians often view results of population analysis with scepticism due to potentially opaque methods or the use of perplexing equations and statistical jargon.[141] Further liability issues arise through software-based

recommendations of unapproved doses or off-label use given that MIPD tools are developed post drug approval.[142]

Through implementing the findings of this thesis into the freely available web application TDMx (www.tdmx.eu), we provide an educational tool, which can already be used to train undergraduate students or healthcare personnel. This, in turn, might bring MIPD closer to clinical practise.

While barriers to implement MIPD software into clinical practise will continue to exist, these are rather logistic and educational but not technological. Through proper training of healthcare professionals and undergraduates, clear legal regulation and consolidation of the goal of favouring maximal therapeutic value rather than financial profit, we may predict a future of gradually advancing treatments for the individual patient.

5 Perspective

Despite the growing recognition of MIPD by healthcare professionals, patients and politics,[45] its common application in clinical practise has yet to come. The introduction of novel multi-model approaches, like the MAA and MSA, as well identifying suitable models and sampling time points to forecast individual drug exposures and, consecutively, precise doses, may serve as necessary steps towards this goal. Nonetheless, a few limitations need to be acknowledged in this thesis.

While the robustness of the MAA/MSA regarding the influence of included models was evaluated in Publication III, more exhaustive investigations may be of benefit. It seems especially interesting to evaluate the maximal number of included models, or interweave different multi-model approaches among each other (e.g. purely including pooled population models in the MAA/MSA, or fusing multiple approaches in hybrid algorithms as introduced by Hughes *et al*.[107]).

As introduced in Chapter 4.1.2, there are ideas to account for instable patients with time-varying PK in Bayesian forecasting.[113], [143] Thereby, the handling of inter-occasion variability in the underlying model is crucial.[111] In further studies, different methods to account for inter-occasion variability, when used in the MAA/MSA may be of interest.

The current work mainly focuses on PK based dosing decisions. Nonetheless, PD measurements, like C-reactive protein or procalcitonin levels as biomarkers for the inflammatory status of infected patients,[144] or the annual bleeding rate of haemophilic patients,[145] should be evaluated in their predictive value.

Out of scope of this thesis were non-parametric approaches[34], [49] and machine learning algorithms,[107], [146] which are fundamentally different from the discussed parametric approaches, as these approaches do not rely on typical distributions but so-called supporting points. Although especially machine learning is nowadays associated with dramatically high expectations, these approaches always come with the drawback of not being easily transferable. Prior implementation, the exact supporting points or the original data plus training data, which matches the later purpose (i.e. directly obtained in the tool-implementing hospital), are required. However, comparing

nonparametric and parametric approaches in future clinical studies could be of interest, given simulation-based comparisons seem promising.[107], [147], [148]

Last but not least, despite the thriving promises in MIPD, we – as pharmacometrician, clinician, or simply as a patient – must always keep aware of Box' paradigm: "All models are wrong but some are useful."[149]

6 References

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7 Appendix

7.1 Supplementary material of Publication I

Supplemental Digital Content 1.

All samples were measured on an ACL TOP (Werfen UK, Cheshire, United Kingdom) in a chromogenic assay (CSA) using a BIOPHEN FVIII kit (Hyphen Biomed, Neuville-sur-Oise, France) and a one-stage activated partial thromboplastin time (APTT) assay (OSA), with the HemoSil SynthaSil APTT reagent (Werfen UK, Cheshire, United Kingdom). The OSA calibrator was traceable to the WHO IS plasma FVIII standard, and the samples were measured against an 8-point calibration curve. If continuous covariates were missing, then the dataset median was imputed.

Supplemental Digital Content 2.

The simulated standard patient weighed 75 kg, was 1.7 m tall, and 35 years old, and a von-Willebrand-factor (vWF) level of 110% was documented. The patient received prophylactic doses (3000 IU) of either B-domain deleted (BDDrFVIII) or full-length recombinant product every 72 h. The pharmacokinetic profile and the time above the target of 2 IU/dL in steady-state conditions were subsequently compared. If the models were developed purely in a one-stage assay (OSA) without BDDrFVIII products, no discrepancies between the chromogenic assay (CSA) and OSA were implemented.

Supplemental Digital Content 3.

The reference model was developed in NONMEM® software (version 7.4.3; ICON plc, Dublin, Ireland) using all FVIII:C values measured using chromogenic assay. The reference model was chosen based on the best objective function value and the best possible visual fit of the individual pharmacokinetic profiles (see Figure, Supplemental Digital Content 4, which demonstrates the reference model fit in the 39 individuals). The structure and parameters can be inspected using the following equations (Eqs. S1–S5). The data were best described using a two-compartment model with first-order elimination. The inter-individual variability was implemented exponentially on the clearance (Cl; 51.3% CV) and on the central volume of distribution (V_{centr}; 24.5% CV), and the combined error model was implemented for the residual unexplained variability (Proportional: 7.8% CV, Additive 1.85 IU/dL). A baseline FVIII level of 0.522 IU/L was used in this study. The coefficient of variation (%CV) was calculated as $\sqrt{\omega^2} \times 100$.

$$Cl\ [\frac{dL}{h}] = 2.51 \times e^{\eta Cl} \quad \text{(Eq. S2)}$$

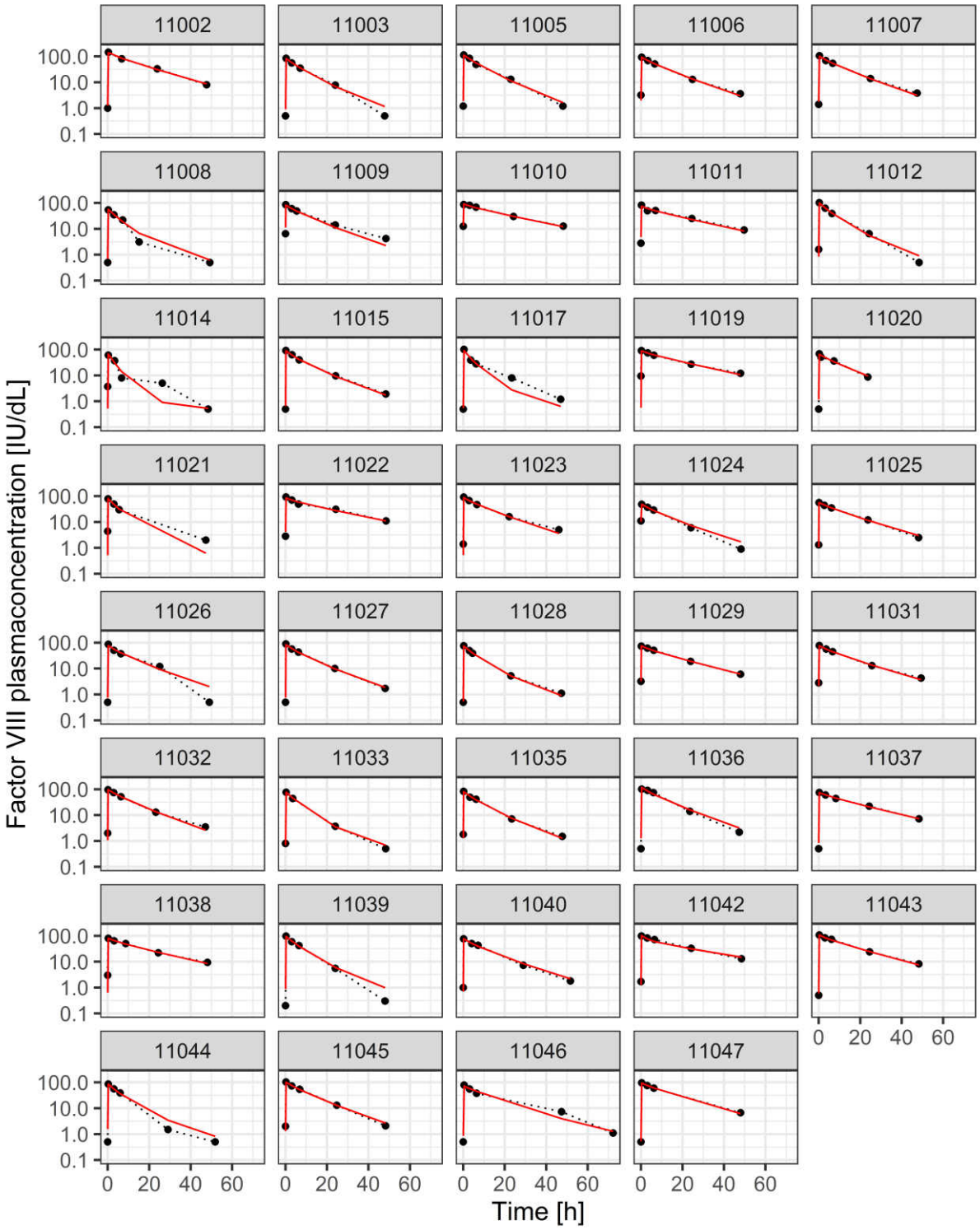
$$V_{centr}\ [dL] = 28.3 \times e^{\eta V_{centr}} \quad \text{(Eq. S3)}$$

$$V_{periph}[dL] = 4.02 \quad \text{(Eq. S4)}$$

$$Q\ [\frac{dL}{L}] = 0.808 \quad \text{(Eq. S5)}$$

$$\text{Baseline}\ [\frac{\text{IU}}{\text{dL}}] = 0.522 \quad \text{(Eq. S6)}$$

η, individual eta value drawn from the variance term (ω^2) describing the respective inter-individual variability



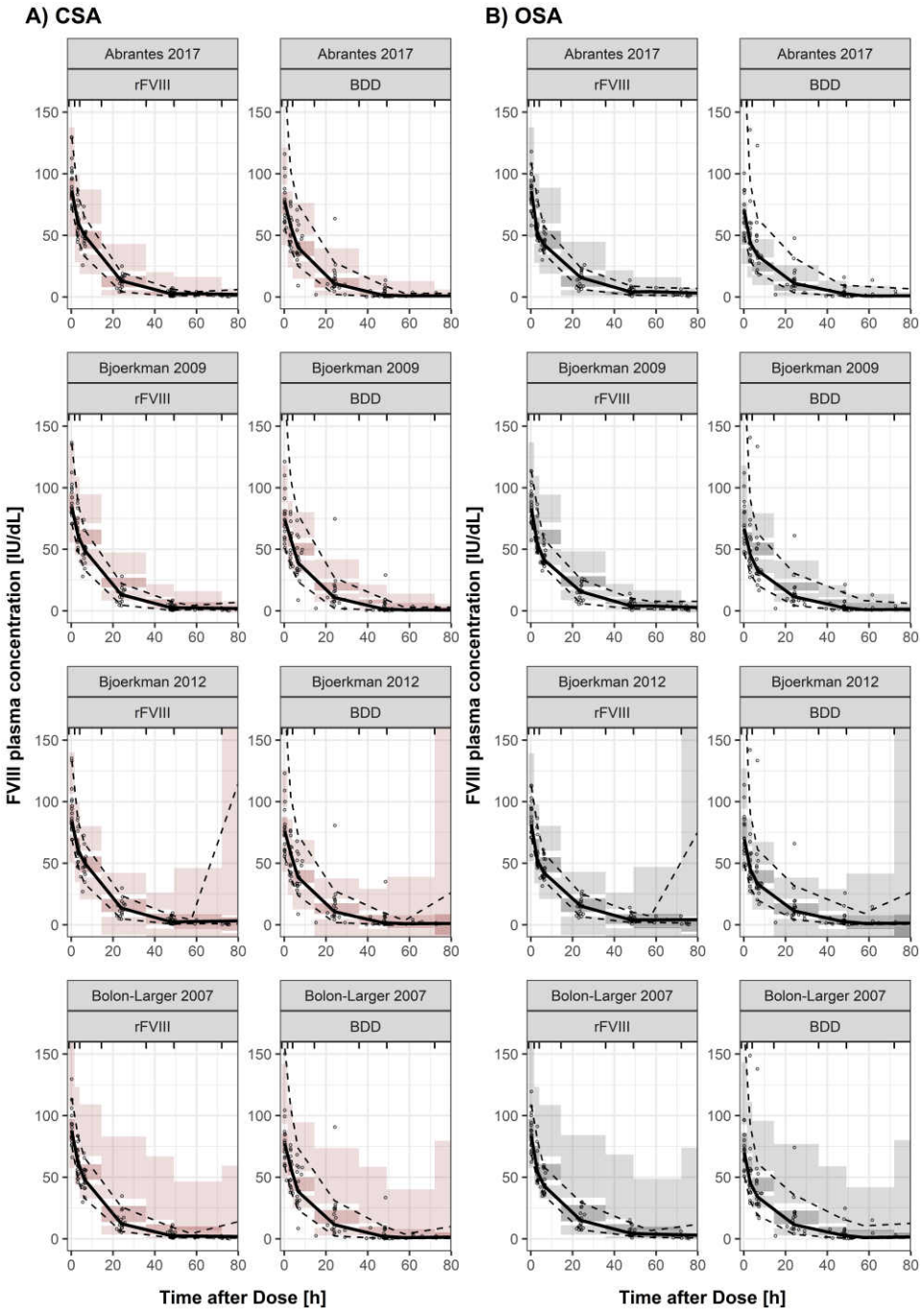
Supplemental Digital Content 4. Individual FVIII plasma concentrations either measured with the chromogenic assay (black dots) or predicted with the internally built reference model (see Text, Supplemental Digital Contant 1) per individual. Time represents the time after the most recent dose.

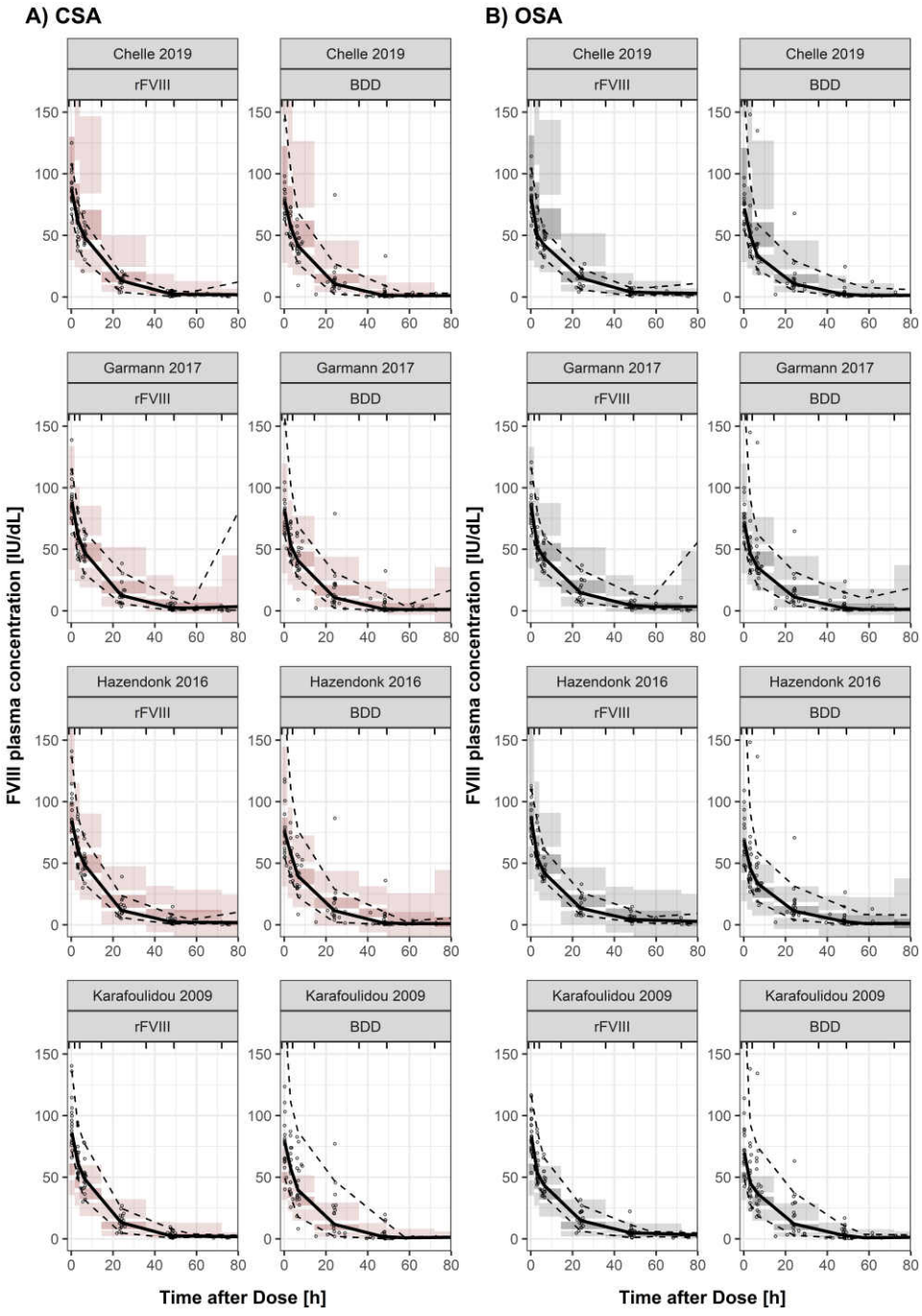
Supplemental Digital Content 5. Details of the evaluated population pharmacokinetic models

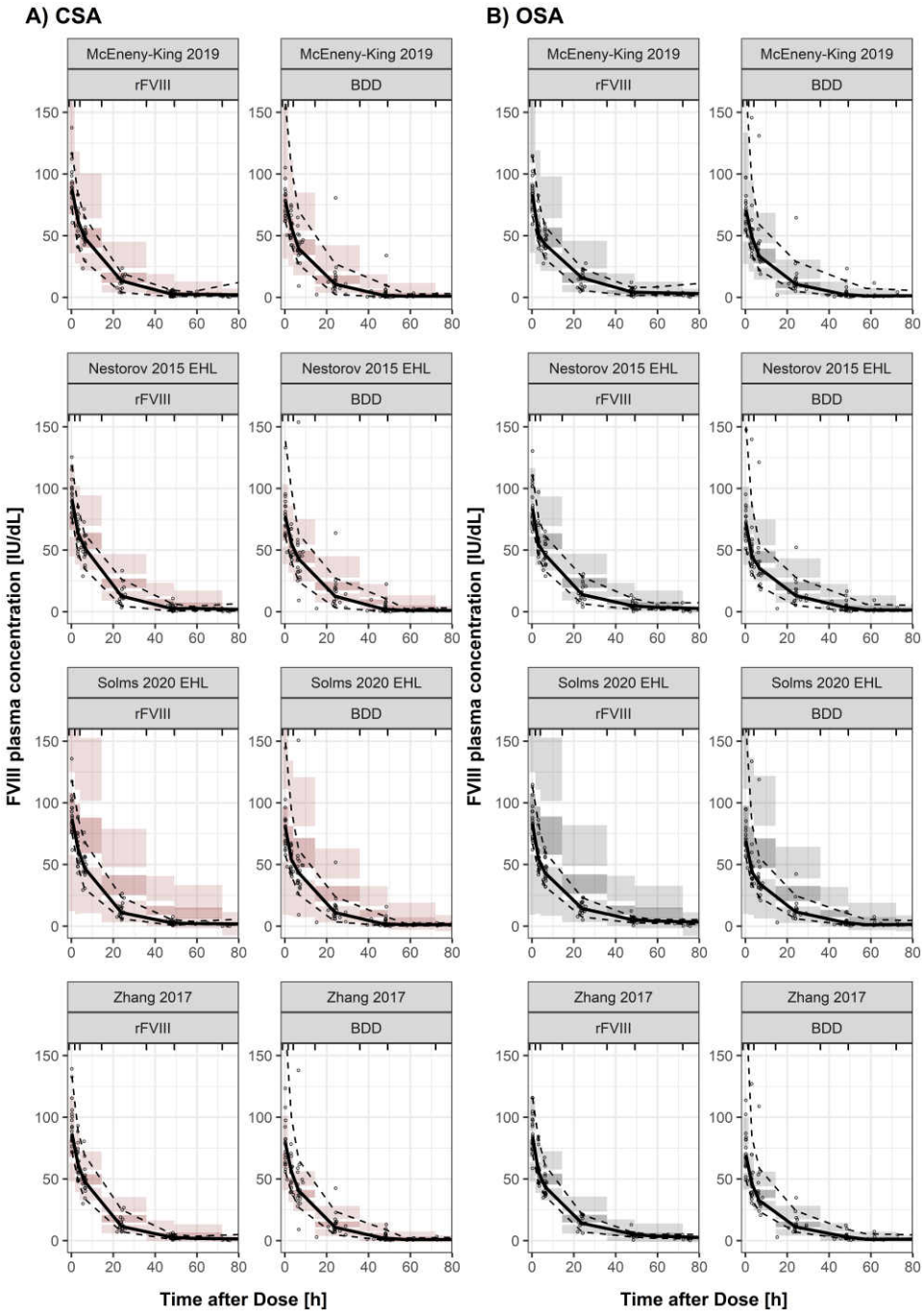
	Compartm	Patients (number)	Investigated severity	Assay	FVIII product	Sampling points, no	Sampling time, h	Covariates	IIV, % CV	IOV, % CV	RUV
Abrantes 2017	2	520 (+234 adolescents)	SHA / MoHA	CSA / OSA	BDDrFVIII (Xyntha® / Refacto®)	2–12	0–72	Age, assay, BW, INH, race, severity, study, FVIII product (FLrFVIII vs. BDDrFVIII)	CL: 31 F: 13 Baseline: 7	CL: 34 V2: 41	A: - P: 19.2
Bjoerkman 2009	2	50	SHA / MoHA	CSA	Various plasmad. / FLrFVIII (/BDDrFVIII)	various	ND	Age, BW, FVIII product (plasmad. vs. rFVIII)	CL: 28 V1: 17 Corr: 0.64	CL: 13 V1: 10	A: 1.2 P: 8.5
Bjoerkman 2012	2	184 (+52 adolescents)	SHA	OSA	FLrFVIII (Advate®)	4–10	0–48	Age, BW	CL: 30 V1: 21 Corr: 0.45	-	A: 8.9 / 7.1 P: -
Bolon-Larger 2007	2	51	SHA / MoHA / MHA	ND	Plasmad. / FLrFVIII	5–9	0–48	BW, BSA	CL: 42 V1: 21 k12: 17 k21: 154	-	A: - P: 9.3
Chelle 2019	2	92	SHA	OSA	Plasmad. (Fanhdi/Alphanate®)	1–8	0–72	Age, fat-free mass	CL: 46 V1: 54 Corr: 0.797	-	A: - P: 20.5
Garmann 2017	2	183	SHA	CSA	FLrFVIII (Kovaltry®)	4–10	0–110	LBW	CL: 37 V1: 11	-	A: 1.1 P: 11.2

Hazendonk 2016	2	119	SHA / MoHA	OSA	Plasmad. / FLrFVIII / BDDrFVIII	various	ND	Age, BW, severity of operation, FVIII product (FLrFVIII vs. BDDrFVIII)	CL: 37 V1: 27	-	A: 15 / 5 P: 18 / 23	A: 0.421 / 0.208 P: 13.6	CL: 21 V1: 12 Corr: 0.64
Karafoulidou 2009	1	28	SHA / MoHA / MHA	OSA	BDDrFVIII (Refacto®)	2–6	0–48	BW, HIV status	CL: 39 V: 13	-	A: - P: 15.2		
McEneny-King 2019	2	704	SHA / MoHA	OSA	Plasmad. / FLrFVIII / BDDrFVIII	4–12	0–72	Age, fat-free mass, FVIII product (plasmad. vs. FLrFVIII vs. BDDrFVIII)	CL: 41 V1: 32 Corr: 0.703	-	A: - P: 17.4		
Nestorov 2015 EHL	2	180	SHA	OSA	EHLrFVIII	5–12	0–240	BW, HCT, vWF, study	CL: 24 V1: 13 Corr: 0.55	-	A: 1.78 P: 41.8		
Solms 2020 EHL	1	198	SHA	CSA (/OSA)	EHLrFVIII (Jivi®)	2–11	0–168	LBW, vWF	CL: 24 V1: 13 Corr: 0.449	-	A: 1.15 P: 10.9		
Zhang 2017	2	130	SHA	CSA	EHLrFVIII (Afstyla®)	5–10	0–96	BW, vWF	CL: 24 V1: 20 Baseline: 59	-			

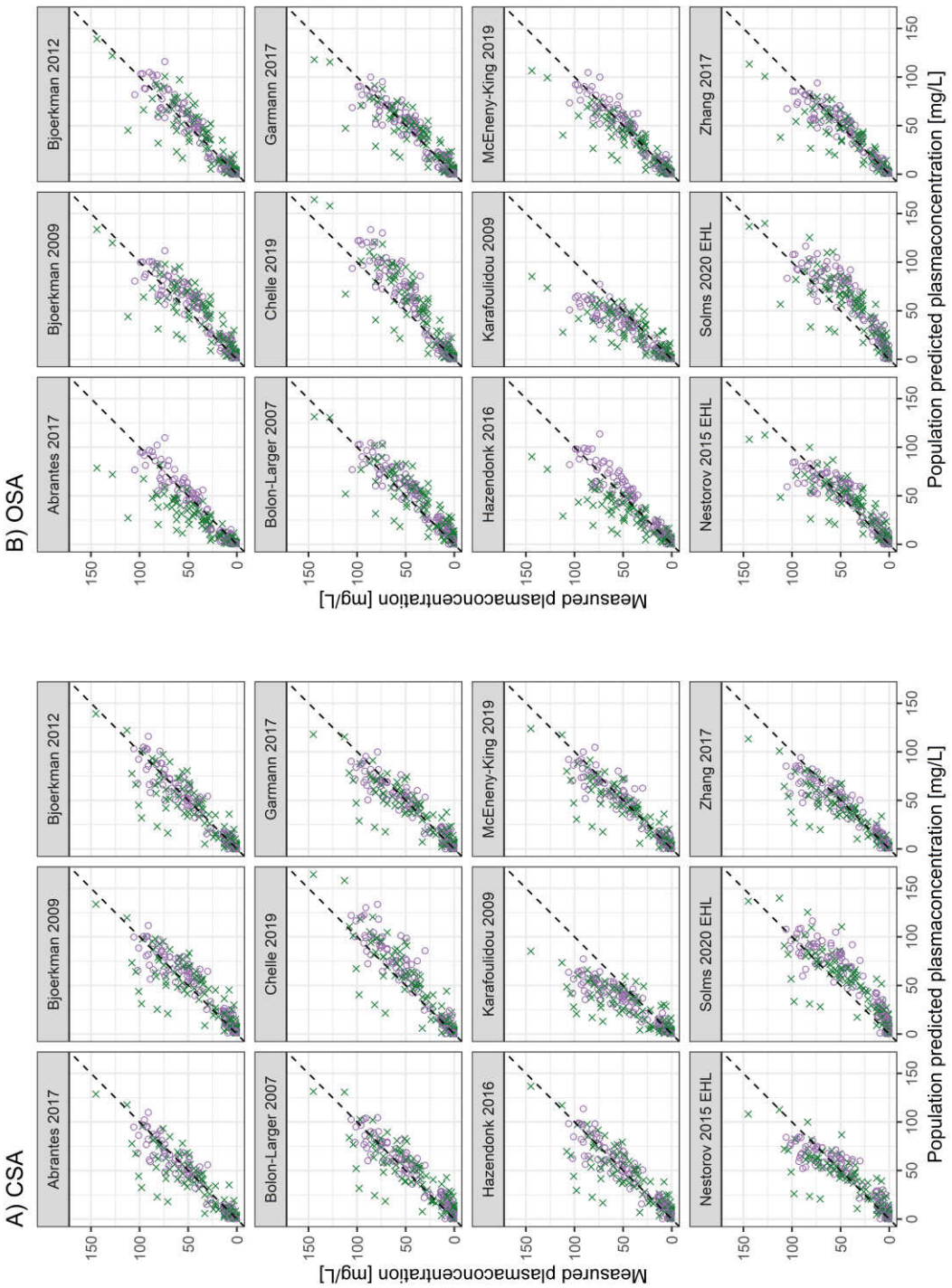
IIV – interindividual variability; IOV – interoccasion variability; RUV – residual unexplained variability with A – additional error, [IU/dL]; P – proportional error, [%];
SHA – severe hemophilia A; MoHA – moderate hemophilia A; MHA – mild heemophilia A;
O – one stage assay, C – chromogenic;
FLrFVIII – full-length recombinant product; BDDrFVIII – B domain deleted product; EHLrFVIII – extended half-life product, Plasmad. – pooled human plasma-derived product;
BW – body weight; BSA – body surface area; HCT – hematocrit; INH – inhibitor status; LBW – lean body weight; vWF – von Willebrand factor;
CV – coefficient of variation; Corr. - Correlation of the variability components;
ND – not defined


A) CSA
B) OSA
Abrantes 2017
Bjoerkman 2009
Bjoerkman 2012
Bolon-Larger 2007
rFVIII
BDD
FVIII plasma concentration [IU/dL]
Time after Dose [h]

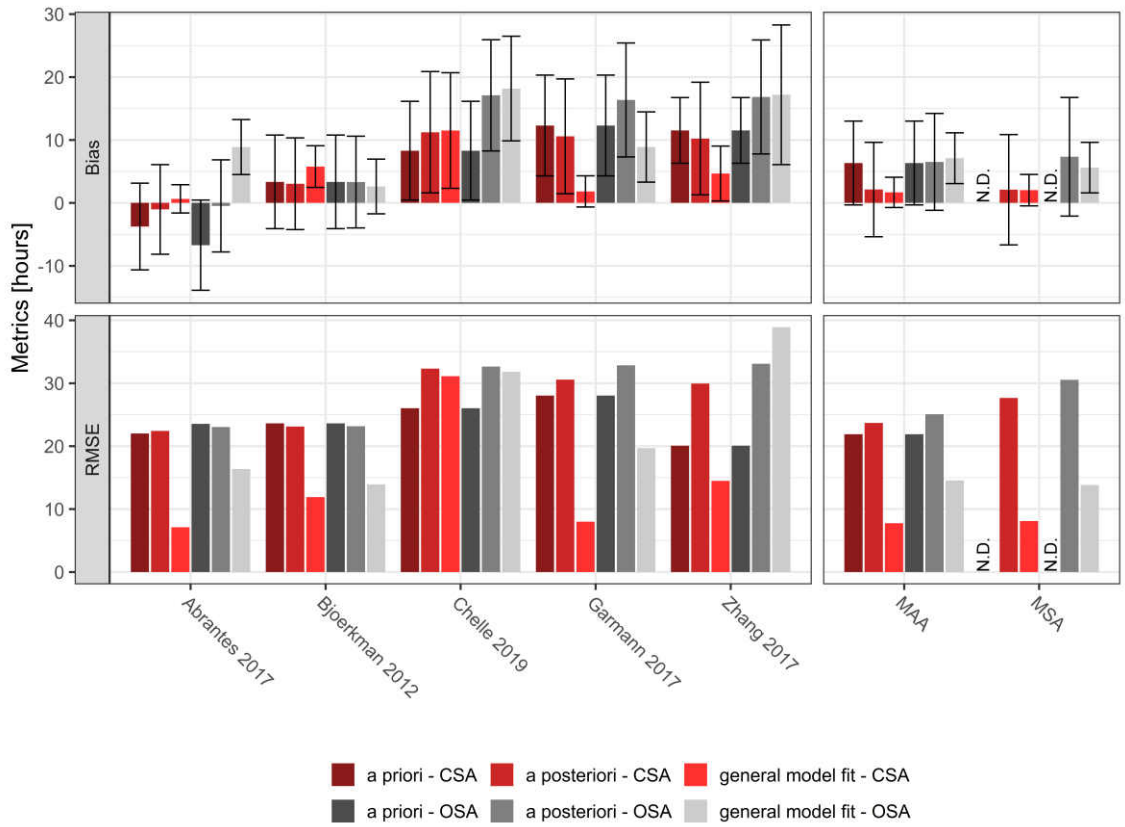

A) CSA
B) OSA
Chelle 2019
Garmann 2017
Hazendonk 2016
Karafoulidou 2009
rFVIII
BDD
FVIII plasma concentration [IU/dL]
Time after Dose [h]



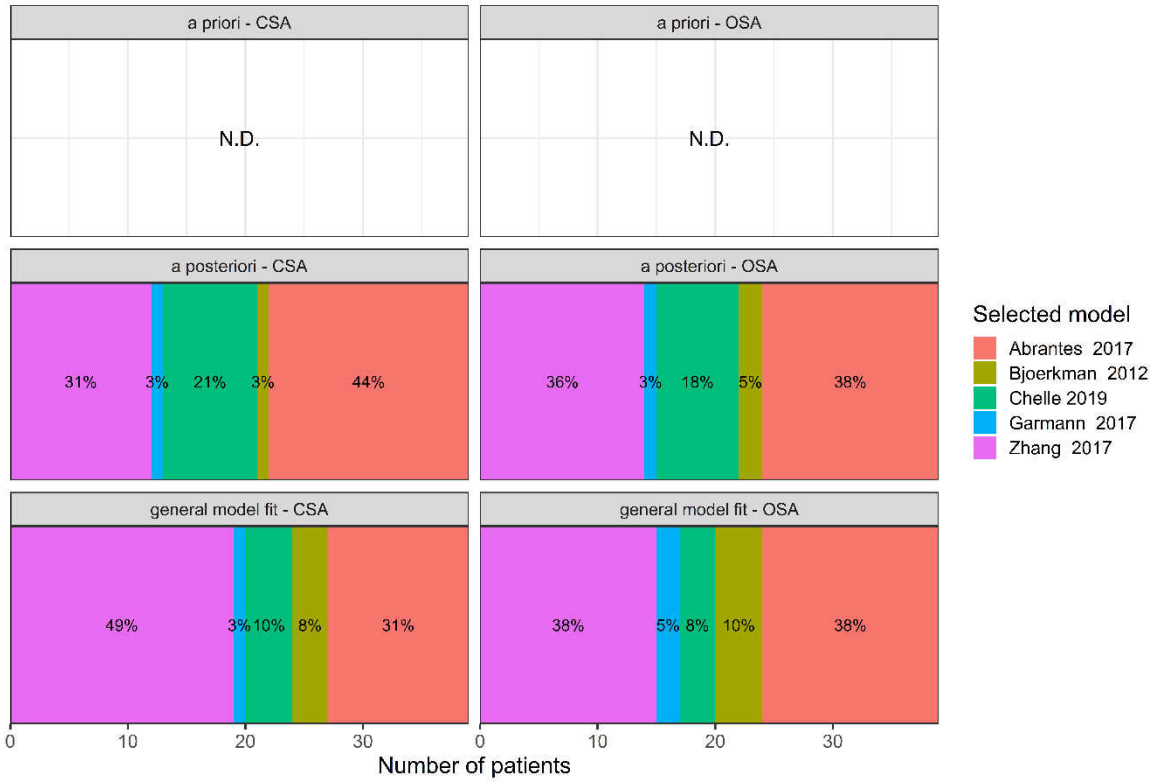
Supplemental Digital Content 6. Prediction corrected visual predictive checks (pcVPC) of the population pharmacokinetic models with observations measured using A) the one-stage assay (OSA) and B) the chromogenic assay (CSA). The pcVPC are furthermore stratified by the applied drug: B-domain deleted (BDD) or a full-length recombinant FVIII product (rFVIII). The x-axis was limited to 80h to improve readability. Six datapoints (trough level from the previous dosing occasion) are not displayed. The black solid and dashed line represents the median of the observed data (black dots) and its 5th / 95th quantiles, respectively. The shaded areas represent the 90% confidence interval of the 5th, 95th (light shaded) and 50th (dark) quantiles of the simulations (n=1000).



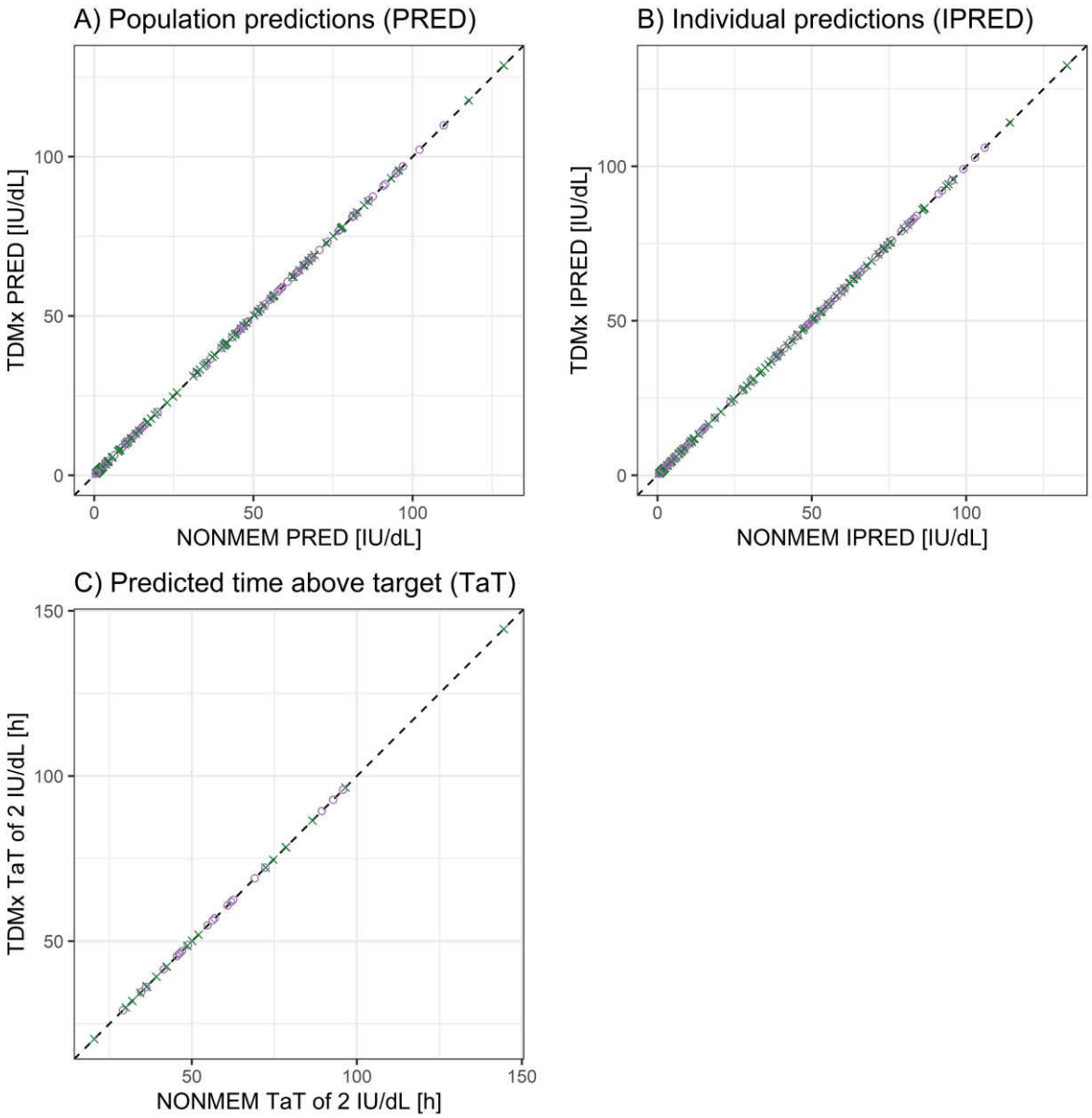
Supplemental Digital Content 7. Goodness-of-fit plots with the population predicted FVIII concentrations vs the measured FVIII concentrations per model. The concentrations were either measured using A) the chromogenic assay (CSA) or B) the one-stage assay (OSA). The dashed line represents the identity line; green crosses – B-domain deleted product(s), purple circles – full-length recombinant product(s)



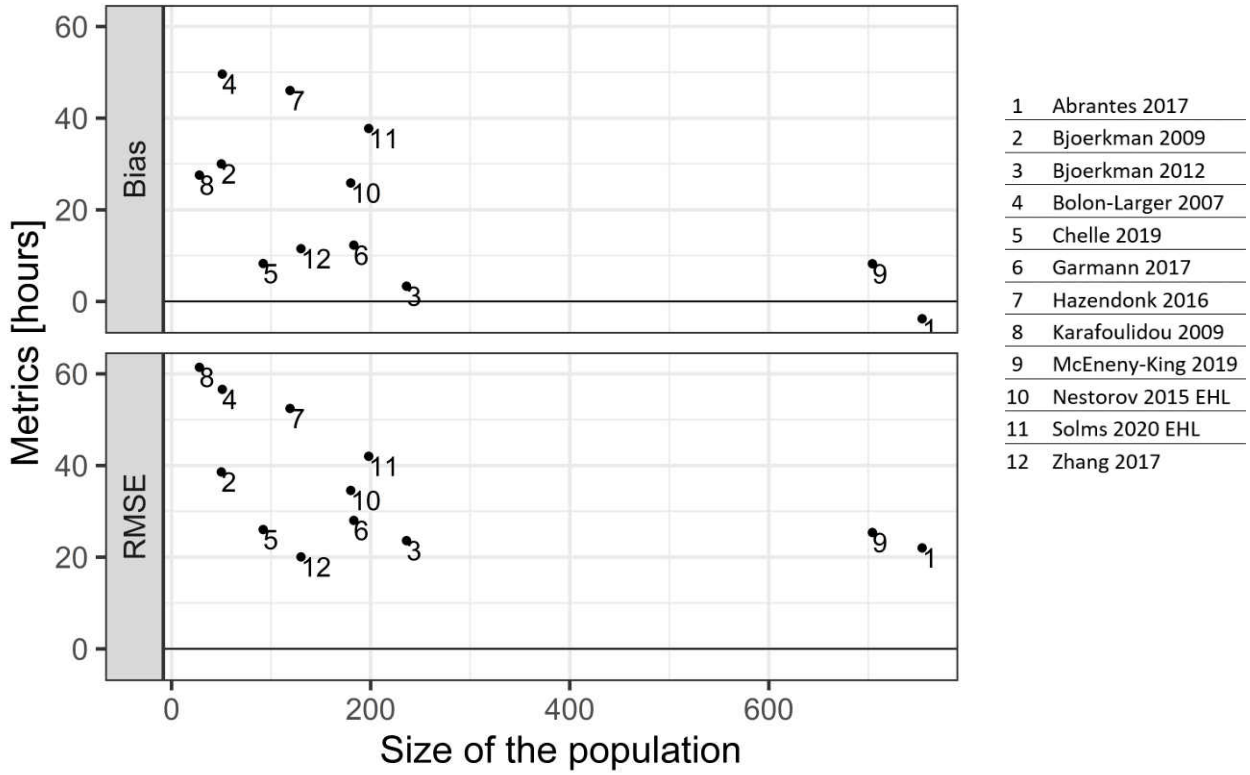
Supplemental Digital Content 8. The accuracy (i.e. bias) and the imprecision (root mean square error, RMSE) of the predicted time above target (TaT) of the model averaging algorithm (MAA) and model selection algorithm (MSA) and the single models used in both. The metrics are separated by the assay used (CSA: red and OSA: grey). The three hues represent the prediction scenarios. Whiskers cover the 95 % confidence interval of the bias calculated via the standard error; N.D. – not defined



Supplemental Digital Content 9. Composition of the model selection algorithm (MSA) within the population stratified by scenario and assay. Each colored bar reflects the number of patients, for which the respective model had been selected automatically. Black values represent the number of patients relative to the total population (%, n=39). N.D. – not defined as historically plasma measurements are required to automatically weight the population PK models



Supplemental Digital Content 10.: **A)** The population predicted and **B)** the individually predicted FVIII concentrations of the clinical CSA data (n=229) using the Abrantes model in either NONMEM or the MIPD-software 'TDMx'. **C)** The predicted time above target of 2 IU/dL in the richly sampled occasion of the 39 individuals using the same model in NONMEM or 'TDMx'. The diagonal line represents the identity line; green crosses – B-domain deleted product(s); purple circles – full-length recombinant product(s).



Supplemental Digital Content 11. The accuracy (i.e., bias) and the imprecision (i.e. root mean square error, RMSE) of the predicted time above target (TaT) in comparison to the true TaT (i.e., time obtained from the internal model and all CSA samples) in the *a priori* scenario versus the number of patients included during model development.

7.2 Supplementary material of Publication II

Supplement Table S1. Properties and standardized PK parameters (standard patient, 50 years old, male, 75 kg, 1,7 m, serum creatinine of 85 µmol/L) of the evaluated pharmacometric models. The table was adapted and modified from Broeker et al., CMI (2019). Nr. of pat: Number of patients, Nr. of samp. Number of vancomycin samples used for model development, CL: Clearance, Vc: central Volume of distribution, Vp: peripheral Volume of distribution (-: one-compartment model), Q: Intercompartmental Clearance (L/h, -: one-compartment model), CLCR: creatinine clearance, cRRT: continuous renal replacement therapy, TBW: total body weight, SCR: serum creatinine, CSF: cerebrospinal fluid

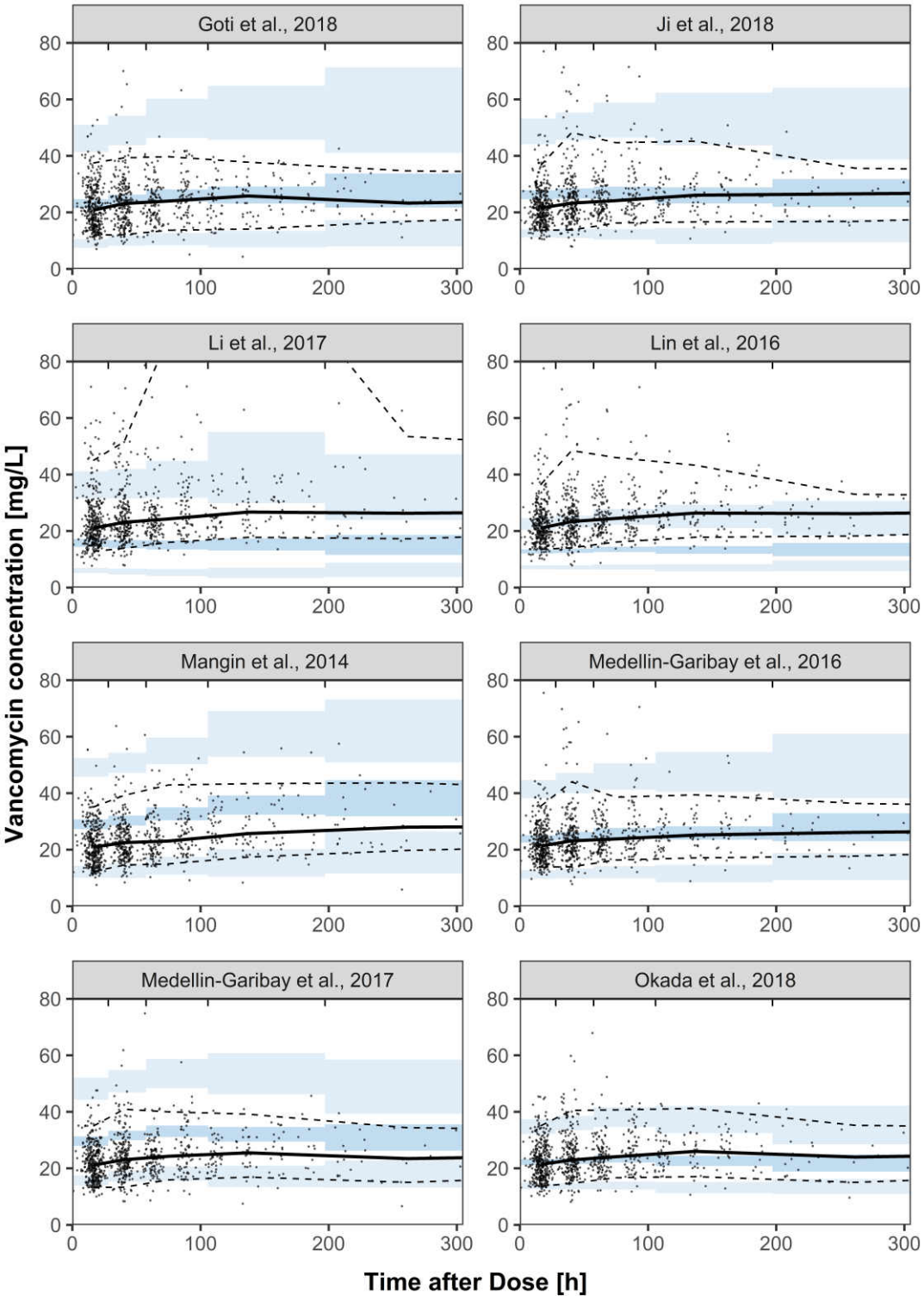
	Patient population	Nr. of pat	Nr. of samp	Covariates	CL	Vc	Vp	Q	Reference
Adane *et al.*, 2015	extremely obese	29	93	CL: CLCR; Vc: TBW	4.74	38.3	-	-	Adane ED, Herald M, Koura F. Pharmacokinetics of vancomycin in extremely obese patients with suspected or confirmed Staphylococcus aureus infections. Pharmacotherapy 2015; 35:127–39. doi:10.1002/phar.1531.
Alqahtani *et al.*, 2018	open heart surgery patients	28	168	CL: CLCR, Albumin; Vc: TBW	6.64	38.9	3.9	0.22	Alqahtani SA, Alsultan AS, Alqattan HM, Eldemerdash A, Albacker TB. Population Pharmacokinetic Model for Vancomycin Used in Open Heart Surgery: Model-Based Evaluation of Standard Dosing Regimens. Antimicrob Agents Chemother 2018; 19:1. doi:10.1128/AAC.00088-18.
Bae *et al.*, 2019	Korean patients under TDM	220	1020	CL: CLCR, hemodialysis, cRRT, Vc: TBW	2.82	31.8	75.4	11.7	Bae SH, Yim D-S, Lee H, et al. Application of Pharmacometrics in Pharmacotherapy: Open-Source Software for Vancomycin Therapeutic Drug Management. Pharmaceutics. 2019;11(5):224. doi:10.3390/pharmaceutics11050224
Bury *et al.*, 2019	Hematologic patients with and without cancer	116	742	CL. CLCR, Neutropenia; Vc/p: Fat free mass	3.22	45.8	51.7	4.03	Bury D, ter Heine R, van de Garde EMW, Nijziel MR, Grouls RJ, Deenen MJ. The effect of neutropenia on the clinical pharmacokinetics of vancomycin in adults. Eur J Clin Pharmacol. 2019;75(7):921-928. doi:10.1007/s00228-019-02657-6

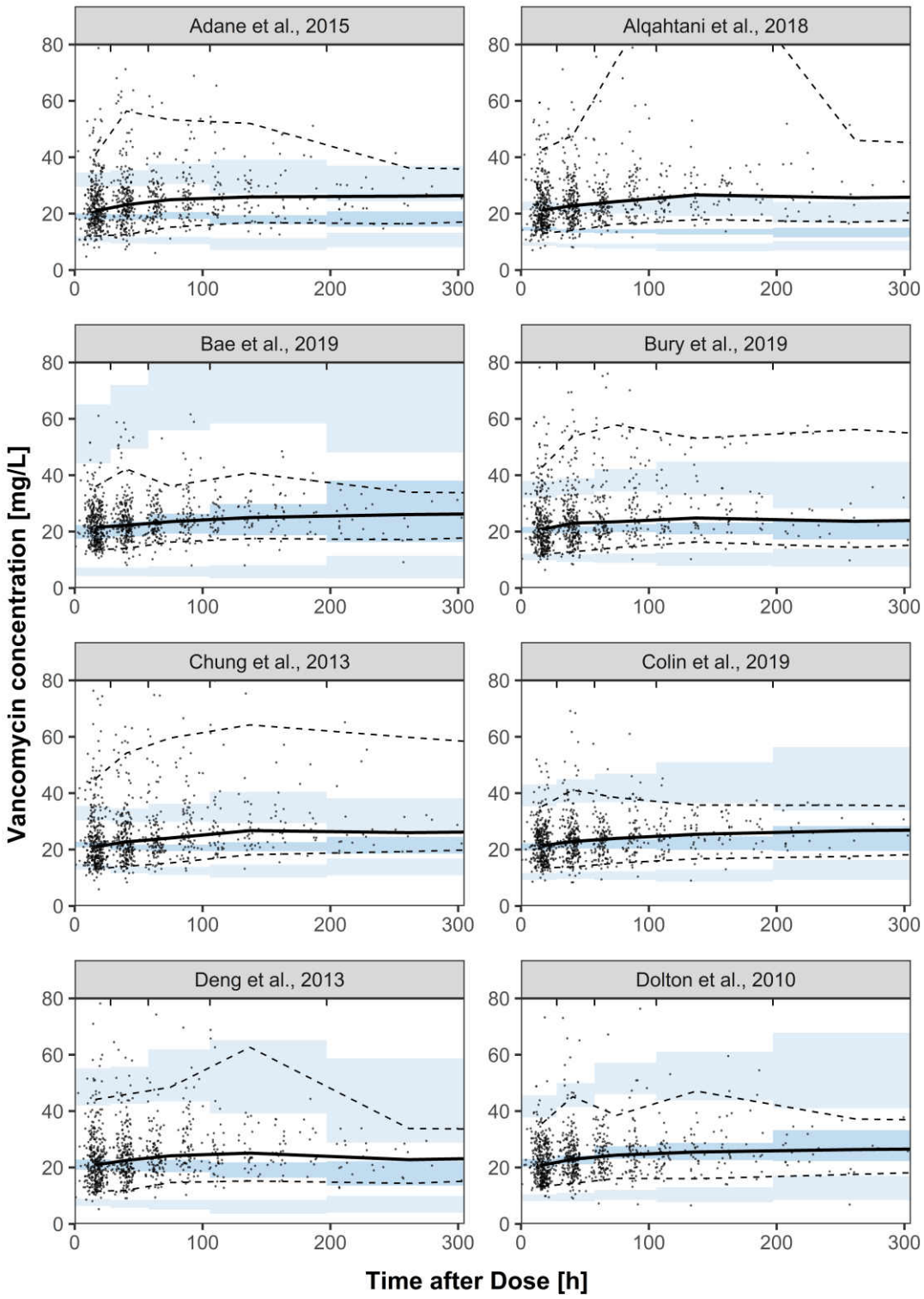
Chung *et al.*, 2013	Korean patients with normal SCR	678	1373	CL: cystatin C, age, TBW, SCR, sex; Vc: age, TBW, sex	5.03	48.5	-	-	Chung J-Y, Jin S-J, Yoon J-H, Song Y-G. Serum cystatin C is a major predictor of vancomycin clearance in a population pharmacokinetic analysis of patients with normal serum creatinine concentrations. J Korean Med Sci 2013; 28:48–54. doi:10.3346/jkms.2013.28.1.48.
Colin *et al.*, 2019	Newborns to elderly patients, underweight to obese adults	2554	8300	CL: age, SCR, studytype; Vc/p: TBW	4.28	46.0	44.7	3.39	Colin PJ, Allegaert K, Thomson AH, et al. Vancomycin Pharmacokinetics Throughout Life: Results from a Pooled Population Analysis and Evaluation of Current Dosing Recommendations. Clin Pharmacokinet. 2019;58(6):767-780. doi:10.1007/s40262-018-0727-5
Deng *et al.*, 2013	adult Chinese patients	72	167	CL: CLCR	4.90	47.8	-	-	Deng C, Liu T, Zhou T, Lu H, Cheng D, Zhong X, et al. Initial dosage regimens of vancomycin for Chinese adult patients based on population pharmacokinetic analysis. Int J Clin Pharmacol Ther 2013; 51:407–15. doi:10.5414/CP201842.
Dolton *et al.*, 2010	patients with severe burns	70	97	CL: CLCR; Vc: TBW, severe burns; Vp: TBW	2.97	73.3	78.2	4.54	Dolton M, Xu H, Cheong E, Maitz P, Kennedy P, Gottlieb T, et al. Vancomycin pharmacokinetics in patients with severe burn injuries. Burns 2010; 36:469–76. doi: 10.1016/j.burns.2009.08.010.
Goti *et al.*, 2018	hospitalized patients with high prevalence of renal impairment	1812	2765	CL: CLCR, hemodialysis status; Vc: TBW, hemodialysis status	3.82	62.6	38.4	6.5	Goti V, Chaturvedula A, Fossler MJ, Mok S, Jacob JT. Hospitalized Patients With and Without Hemodialysis Have Markedly Different Vancomycin Pharmacokinetics: A Population Pharmacokinetic Model-Based Analysis. Ther Drug Monit 2018; 40:212–21.
Ji *et al.*, 2018	Adult Chinese patients	160	251	CL: CLCR, age	2.83	52.1	-	-	Ji X, Ji S, He X, Zhu X, Chen R, Lu W. Influences of renal function descriptors on population pharmacokinetic modeling of vancomycin in Chinese adult patients. Acta Pharmacol Sin. 2018;39(2):286-293. doi:10.1038/aps.2017.57

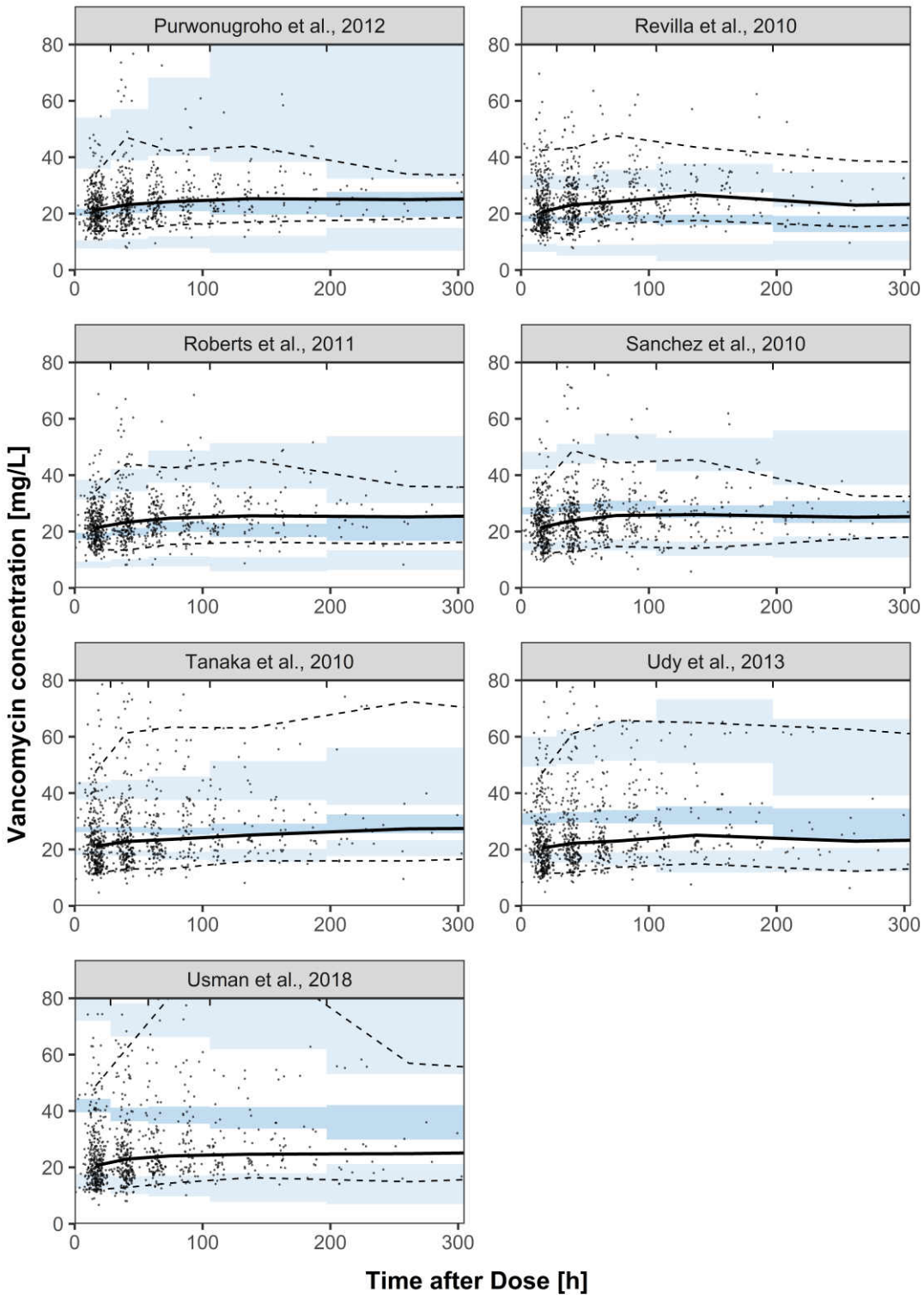
Li *et al.*, 2017	postoperative neurosurgical patients	25	262	CL: CLCR; CL_{CSF}: drainage amount, elapsed time	5.84	11.9	Q1: 21.5	Vp1: 15.4Vp2: 0.04	Li X, Sun S, Ling X, Chen K, Wang Q, Zhao Z. Plasma and cerebrospinal fluid population pharmacokinetics of vancomycin in postoperative neurosurgical patients after combined intravenous and intraventricular administration. Eur J Clin Pharmacol 2017; 73:1599–607. doi:10.1007/s00228-017-2313-4.
Lin *et al.*, 2016	Chinese post cranial meningitis patients	100	179	CL: CLCR	7.11	101.0	-	-	Lin WW, Wu W, Jiao Z, Lin RF, Jiang CZ, Huang PF, et al. Population pharmacokinetics of vancomycin in adult Chinese patients with post-craniotomy meningitis and its application in individualised dosage regimens. Eur J Clin Pharmacol 2016; 72:29–37. doi:10.1007/s00228-015-1952-6.
Mangin *et al.*, 2014	critically ill with post sternotomy mediastinitis	30	359	CL: sex, TBW, SCR, SAPSII-score; Vc: TBW, Q: TBW, diabetes mellitus; Vp: TBW	2.60	23.5	72.9	6.01	Mangin O, Urien S, Mainardi J-L, Fagon J-Y, Faisy C. Vancomycin pharmacokinetic and pharmacodynamic models for critically ill patients with post-sternotomy mediastinitis. Clin Pharmacokinet 2014; 53:849–61. doi:10.1007/s40262-014-0164-z.
Medellín-Garibay *et al.*, 2016	trauma patients	118	392	CL: CLCR, furosemide co-medication; Vc: TBW, age; Vp: TBW	2.87	55.5	442.5	0.81	Medellín-Garibay SE, Ortiz-Martín B, Rueda-Naharro A, García B, Romano-Moreno S, Barcia E. Pharmacokinetics of vancomycin and dosing recommendations for trauma patients. J Antimicrob Chemother 2016; 71:471–9. doi:10.1093/jac/dkv372.
Medellín-Garibay *et al.*, 2017	Critically ill	54	641	CL: CLCR, mechanical ventilation; Vc: TBW	2.64	77.3	-	-	Medellín-Garibay SE, Romano-Moreno S, Tejedor-Prado P, Rubio-Álvaro N, Rueda-Naharro A, Blasco-Navalpotro MA, et al. Influence of mechanical ventilation on the pharmacokinetics of vancomycin administered by continuous infusion in critically ill patients. Antimicrob Agents Chemother 2017;61. doi:10.1128/AAC.01249-17.

Okada *et al.*, 2018	patients undergoing stem-cell transplantation	95	285	CL: CLCR; Vc: TBW	3.64	47.0	56.1	1.95	Okada A, Kariya M, Irie K, Okada Y, Hiramoto N, Hashimoto H, et al. Population Pharmacokinetics of Vancomycin in Patients Undergoing Allogeneic Hematopoietic Stem-Cell Transplantation Ther Drug Monit 2018:1–10. doi:10.1002/jcph.1106.
Purwonugroho *et al.*, 2012	Thai patients	212	391	CL: CLCR; Vc: age	4.30	27.1	44.2	6.95	Purwonugroho TA, Chulavatnatol S, Preechagoon Y, Chindavijak B, Malathum K, Bunuparadah P. Population Pharmacokinetics of Vancomycin in Thai Patients. Sci World J 2012; 2012:1–8. doi:10.1100/2012/762649.
Revilla *et al.*, 2010	intensive care patients	191	569	CL: age, CLCR; Vc: SCR, TBW	4.84	61.5	-	-	Revilla N, Martín-Suárez A, Pérez MP, González FM, Fernández De Gatta MDM. Vancomycin dosing assessment in intensive care unit patients based on a population pharmacokinetic/pharmacodynamic simulation. Br J Clin Pharmacol 2010; 70:201–12. doi:10.1111/j.1365-2125.2010.03679.x.
Roberts *et al.*, 2011	septic, critically ill	206	579	CL: CLCR; Vc: TBW	4.15	114.8	-	-	Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J. Vancomycin dosing in critically ill patients: Robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother 2011; 55:2704–9. doi:10.1128/AAC.01708-10.
Sánchez *et al.*, 2010	adult patients	141	254	CL: CLCR; Vc: TBW; Vp: age; Q: TBW	3.46	21.2	34-29	8.25	Sanchez JL, Dominguez AR, Lane JR, Anderson PO, Capparelli E V, Cornejo-Bravo JM. Population pharmacokinetics of vancomycin in adult and geriatric patients: comparison of eleven approaches. Int J Clin Pharmacol Ther 2010; 48:525–33.
Tanaka *et al.*, 2010	patients with MRSA infections	86	181	CL: GFR (Hoek formula), Vc: TBW	3.64	64.8	-	-	Tanaka A, Aiba T, Otsuka T, Suemaru K, Nishimiya T, Inoue T, et al. Population pharmacokinetic analysis of vancomycin using serum cystatin C as a marker of renal function. Antimicrob Agents Chemother 2010; 54:778–82. doi:10.1128/AAC.00661-09.
Udy *et al.*, 2013	Septic CRRT patients	81	199	Vc: TBW	2.90	60.0	-	-	Udy AA, Covajes C, Taccone FS, Jacobs F, Vincent JL, Lipman J, et al. Can population pharmacokinetic modelling guide vancomycin dosing during continuous renal replacement therapy in critically ill patients? Int J Antimicrob Agents 2013; 41:564–8. doi:10.1016/j.ijantimicag.2013.01.018.
Usman *et al.*, 2018	TDM patients	144	256	CL: CLCR	2.35	19.2	-	-	Usman M, Fobker M, Hempel G. Investigation of the age dependency of vancomycin clearance by population pharmacokinetic modeling. Int J Clin Pharmacol Ther 2018; 56:56–63. doi:10.5414/CP203033.

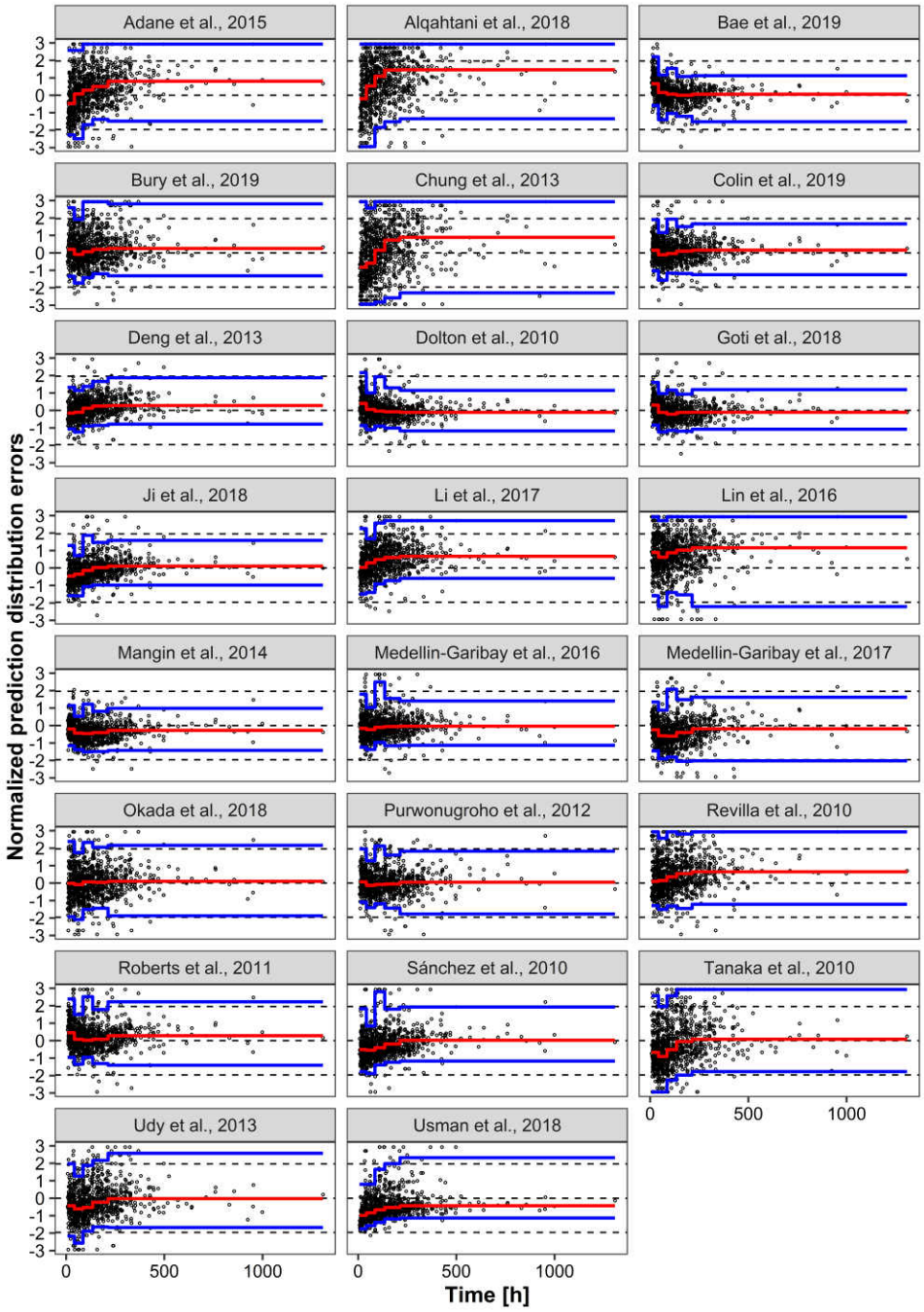
Supplement Figure S1. Prediction corrected visual predictive checks of the population PK models. The black solid and dashed line represents the median of the observed data (black dots) and its 5th / 95th quantiles, respectively. The shaded areas represent the 90% confidence interval of the 5th, 95th (light shaded) and 50th (dark) quantiles of the simulations (n=1000).



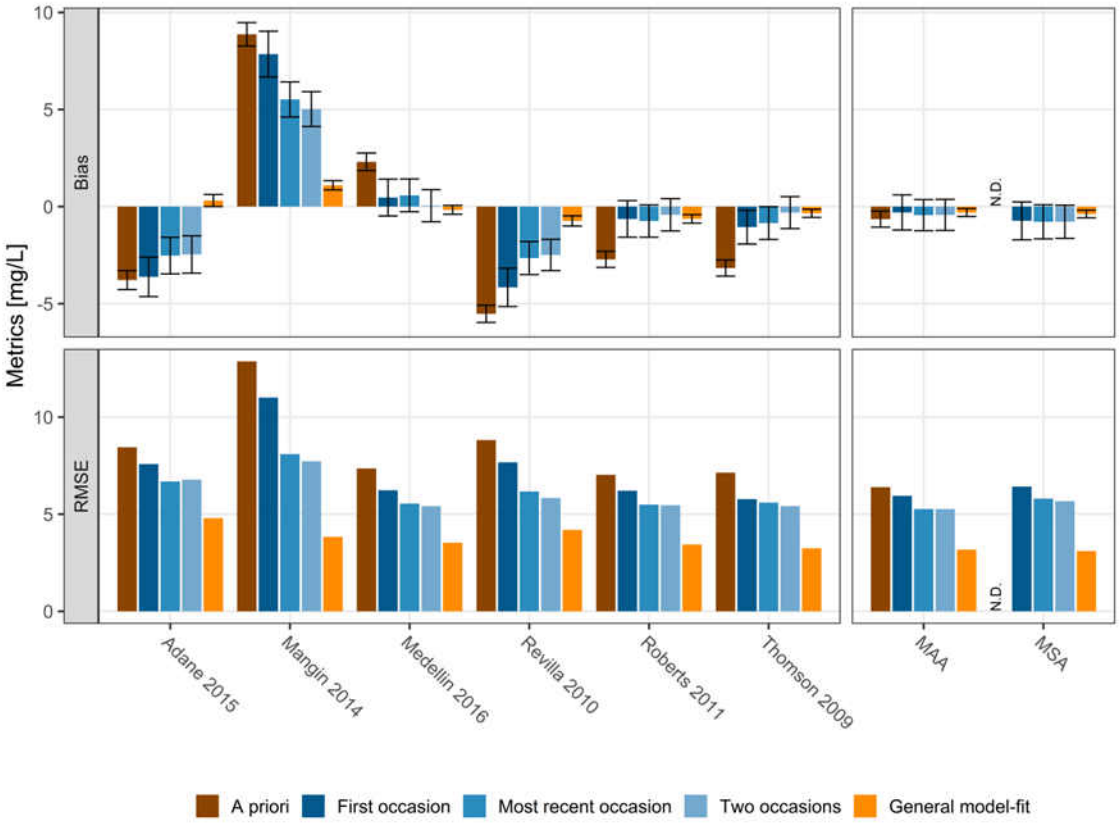

Adane et al., 2015
Alqahtani et al., 2018
Bae et al., 2019
Bury et al., 2019
Chung et al., 2013
Colin et al., 2019
Deng et al., 2013
Dolton et al., 2010
Vancomycin concentration [mg/L]
Time after Dose [h]
0
20
40
60
80
0
100
200
300


Purwonugroho et al., 2012
Revilla et al., 2010
Roberts et al., 2011
Sanchez et al., 2010
Tanaka et al., 2010
Udy et al., 2013
Usman et al., 2018
Vancomycin concentration [mg/L]
Time after Dose [h]
0
20
40
60
80
100
200
300

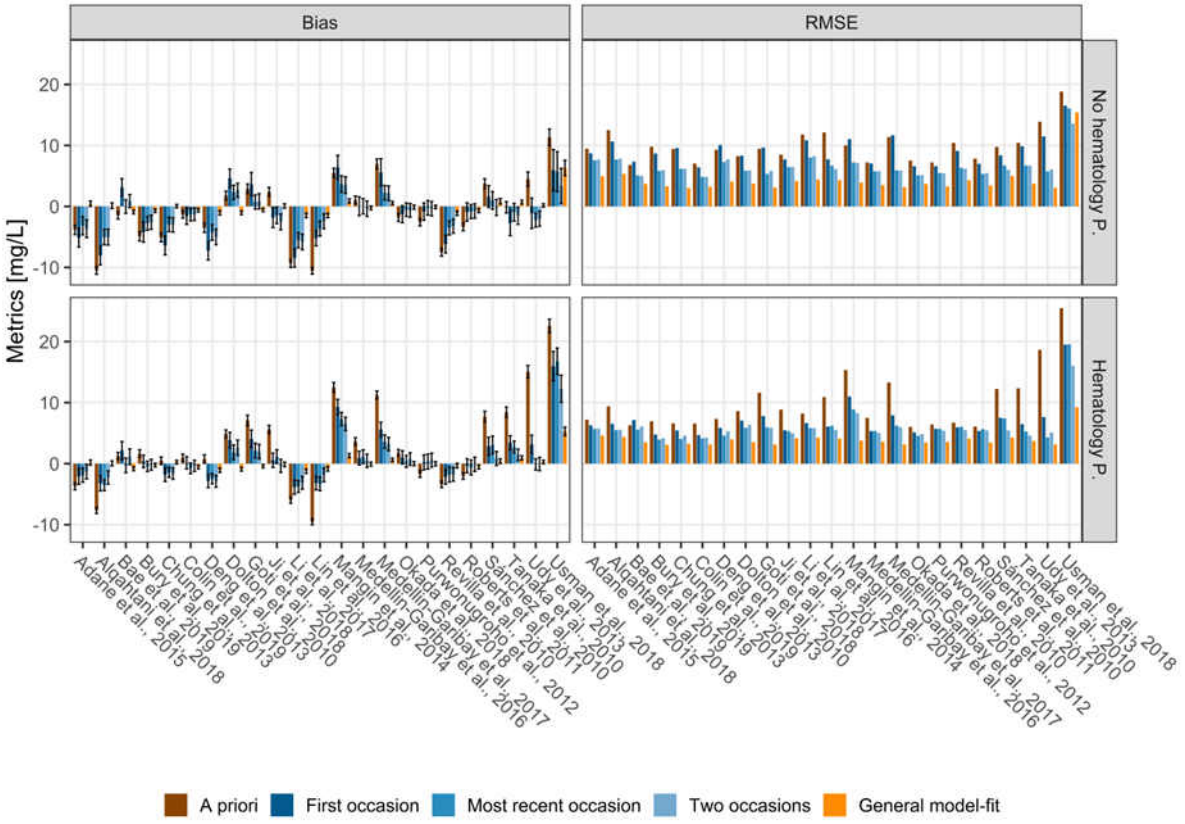
Supplement Figure S2. Normalized prediction distribution errors of the population PK models. If the model adequately described the data, NPDEs display a normal distribution. Therefore, the NPDEs using all available observations were calculated (black dots). The blue and red lines represent 2.5th, 97.5th and 50th quantiles of the NPDEs over the treatment time, respectively, and should ideally overlap with the dotted lines, i.e., the approximate values for the 2.5th, 50th and 97.5th quantiles of the standard normal distributions.



Supplement Figure S3. Performance metrics of the model selection algorithm (MAA) and model selection algorithm (MSA) (right) and the single models being part of the set (left). The bias and root mean square error (RMSE) of the predicted vancomycin plasma concentrations were calculated in five forecasting scenarios. Error bars represent the 95% confidence interval based on the standard error. N.D. – not defined



Supplement Figure S4. Bias and root mean square error (RMSE) of the population PK models stratified by the medical discipline the patients were assigned to: 55 patients had hematological malignancies, e.g., chronic myeloid leukemia (lower panels). Either all available observations were predicted using covariate dosing information with (general model-fit, orange) or without (a priori, brown) supplying individual vancomycin samples. The blue bars represent the metrics in Bayesian forecasting using samples from one occasion (i.e., the first or most recent) or two occasions to forecast the hidden vancomycin concentration from the subsequent occasion. Error bars represent the 95% confidence interval based on the standard error. N.D. – not defined



7.3 Supplementary material of Publication III

Table S1: Model properties and standardized PK parameters of the pharmacometric models included in the algorithms

Reference	Patient population	Nr. of samp N		Covariates	CL	Vc	Vp	Q	IIV**	RUV**
Adane *et al.*, 2015	extremely obese	29	93	CL: CLCR; Vc: TBW	4.74	38.3	-	-	CL: 26.7% Vp:	P: 18.9% A: -
Mangin *et al.*, 2014	critically ill with post sternotomy mediastinitis	30	359	CL: sex, TBW, SCR, SAPSII-score; Vc: TBW; Vp: TBW; Q: TBW, diabetes mellitus	2.60	23.5	72.9	6.01	CL: 29% Vc: 53% Q: 101%	P: - A: 7.3 mg/L
Medellín-Garibay *et al.*, 2016	trauma patients	118	392	CL: CLCR, furosemide co-medication; Vc: TBW, age; Vp: TBW	2.87	55.5	442.5	0.81	CL:36.7% Vc: 40.0%	P: 19.2% A: 3.5 mg/L
Revilla et al., 2010	intensive care patients	191	569	CL: age, CLCR; Vc: SCR, TBW	4.84	61.5	-	-	CL: 30.1% Vc:	P: - A: 4.2 mg/L
Roberts *et al.*, 2011	septic, critically ill	206	579	CL: CRCL; Vc: TBW	4.15	114.8	-	-	CL: 38.9% Vc:	P: 19.9% A: 2.4 mg/L
Thomson *et al.*, 2009	hospitalized patients	398	1557	CL: CLCR; Vc: TBW, Vp: TBW	4.45	50.6	54.9	2.28	CL: 27%, Q: 49% Vc: 15%,	P: 15% A: 1.6 mg/L
Goti *et al.*, 2018	hospitalized patients with high prevalence of renal impairment	1812	2765	CL: CLCR, hemodialysis status; Vc: TBW, hemodialysis status	3.82	62.6	38.4	6.5	CL: 38.4% Vc: 81.9%, Vp: 57.1%	P: 22.7% A: 3.4 mg/L

Goti *et al.*, 2018 (re-estimated parameters)	CL: CLCR, hemodialysis status; Vc: TBW, hemodialysis status	4.44	56	65.8	1.33	Vp: 99.7%	Vc: 45.4%,	CL: 37.0%	P: 18.4% A: 1.4 mg/L

*standard patient, 50 years old, male, 75 kg, 1.7 m, serum creatinine of 85 µmol/L.
** CV: coefficient of variation was calculated as square root of omega or sigma multiplied by 100, if not otherwise stated in the publication
N: Number of patients, Nr. of samp.: Number of vancomycin samples used for model development, CL: Clearance, Vc: central Volume of distribution, Vp: peripheral Volume of distribution (-: one-compartment model), Q: Intercompartmental Clearance (L/h, -: one-compartment model), IIV: interindividual variability (coefficient of variation (CV)**), RUV: residual unexplained variability, with P: proportional (CV**) and A: additive component, CLCR: creatinine clearance, TBW: total body weight, SCR: serum creatinine

Table S2: Basic structure and patient characteristics of the 1000 individuals in each of the six simulated populations (extremely obese, critically ill, hospitalized, critically ill with sepsis, post heart surgery and trauma, respectively.

Basic structure	**Value**	**Additional information**
Patients, per simulation	1000	
Dose, mg	1000	1h infusion every 12h for 36h
Plasma measurements	three peak	at 15 minutes post infusion
	three trough	and 15 min prior next infusion

Characteristics	**Value, median (range)**	**Additional information**
Age, years	57 (24 – 91)	
Body mass index (BMI), kg/m^2	25 (18 – 33)	
Height, cm	170 (151 – 184)	
Serum creatinine, µmol/L	82 (38 – 267)	
Sex, female / male	515 / 485	
Weight, kg	72 (52 – 97)	calculated as BMI * height^2

Table S3: Patient characteristics of the clinical data consisting of routine vancomycin TDM samples of the evaluated 180 patients. The data was acquired in three studies from January 2010 to July 2011, from June 2015 to July 2016 and from July 2018 to August 2019. The data was used to assess the performance of the multi- and single-model approaches in predicting individual vancomycin plasma concentrations (i.e. Bayesian forecasting)

Characteristics, continuous	**Value, median (range)**	**Missing data, %**
Age, years	58 (20 – 90)	0
Height, cm	172 (150 – 192)	0
Weight, kg	76.6 (39 – 159)	0
Albumin	28.0 (15 – 44)	59
Serum creatinine, µmol/L	90.0 (18 – 735)	0
SOFA-Score	10 (0 – 22)	59

Characteristics, categorical	+ / -	**Missing data, %**
Diabetes status	+: 17 / -: 163	0
Extracorporeal membrane oxygenation	+: 11 / -: 72	59
Furosemide co-medication	+: 51 / -: 68	59
Sex, female / male	51 / 129	0
Renal replacement therapy	+: 45 / -: 135	0

'+' – Number of individuals with positive status/which received drug

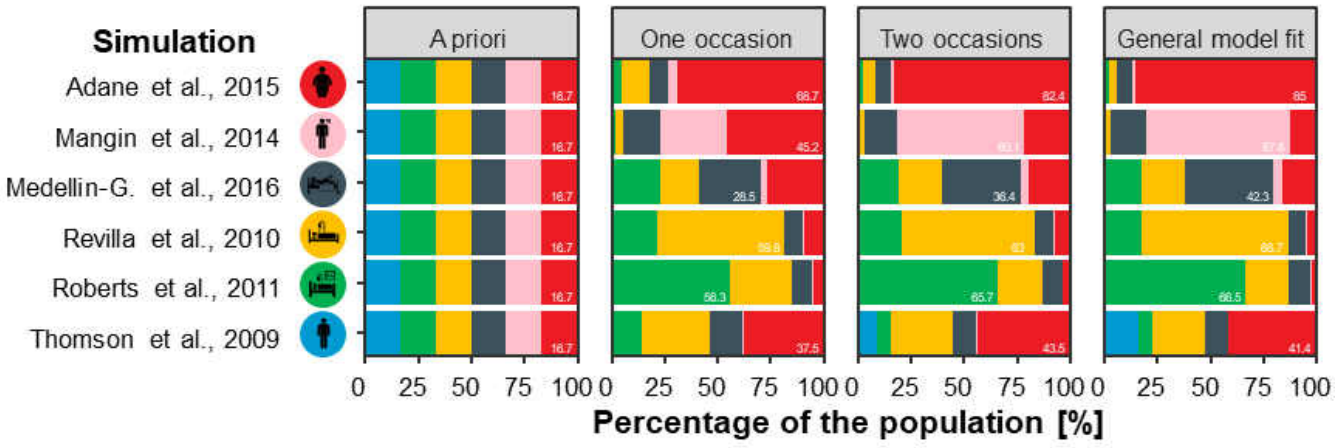


Figure S1: Influence of the models in the model averaging algorithm using the weighting scheme W_{AIC} and stratified by the simulated populations. Each patient was stained in the color of the particular model, which obtained the highest weight in the algorithm. (*A priori*) *a priori* prediction using the patient covariates only; Bayesian forecasting employing measurements from (*One occasion*) the second (i.e. most recent) dosing interval and (*Two occasions*) the first and second dosing interval; (*General model fit*) Bayesian estimation employing measurements from all three dosing intervals. White numbers – numerical value of the biggest portion in the subpopulation and scenario, respectively

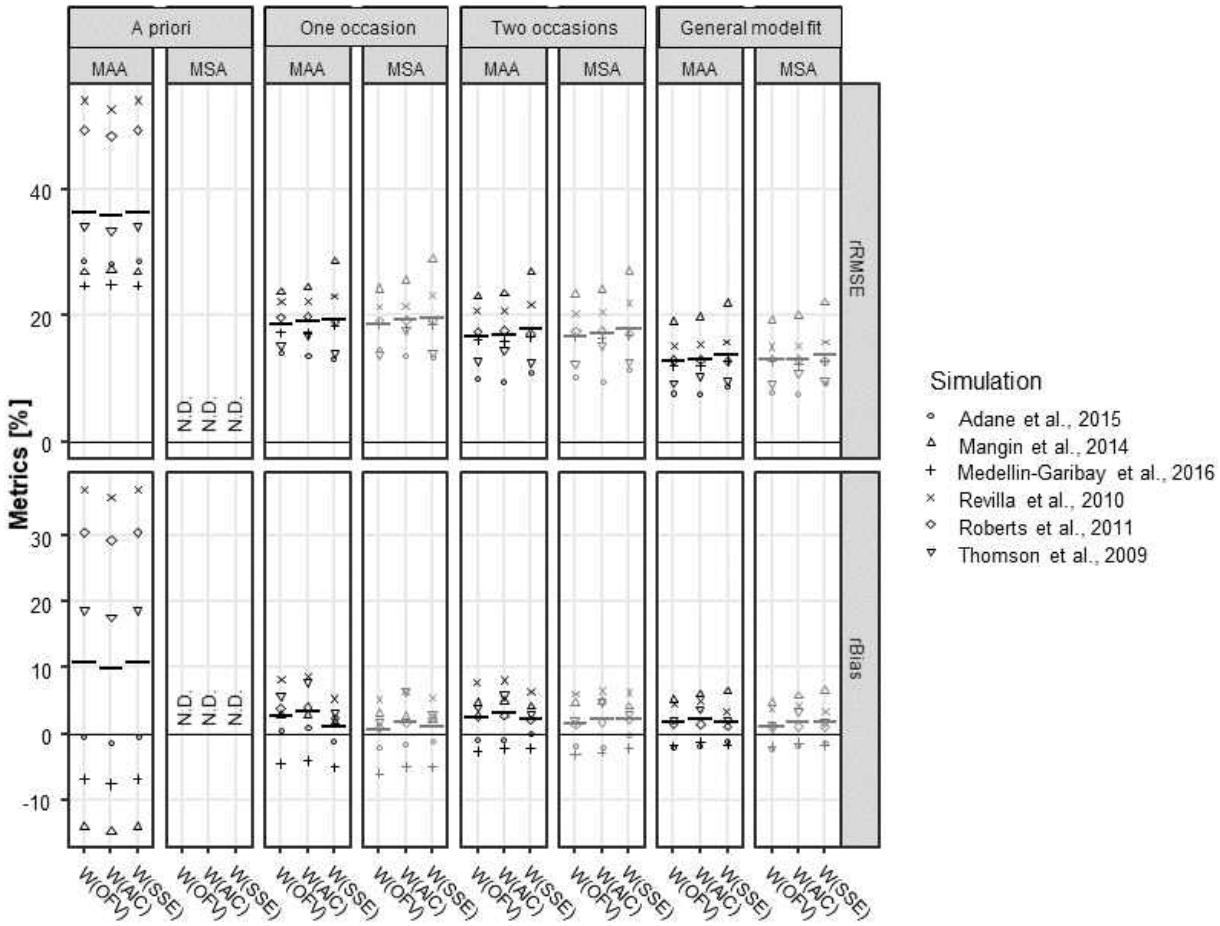


Figure S2: The relative root mean square error (rRMSE) and relative bias (rBias) of the predicted versus true simulated area under the curve (AUC) between 24 h and 36 h calculated in 6000 simulated patients (*horizontal line*) and the (sub-)populations (*shapes*). Comparison of the three weighting schemes ($W_{OFV,}$ W_{AIC} and W_{SSE}) in the model averaging algorithm (MAA) and the model selection algorithm (MSA). (*A priori*) *a priori* prediction using the patient covariates only; Bayesian forecasting employing measurements from (*One occasion*) the second (i.e. most recent) dosing interval and (*Two occasions*) the first and second dosing interval; (*General model fit*) Bayesian estimation employing measurements from all three dosing intervals. N.D. – not defined.

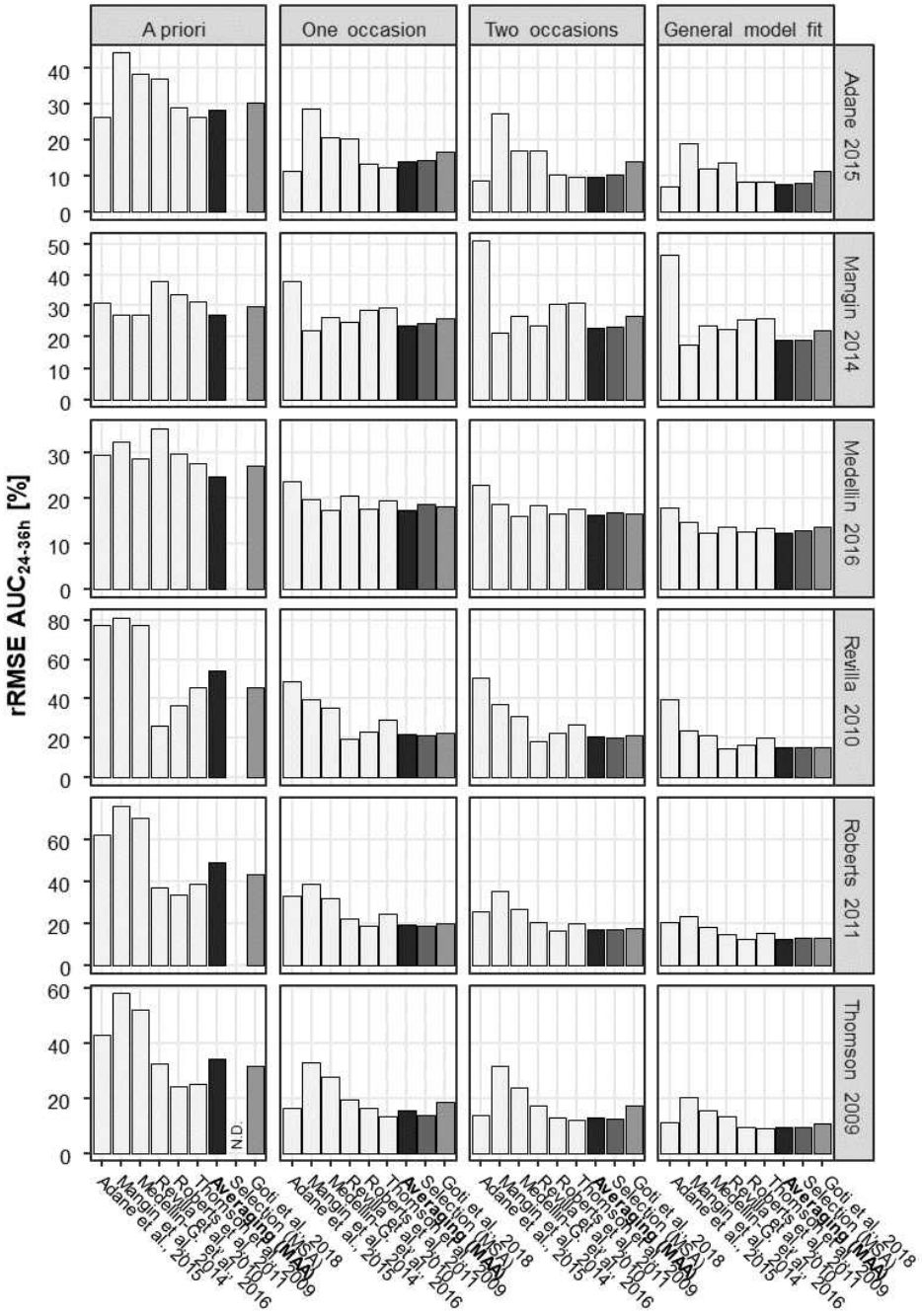


Figure S3: The imprecision represented by the relative root mean square error (rRMSE) of the predicted versus simulated area under the curve (AUC) between 24 h and 36 h calculated in each of the simulated (sub-)populations (*horizontal facets*). (*A priori*) *a priori* prediction using the patient covariates only; Bayesian forecasting employing measurements from (*One occasion*) the second (i.e. most recent) dosing interval and (*Two occasions*) the first and second dosing interval; (*General model fit*) Bayesian estimation employing measurements from all three dosing intervals. The ordinate is displaying the six single model approaches (*light grey*), the MAA (*black*), the MSA (*dark grey*) and the external model (*grey*) per scenario. N.D. – not defined

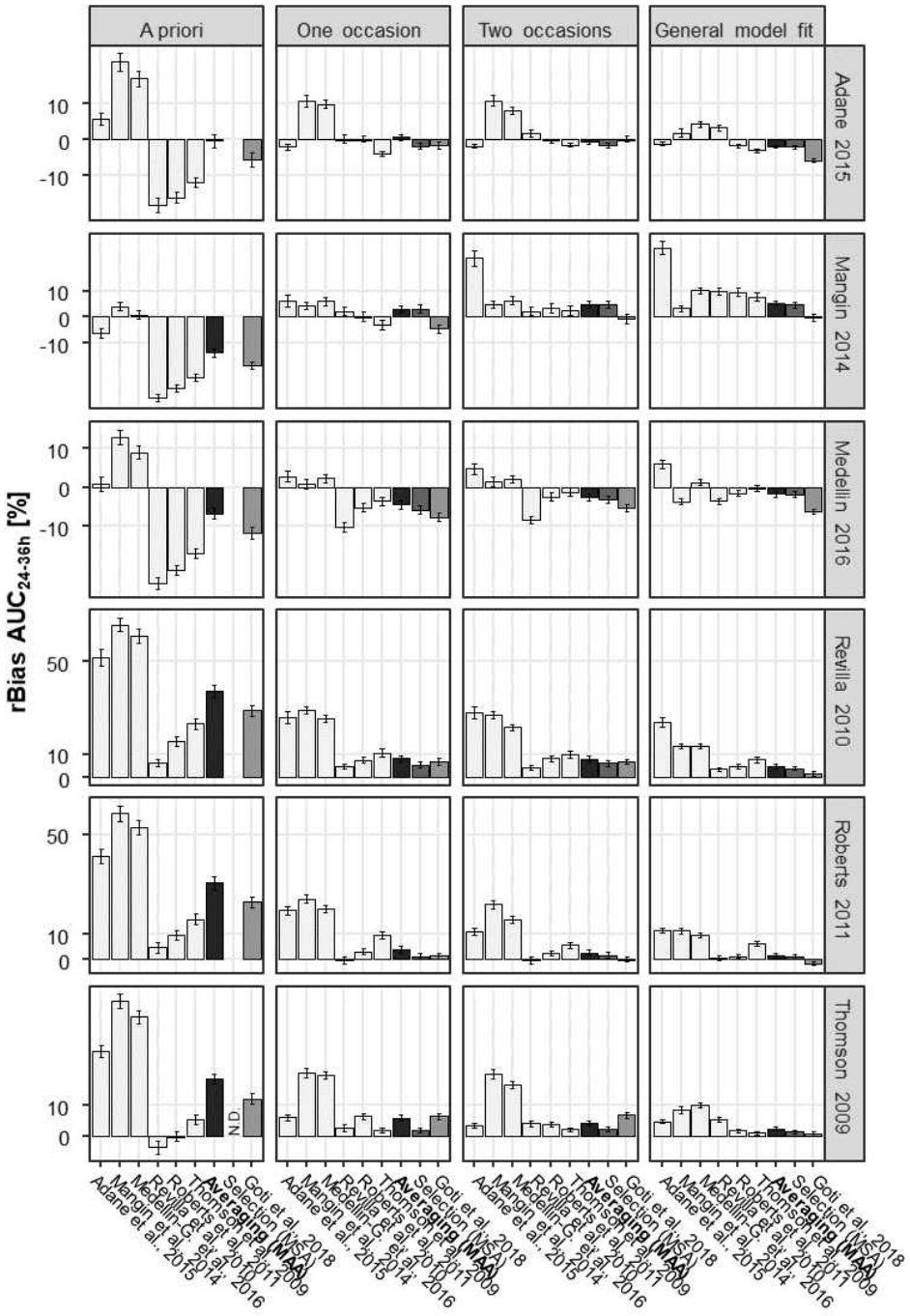


Figure S4: The inaccuracy represented by the relative bias (rBias) of the predicted versus simulated area under the curve (AUC) between 24 h and 36 h calculated in each of the simulated (sub-)populations (*horizontal facets*). (*A priori*) *a priori* prediction using the patient covariates only; Bayesian forecasting employing measurements from (*One occasion*) the second (i.e. most recent) dosing interval and (*Two occasions*) the first and second dosing interval; (*General model fit*) Bayesian estimation employing measurements from all three dosing intervals. The ordinate is displaying the six single model approaches (*light grey*), the MAA (*black*), the MSA (*dark grey*) and the external model (*grey*) per scenario. Whiskers cover the 95 % confidence interval of the rBias calculated via the standard error; N.D. – not defined

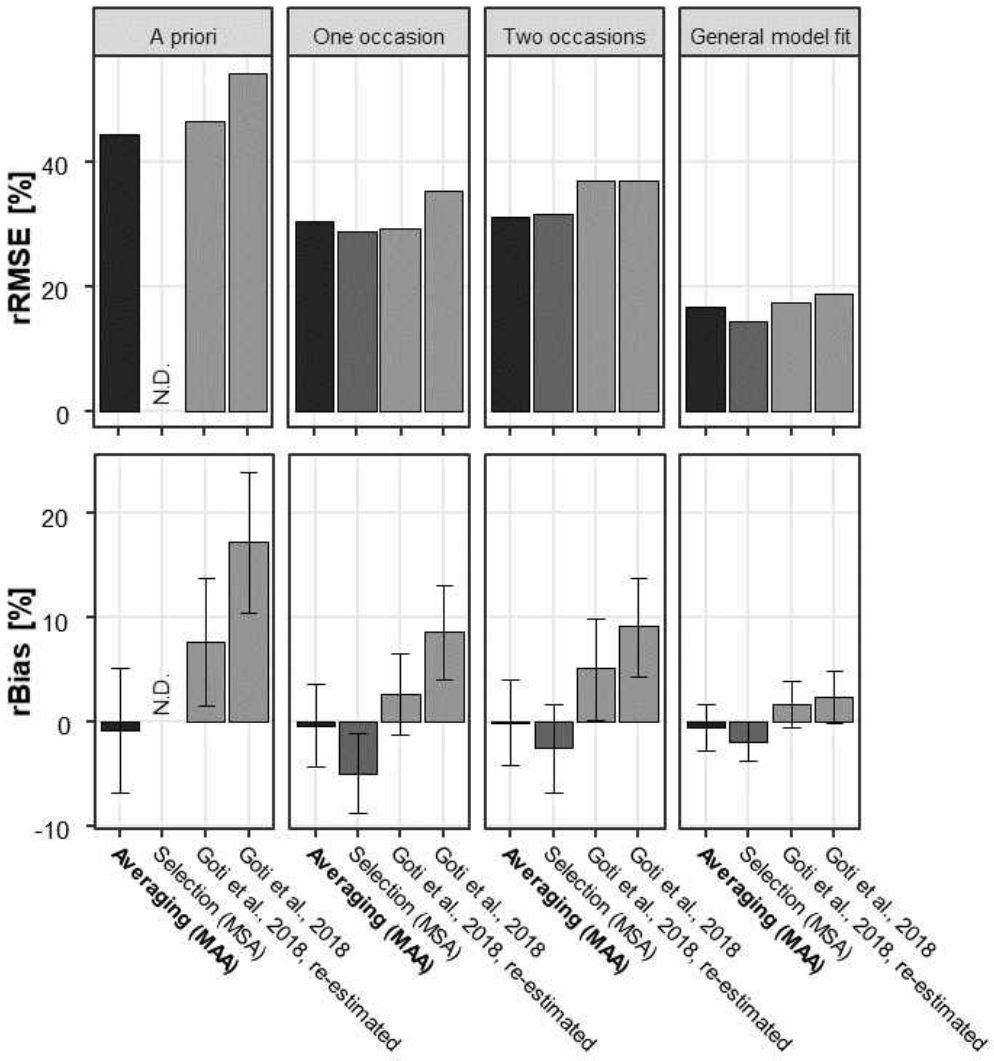


Figure S5: The relative root mean square error (rRMSE) and relative bias (rBias) of the clinical concentration-time data in the third observed dosing occasion, which is blinded to the models/algorithms in various settings: (*A priori*) *a priori* prediction using the patient covariates only; Bayesian forecasting employing plasma vancomycin concentrations from (*One occasion*) the second (i.e. most recent) observed dosing occasion and (*Two occasions*) the first and second observed dosing occasions; (*General model fit*) Bayesian estimation employing plasma vancomycin concentrations from all three dosing occasions. The ordinate is displaying the MAA (*black*), the MSA (*dark grey*) and the external model (*grey*) with either the published parameters (*Goti et al. 2018*) or adjusted parameters (*Goti … re-estimated)* per scenario. The adjusted parameters can be found in Supplement Table S1. Whiskers cover the 95 % confidence interval of the rBias calculated via the standard error; N.D. – not defined

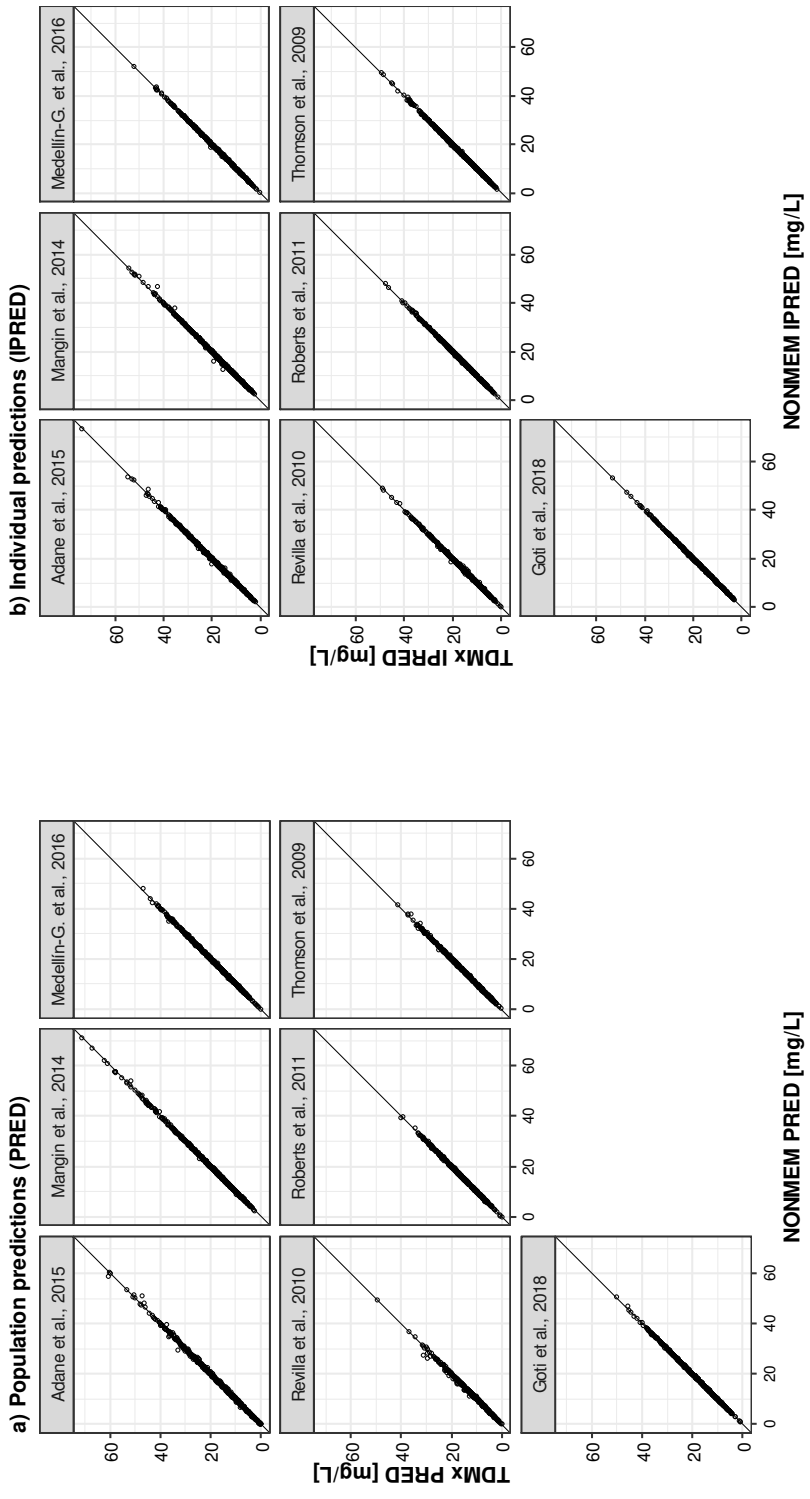


Figure S6: a) The population predicted and **b)** the individually predicted vancomycin plasma concentrations of the clinical data (n=741) using the six single models and the reference model in either NONMEM or the MIPD-software 'TDMx'. The diagonal line represents the identity line.

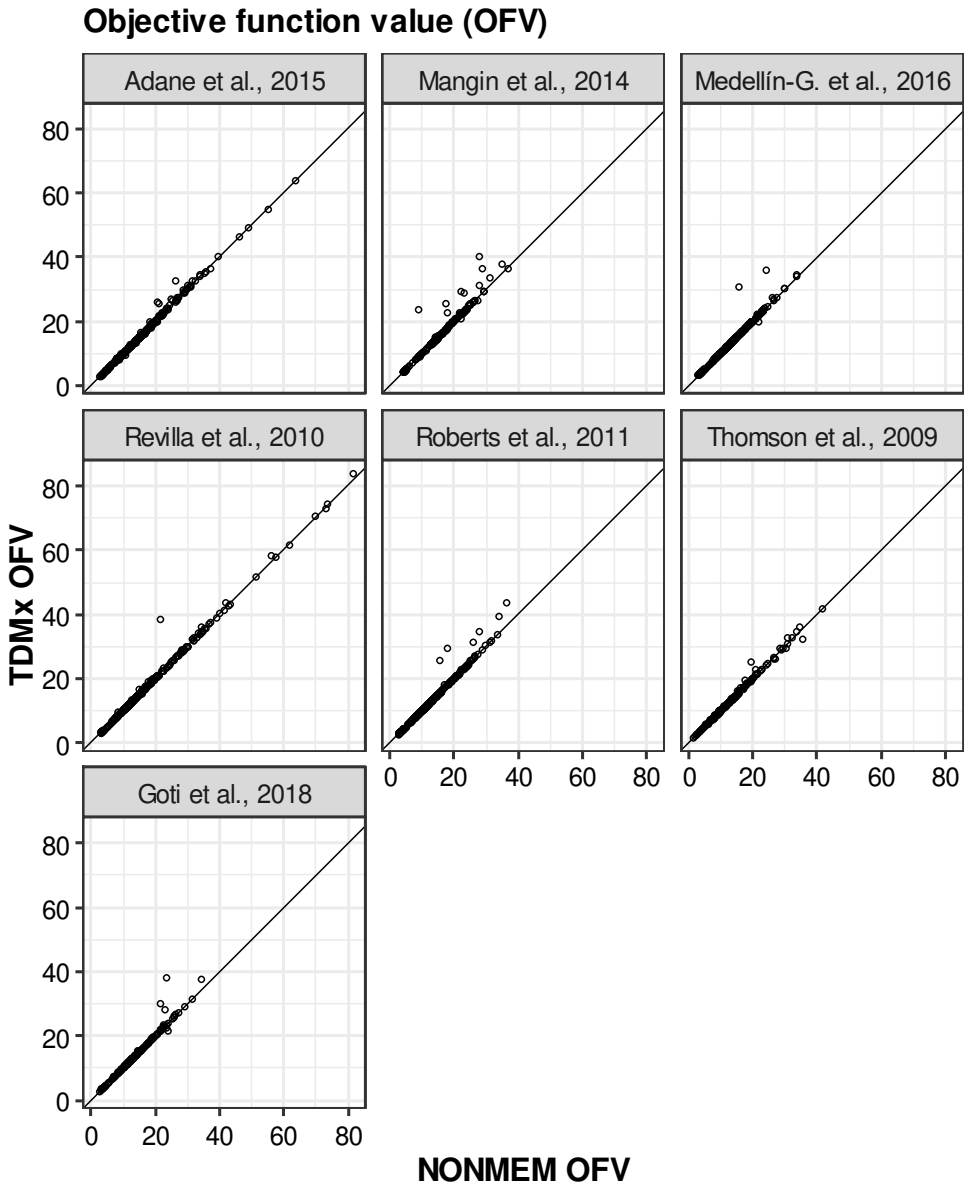


Figure S7: The individual objective function values (OFV) calculated for the clinical data either using NONMEM or the MIPD software 'TDMx'. Each black circle represents the OFV in one patient. The diagonal line represents the identity line.

7.4 Supplementary material of Publication IV

7.4.1 Supplementary file S1: Workflow of the simulation

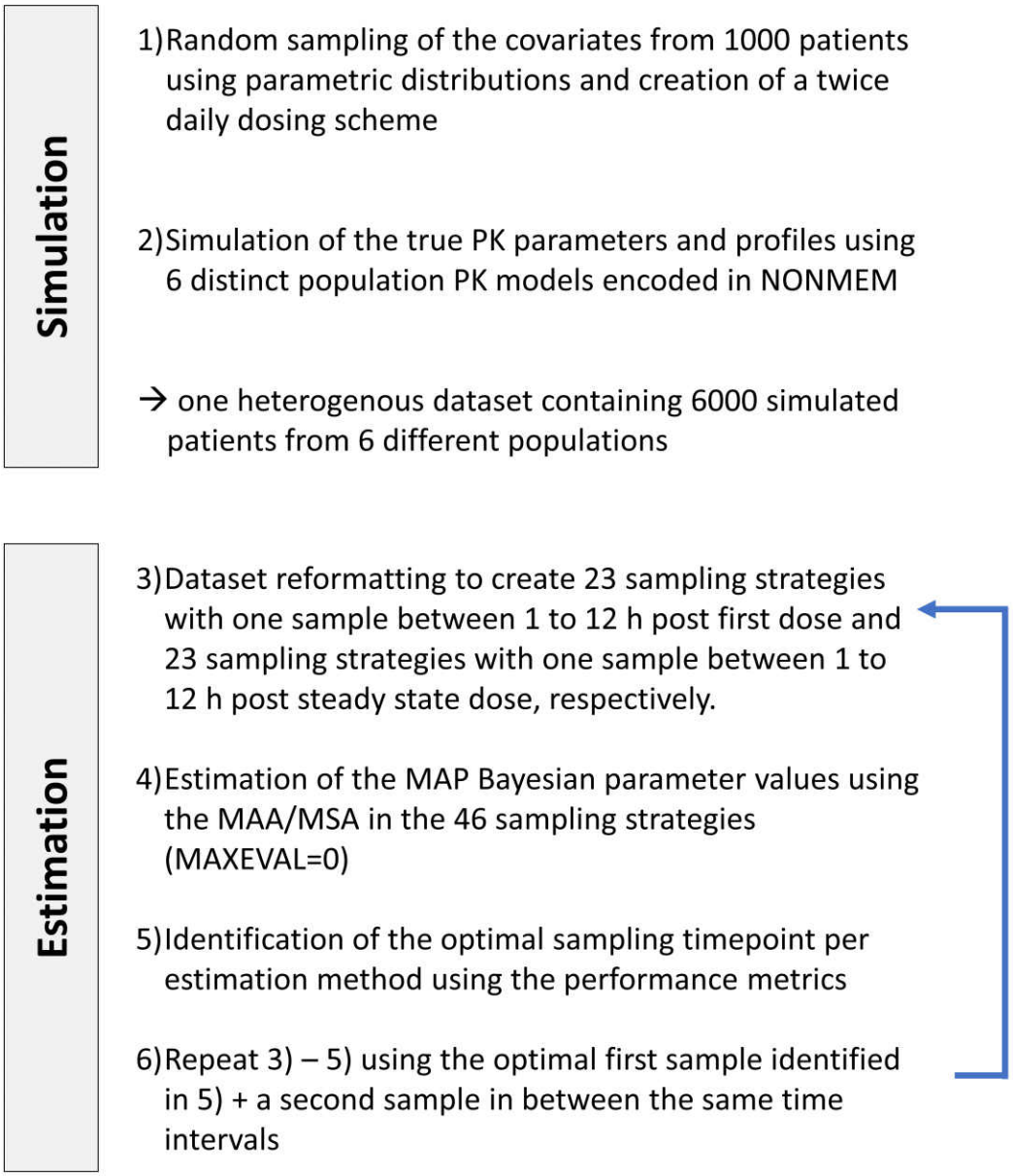


Figure 3 Workflow of the simulation-estimation study consisting of six main steps. MAP – Maximum a posteriori prediction; MAA – Model averaging algorithm; MSA – Model selection algorithm

1) Random sampling of the covariates

In brief, a virtual set of 1000 patients were created in R (Version 4.0.2). The resulting dataset consisted of the same dosing regimen (i.e. a 60-minutes loading dose of 2000 mg and 60-mintues maintenance doses of 1250 mg every 12 hours) for all patients. Furthermore, observations were added between 0-24 hours and 48-72 hours in increments of 0.5 hours. The covariates were randomly sampled according to the following code example.

```
# R-code ------------------------------------------------------------------------------

    for(i in seq_along(data$ID)){
    # AGE ---------------------------------------------------------------
     repeat {
      age = rnorm(1, mean = 50, sd = 10)       ## repeat if AGE is out of boundaries:
      if(age>20 & age<75) break
     }
     data$AGE[i] = age

    # Height ------------------------------------------------------------------
     data$HTM[i] = round(
      ifelse(data$SEX[i]==1,
           rnorm(1, mean = 1.65 , sd = .035),  ## height for woman
           rnorm(1, mean = 1.75 , sd = .035)   ## men
      ),
      2)
    # BMI ---------------------------------------------------------------
     data$BMI[i] = round(
      rlnorm(1, mean = log(25), sd = 0.1),
      1)
    }

    # serum creatinine ----------------------------------------------------------------
    data$SCR = rlnorm(n_ID, mean = log(82), sdlog = 0.3)

    # body weight ---------------------------------------------------------------
    data$WTKG = data$HTM^2 * data$BMI
```

END ----------

Dataset structure after random sampling (1 example patient)

Column specification

TIME	Time since first infusion
AMT	Administer dose of vancomycin
DUR	Infusion duration in hours
DV	Dependent variable, vancomycin concentration mg/L
EVID	NONMEM event identifier
RATE	Infusion rate [mg/hours]
ID	Patient identifier
CMT	NONMEM compartment identifier
OCC	Dosing occasion
MDV	Identifier for missing dependent variables
SEX	Sex of the patients 1=female
AGE	Age of the patient in years
HTM	Body height of the patient in m
BMI	Body mass index in kg/m^2
SCR	Serum creatinine in µmol/L
WTKG	Total body weigh in kg

TIME	AMT	DUR	DV	EVID	RATE	ID	CMT	OCC	MDV	SEX	AGE	HTM	BMI	SCR	WTKG
0	2000	1	.	1	2000	1	1	1	1	0	50.43	1.77	28.5	59.22	89.29
0.5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
1	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
1.5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
2	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
2.5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
3	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
3.5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
4	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
4.5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
5.5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
6	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
6.5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
7	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
7.5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
8	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
8.5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
9	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
9.5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
10	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
10.5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29

11	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
11.5	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
11.99	0	.	.	0	0	1	1	1	0	0	50.43	1.77	28.5	59.22	89.29
12	1250		1	.	1	1250	1	1	2	1	0	50.43	1.77	28.5	59.22	89.29
12.5	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
13	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
13.5	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
14	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
14.5	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
15	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
15.5	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
16	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
16.5	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
17	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
17.5	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
18	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
18.5	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
19	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
19.5	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
20	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
20.5	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
21	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
21.5	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
22	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
22.5	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
23	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
23.5	0	.	.	0	0	1	1	2	0	0	50.43	1.77	28.5	59.22	89.29
24	1250		1	.	1	1250	1	1	3	1	0	50.43	1.77	28.5	59.22	89.29
36	1250		1	.	1	1250	1	1	4	1	0	50.43	1.77	28.5	59.22	89.29
48	1250		1	.	1	1250	1	1	5	1	0	50.43	1.77	28.5	59.22	89.29
48.5	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
49	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
49.5	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
50	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
50.5	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
51	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
51.5	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
52	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
52.5	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
53	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
53.5	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
54	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
54.5	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
55	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
55.5	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
56	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
56.5	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
57	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29

57.5	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
58	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
58.5	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
59	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
59.5	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
59.99	0	.	.	0	0	1	1	5	0	0	50.43	1.77	28.5	59.22	89.29
60	1250	1	.	1	1250	1	1	6	1	0	50.43	1.77	28.5	59.22	89.29
60.5	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
61	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
61.5	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
62	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
62.5	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
63	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
63.5	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
64	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
64.5	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
65	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
65.5	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
66	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
66.5	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
67	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
67.5	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
68	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
69	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
70	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
71	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
71.5	0	.	.	0	0	1	1	6	0	0	50.43	1.77	28.5	59.22	89.29
72	1250	1	.	1	1250	1	1	7	1	0	50.43	1.77	28.5	59.22	89.29

2) Simulation of the true PK parameters, true vancomycin plasma concentration and true area under the curve

In brief, six population PK models were encoded in NONMEM (example from the Adane model below). These models were each used to simulate the PK parameters, true vancomycin plasma concentrations and true area under the curve of 1000 patients, respectively.

Example NONMEM file used for simulation

```
$PROBLEM Simulation of the PK – recoded from Adane et al. 2015

;-------------------------------------------------------------------------------

$INPUT
TIME AMT DUR DV EVID RATE ID CMT OCC MDV SEX AGE HEIGHT BMI SCR
WEIGHT ;DUIN;
;-------------------------------------------------------------------------------

$DATA sim_temp.csv IGNORE=@
$SUBROUTINES ADVAN13 TOL=9

$MODEL NCOMPARTMENTS=3

;-------------------------------------------------------------------------------

$PK

IF (SEX.EQ.0) THEN
F_SEX = 1.23
ELSE
F_SEX = 1.04
ENDIF

BSA = ((TBW**0.425)*((HT*100)**0.725))*0.007184          ;m**2  DuBois  DuBois
Formula

CLCR = ((((140-AGE)*TBW*F_SEX)/SCR)*1.73)/BSA ;mL/min/1.73m**2      Cockcroft
Gault standardised to BSA

TVCL = THETA(1)*(CLCR/125)

CL = TVCL*EXP(ETA(1))          ;L/h

TVV = THETA(2)*TBW

V = TVV*EXP(ETA(2)) ;L
```

```
TVV1=TVV
S1 = V
V1=V
S1              = V1
KE              = CL/V1

$DES

DADT(1) =  - KE*A(1)
DADT(2) =  1
DADT(3) =      A(1)/V1
AUC=A(3)
;-----------------------------------------------------------------------------------------
$ERROR
IPRED = A(1)/V1
SIG_PROP = EPS(1)

Y = IPRED*(1+EPS(1))

EP1 = SIG_PROP
EP2 = 0
;-----------------------------------------------------------------------------------------

$THETA
6.54    ;CL
0.51    ;V

;-----------------------------------------------------------------------------------------

$OMEGA
0.071289        ;IIV CL
0.057121        ;IIV V

$SIGMA
0.035721        ;proportional model

;-----------------------------------------------------------------------------------------
```

$SIMULATION (101017) ONLYSIM

3) Dataset reformatting to create the sampling strategies

In brief, the full dataset containing 5925 patients were reformatted to only contain a single sample per patient in the single-sampling strategies. An example dataset can be found below. 75 virtual patients were excluded to remove any potential influence of unreasonable eta values (i.e. patients with eta values larger than 2.8 times standard deviation were removed).

Dataset structure of the simulated and reformatted output (1 example patient in the sampling strategy: 2 hours post start of infusion, simulated with the Adane model)

Column specification

TIME	Time since first infusion
AMT	Administer dose of vancomycin
DUR	Infusion duration in hours
DV	Dependent variable, vancomycin concentration mg/L
EVID	NONMEM event identifier
RATE	Infusion rate [mg/hours]
ID	Patient identifier
CMT	NONMEM compartment identifier
OCC	Dosing occasion
MDV	Identifier for missing dependent variables
SEX	Sex of the patients 1=female
AGE	Age of the patient in years
HTM	Body height of the patient in m
BMI	Body mass index in kg/m^2
SCR	Serum creatinine in µmol/L
WTKG	Total body weigh in kg
DVHID	True vancomycin concentration in mg/L hidden to the approaches
SIMN	Identifier of the models used to simulate the respective patient
SATI	Identifier of the sampling strategy

TIME	AMT	DUR	DV	EVID	RATE	ID	CMT	OCC	MDV	SEX	AGE	HTM	BMI	SCR	WTKG	DVHID	SIMN	SATI
0	2000	1	.	1	2000	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	.	1	3
0.5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	23.054	1	3
1	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	36.569	1	3
1.5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	24.672	1	3
2	0	.	29.133	0	0	10001	1	1	0	0	50.43	1.77	28.5	59.22	89.29	29.133	1	3

2.5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	21.085	1	3
3	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	31.477	1	3
3.5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	17.677	1	3
4	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	20.515	1	3
4.5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	22.668	1	3
5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	17.188	1	3
5.5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	14.871	1	3
6	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	19.619	1	3
6.5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	11.656	1	3
7	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	10.44	1	3
7.5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	9.4714	1	3
8	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	5.798	1	3
8.5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	11.008	1	3
9	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	8.5556	1	3
9.5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	9.1017	1	3
10	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	8.4579	1	3
10.5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	6.5751	1	3
11	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	5.3729	1	3
11.5	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	4.0975	1	3
11.99	0	.	.	2	0	10001	1	1	1	0	50.43	1.77	28.5	59.22	89.29	4.336	1	3
12	1250	1	.	1	1250	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	.	1	3
12.5	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	22.781	1	3
13	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	29.429	1	3
13.5	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	25.356	1	3
14	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	19.596	1	3
14.5	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	26.667	1	3
15	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	18.137	1	3
15.5	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	15.223	1	3
16	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	15.337	1	3
16.5	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	14.23	1	3
17	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	12.411	1	3
17.5	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	10.806	1	3
18	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	12.223	1	3
18.5	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	11.094	1	3
19	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	7.9235	1	3
19.5	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	11.312	1	3
20	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	7.7734	1	3
20.5	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	7.0833	1	3
21	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	6.6701	1	3
21.5	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	8.7447	1	3
22	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	4.4152	1	3
22.5	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	4.2194	1	3
23	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	5.1198	1	3
23.5	0	.	.	2	0	10001	1	2	1	0	50.43	1.77	28.5	59.22	89.29	4.5451	1	3
24	1250	1	.	1	1250	10001	1	3	1	0	50.43	1.77	28.5	59.22	89.29	.	1	3
....	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...

4) Estimation using MAA/MSA

In brief, the reformatted datasets were supplied to the multi-model approaches, which in turn estimated the individual PK parameters, vancomycin concentration and AUC of the 6000 individuals based on the supplied information (MAXEVAL=0). For detailed code examples of the MAA/MSA, including hands-on material, we kindly refer to the supplement file "cpt2065-sup-0002-Supinfo.zip" of the primordial publication of Uster *et al.* https://doi.org/10.1002/cpt.2065

Model averaging and model selection R code

```
##
#- Packages ------------------------------------------------------------------
##

library(tidyr)
library(dplyr)
library(readr)
library(xpose4)
#library(foreach)

##
#- Prerequisites -------------------------------------------------------------------------------
-
##

modelest_info <- read_csv("modelest_info.csv", col_names = F, skip= 1)  ## v3
sum of: v4 Thetas, v5 omegas, v6 sigmas

#runnumber
model_run = modelest_info$X1          ## (eg run001, ..)
model_name = modelest_info$X2         ## (eg Adane 2015, ..)
model_position = modelest_info$X8     ## (eg 1 2 3 4 5 6)
#modelnumbers
n_model = length(model_run)           ## eg 6

##
#- Dataset -------------------------------------------------------------------------------------
```

```
##

## dataset containing the patient
data0 <- read_csv("data0.csv",skip = 0, col_names = T)

##
#---------------------ESTIMATION-----------------------------------------------------
##

#-1 Estimate with (n_model)models-------
n_model = n_model
j <- NA   ##m_loop: loop over set of models
m_out <- vector("list", n_model)

for(j in model_position){

   #execute NM model for estimation
   system( paste("execute -model_dir_name -clean=2 -silent run00",j, ".mod",sep
= ""), wait = T, intern = F)

   ##read results
   lstfile = read.lst( paste("run00",j,".lst",sep = ""))
   est_sdtab = read.table(paste("sdtab00",j, sep = ""),skip = 1, header = T)

   ## add OFV, Likelihood L, modelname, ...
   m1 <- est_sdtab %>%
    mutate(
     OFV = lstfile$ofv,
     LL = exp(-0.5 * OFV),
     SCE = NA,
     SCEN = 1,
     MOD = model_name[j],
     MODN = model_position[j]
    )

 m_out[[j]] <- m1                  ## produce one loop output

 # remove unnecessary output
```

```
 system(paste("rm -r run00*.dir*", sep=''))
 rm("lstfile", "est_sdtab")
}

m_out = dplyr::bind_rows(m_out)

#-2 calculate weights ------------------------------------------------------------
w1 <- m_out %>%
 dplyr::distinct( ID, MOD, MODN, OFV, LL, .keep_all= F) %>%
 dplyr::mutate( W = LL/sum(LL) )

w2 <- dplyr::right_join(m_out, w1)                    ## add weighting term for
each observation

#-3.1 MSA ------------------------------------------------------------------
msa <- w2 %>%
 group_by(ID, TIME ) %>%
 dplyr::filter(LL==max(LL)) %>%  ## same as   dplyr::filter(W==max(W)) %>%
 mutate(MOD2=MOD,             ##add identifier column
      MOD = "Selection (MSA)",
      MODN = 7)

#-3.2 MAA ------------------------------------------------------------------

maa <- w2 %>%
 group_by(ID, TIME) %>%                  ##not urgently necessary, but more a
precaution
 mutate(
  AUC = sum(AUC*W),          ##average AUC if supplied
  PRED = sum(PRED*W),
  IPRED = sum(IPRED*W)) %>%          ##average results
 ungroup() %>%
 distinct(ID, TIME, .keep_all = T) %>%
 mutate(MOD = "Averaging (MAA)",        ##add identifier
      MODN= 8,
      W   = NA)
```

5) Identification of the optimal sampling strategies

In brief, to assess the sampling strategies of the multi-model approaches in FD or SS across the total population, trends of the median percentage error (MdPE; Eq. 2) and the interquartile range (IQR; Eq. 3) of the relative prediction errors (Eq. 1) were evaluated.

$$\mathrm{rPE} = \frac{predicted\ AUC - simulated\ AUC}{simulated\ AUC} * 100 \quad \text{(Eq. 1)}$$

$$\mathrm{MdPE} = median(\{rPE_0; \dots; rPE_i\}) \quad \text{(Eq. 2)}$$

$$\mathrm{IQR} = quartile_3(\{rPE_0; \dots; rPE_i\}) - quartile_1(\{rPE_0; \dots; rPE_i\}) \quad \text{(Eq. 3)}$$

With $\mathrm{quartile}_1$ and $\mathrm{quartile}_3$ being the 25^{th} and 75^{th} percentile of the relative prediction errors of the AUC (rPE) over the 5925 patients, respectively.

The resulting performance metrics of the sampling-strategies per approach were ordered from best to worst and assigned with a ranking number representing the respective position in the order (example below). The best combination of the MdPE and IQR was identified as optimal sampling strategy per approach in the case of the MAA in the first dose scenarios at 2.0 hours.

Table: Exemplified ranking of the single-sampling strategies according to the median percentage error (MdPE) and interquartile range (IQR): The performance metrics of the top five single-sampling strategies (First dose) using the MAA are displayed below. Each metric (MdPE and IQR) is given a rank between 1 and 23 with 1 being the best. These numbers are subsequently summed and the lowest sum is impartially identifying the optimal sampling timepoint (→) in the respective estimation method. MdPE – median percentage error of the area under the concentration time curve; IQR – interquartile range of the relative prediction errors

Estimation Model	Dosing interval	Single-sampling strategy [h]	MdPE [%]	IQR [%]	Ranking of the MdPE	Ranking of the IQR	Sum of the Rankings	
					X	Y	X+Y	
MAA	First dose	2	-0.04	23.88	2	3	5	→
MAA	First dose	3	0.44	23.96	4	4	8	
MAA	First dose	3.5	0.94	23.33	9	1	10	
MAA	First dose	1.5	0.38	25.38	3	7	10	
MAA	First dose	1	-0.07	26.41	1	10	11	
…	…	…	…	…	…	…	…	

6) Repeating 3) – 5) for the two-sampling strategies

After identifying the optimal single-sample timepoints per approach, step 3) to 5) was repeated with the optimal single sample (in the case of the MAA in the first dose scenarios at 2.0 hours) being always supplied next to a second sample in between 0 and 12 hours post start of infusion.

7.4.2 Supplementary file S2

Supplement Text S1:

To calculate the AUC using the equation-based approach proposed by Pai et al.1, the individual plasma concentration at the theoretical start of infusion (CT0) and the true trough concentration immediately before the next dose (CT12) are needed. In detail, the concentrations were back-extrapolated from the mono-exponential curve via transposing Eq. 1 as represented below.

$$Ke = \frac{Ln\left(\frac{C_P}{C_T}\right)}{T_T - T_P} \quad \text{(Eq. 4)}$$

$$C_{T0} = \exp(\, Ke * (T_T - T_{T0})) * \; C_T \quad \text{(Eq. 5)}$$

$$C_{T12} = \frac{C_P}{\exp(\, Ke * (T_{T12} - T_P))} \quad \text{(Eq. 6)}$$

Table S1: Model properties and representative* PK parameters of the pharmacometric models included in the algorithms**.

Reference	Patient population	N	Nr. o samp.	Covariates	CL	Vc	Vp	Q	IIV***	RUV***
Adane *et al.*, 2015 **	extremely obese	29	93	CL: CLCR; Vc: TBW	4.74	38.3	-	-	CL: 26.7% Vp: 23.9%	P: 18.9% A: -
Mangin *et al.*, 2014 **	critically ill with post sternotomy mediastinitis	30	359	CL: sex, TBW, SCR, SAPSII-score; Vc: TBW; Vp: TBW; Q: TBW, diabetes mellitus	2.60	23.5	72.9	6.01	CL: 29% Vc: 53% Q: 101%	P: - A: 7.3 mg/L

Medellín-Garibay *et al.*, 2016 **	trauma patients	118	392	CL: CLCR, furosemide co-medication; Vc: TBW, age; Vp: TBW	2.87	55.5	442.5	0.81	CL:36.7% Vc: 40.0%	P: 19.2% A: 3.5 mg/L
Revilla et al., 2010 **	intensive care patients	191	569	CL: age, CLCR; Vc: SCR, TBW	4.84	61.5	-	-	CL: 30.1% Vc: 22.8%	P: - A: 4.2 mg/L
Roberts *et al.*, 2011 **	septic, critically ill	206	579	CL: CRCL; Vc: TBW	4.15	114.8	-	-	CL: 38.9% Vc: 37.4%	P: 19.9% A: 2.4 mg/L
Thomson *et al.*, 2009 **	TDM patients	398	1557	CL: CLCR; Vc: TBW, Vp: TBW	4.45	50.6	54.9	2.28	CL: 27% Vc: 15% Vp: 130% Q: 49%	P: 15% A: 1.6 mg/L

* parameters were calculated for comparability-reasons using a representative patient: 50 years old, male, 75 kg, 1.7 m, serum creatinine of 85 µmol/L

** population pharmacokinetic models, which are also included in the model averaging and model selection algorithms

*** CV was calculated as square root of omega or sigma multiplied by 100, if not otherwise stated in the publication

N: Number of patients, Nr. of samp.: Number of vancomycin samples used for model development, CL: Clearance, Vc: central Volume of distribution, Vp: peripheral Volume of distribution (-: one-compartment model), Q: Intercompartmental Clearance (L/h, -: one-compartment model), IIV: interindividual variability (coefficient of variation (CV)**), RUV: residual unexplained variability, with P: proportional (CV**) and A: additive component, CLCR: creatinine clearance, TBW: total body weight, SCR: serum creatinine

Table S2: Exemplified ranking of the single-sampling strategies according to the median percentage error (MdPE) and interquartile range (IQR): The performance metrics of the top five single-sampling strategies (First dose) using the MAA are displayed below. Each metric (MdPE and IQR) is given a rank between 1 and 23 with 1 being the best. These numbers are subsequently summed and the lowest sum is impartially identifying the optimal sampling timepoint (→) in the respective estimation method. MdPE – median percentage error of the area under the concentration time curve; IQR – interquartile range of the relative prediction errors

Estimation Model	**Dosing interval**	**Single-sampling strategy [h]**	**MdPE [%]**	**IQR [%]**	**Ranking of the MdPE**	**Ranking of the IQR**	**Sum of the Rankings**	
					X	Y	X+Y	
MAA	First dose	2	-0.04	23.88	1	3	4	→
MAA	First dose	3	0.44	23.96	4	4	8	
MAA	First dose	3.5	0.94	23.33	9	1	10	
MAA	First dose	1.5	0.38	25.38	3	7	10	
MAA	First dose	1	-0.07	26.41	2	9	11	
...	...	...	...	...	...	...	...	

Table S3: Timing and performance metrics of the optimized single- and two-sampling and mainly recommended peak-trough strategies of the same population PK models used to simulate the 6000 patients after the first dose of vancomycin as well as in steady-state.

	Population PK model	First sample [h]	Second sample [h]	Single-sample strategy[*1]		Two-sample strategy[*2]		"peak-trough" strategy[*3]	
				MdPE [%]	rRMSE [%]	MdPE [%]	rRMSE [%]	MdPE [%]	rRMSE [%]
First Dose	Adane 2015	4.5	4	10.7	35.3	5.2	24.5	12.9	34.9
	Mangin 2014	2	1	0.4	30.8	-0.6	25.1	-14.9	24.5
	Medellin 2016	6.5	4.5	1.6	30.5	0.2	21.7	8.2	25.2
	Revilla 2010	2	5	0.5	29.1	-1.0	20.9	1.6	25.1
	Roberts 2011	3.5	4.5	-8.4	21.7	-5.5	17.3	-5.4	20.2
	Thomson 2009	5.5	3.5	-3.2	28.6	-3.2	21.0	-0.5	30.1
Steady-state	Adane 2015	6.5	5	-2.3	23.4	-2.5	17.9	4.2	21.8
	Mangin 2014	1	10	8.1	37.8	3.6	24.1	2.6	25.3
	Medellin 2016	7	5	4.8	27.3	1.6	19.8	5.3	21.3
	Revilla 2010	5.5	4.5	-3.5	23.3	-1.6	18.2	4.0	22.5
	Roberts 2011	6.5	5	-6.9	22.1	-4.9	17.0	-1.4	19.0
	Thomson 2009	8	3.5	-3.0	23.6	-1.9	18.0	-1.4	20.0

[*1] performance metrics using the "First sample" timepoint

[*2] performance metrics using the "First sample" and "Second Sample" timepoint

[*3] performance metrics using a sample at 1 h and at 11.5 h post start of infusion

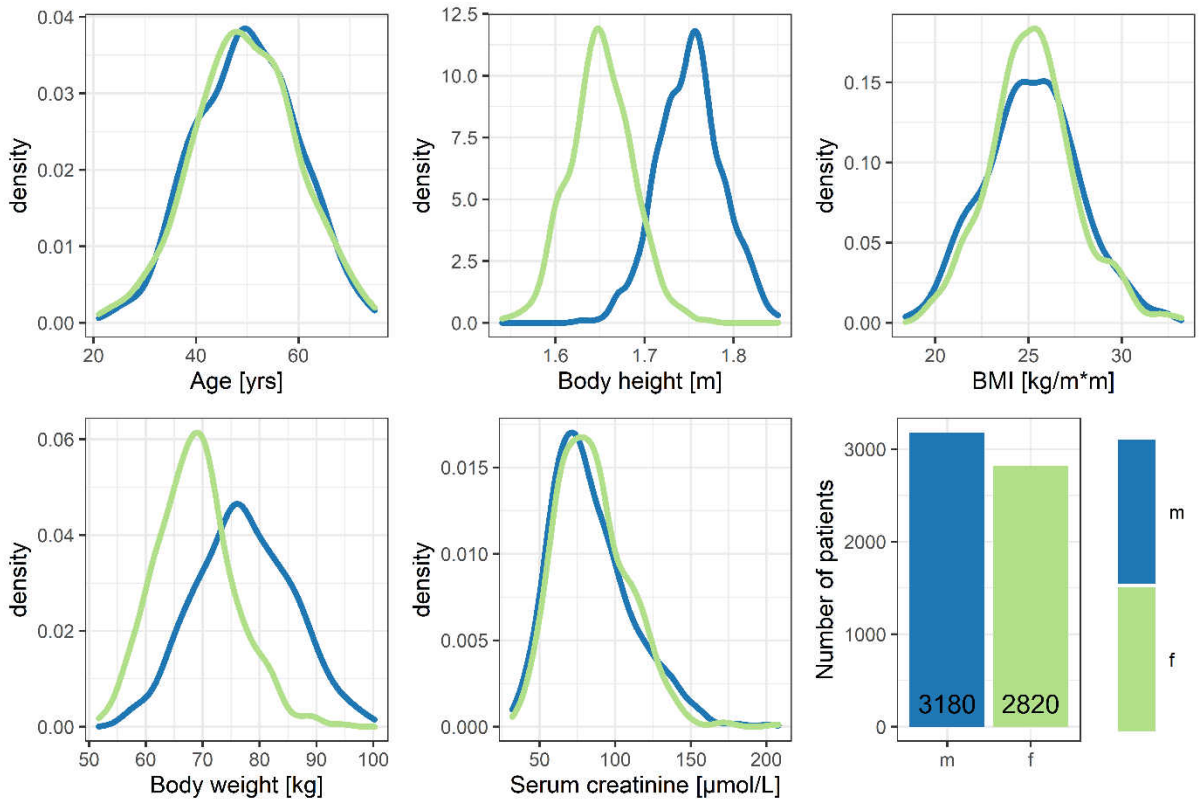


Figure S1: Distribution of the demographics of the simulated population (n=6000). f – female, m – male

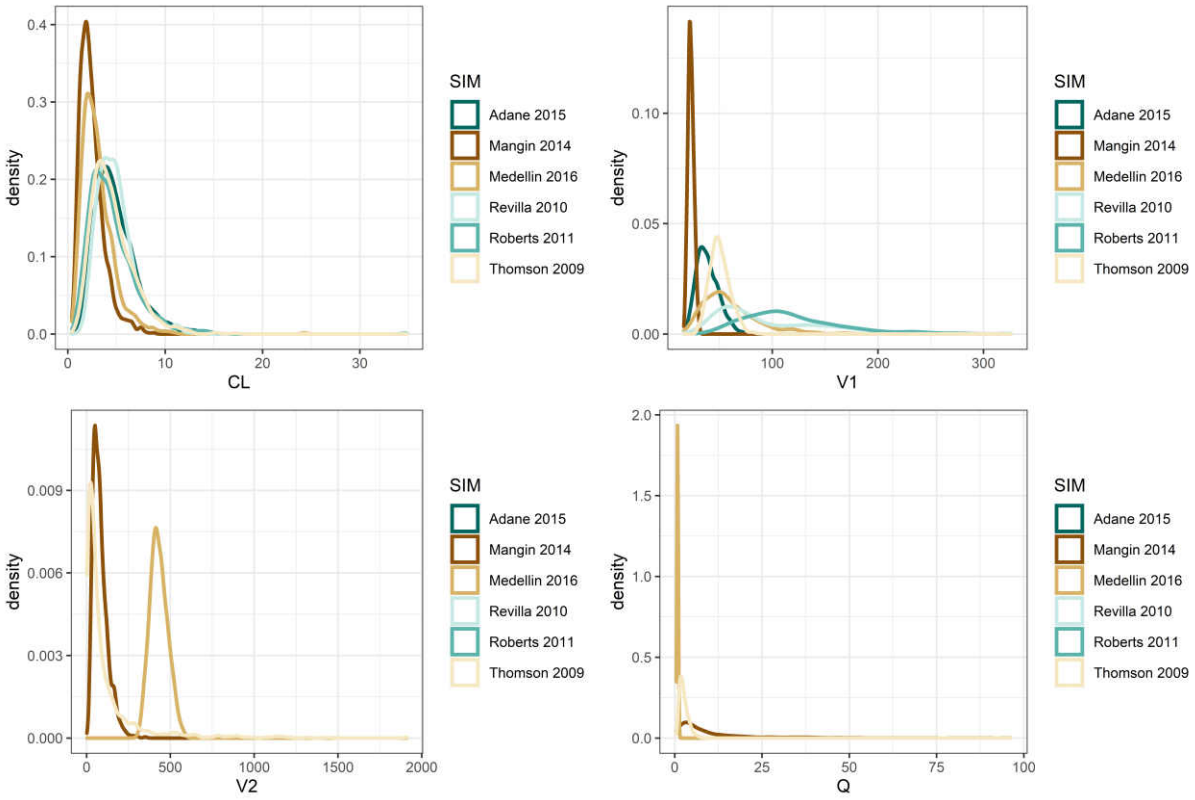


Figure S2: Distributions of the simulated parameters (in total 5925) stratified by the six simulation models. Green colors indicate a one-compartmental structure; brown colors indicate a two-compartmental structure

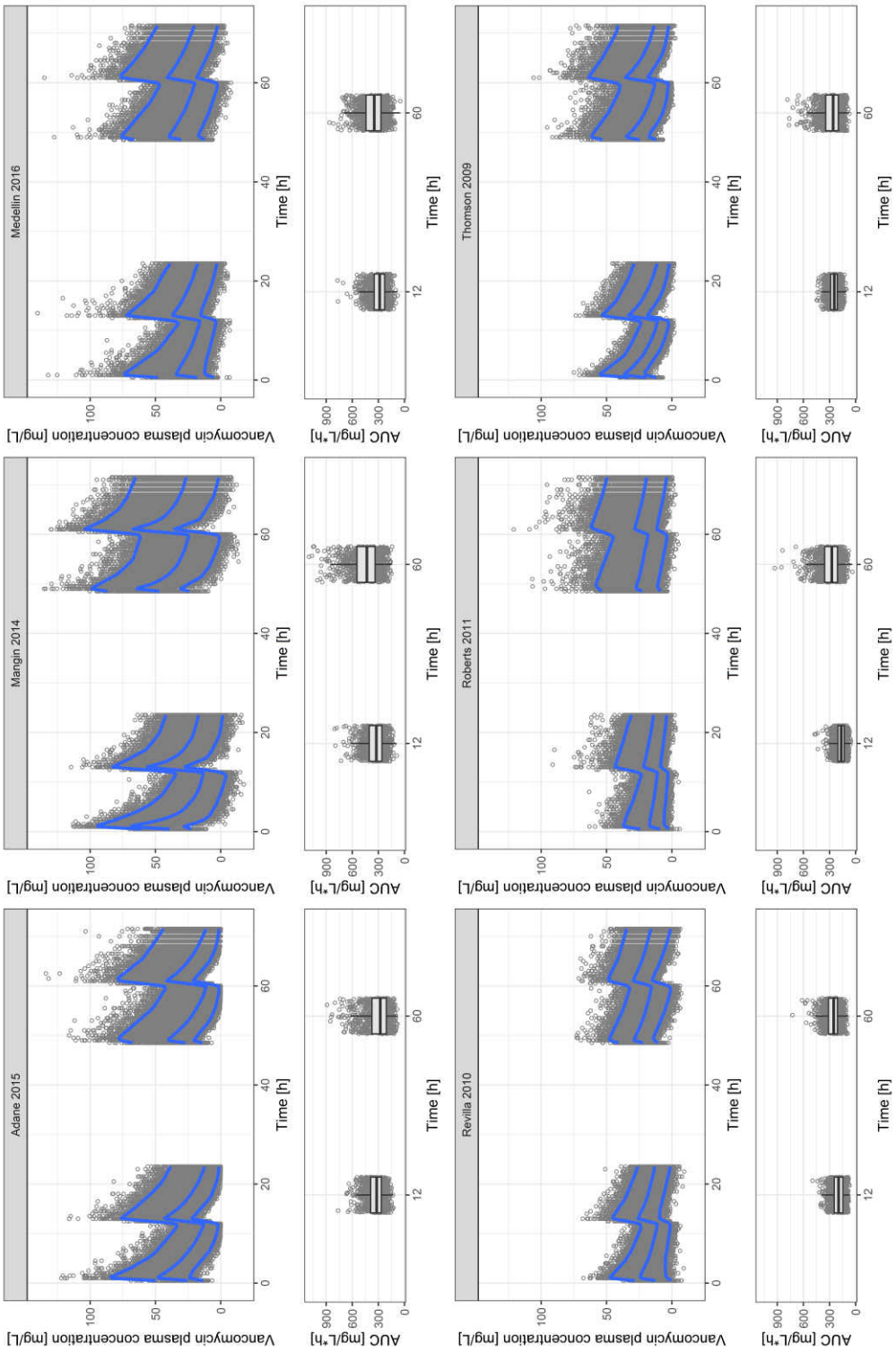


Figure S3: Simulated PK profiles (in total 5925) stratified by the population PK models used for simulation. The lower panels display the individual true AUC values either from 0-12 hours (12) or from 48-60 hours) obtained via numerical integration of the simulated PK profiles. The AUC was determined by integration and hence included no residual unexplained variability (RUV), while the individual vancomycin plasma concentrations included the RUV of the simulation model. The three blue lines indicate the 2.5th, 50th and 97.5th percentiles of the PK profiles, respectively.

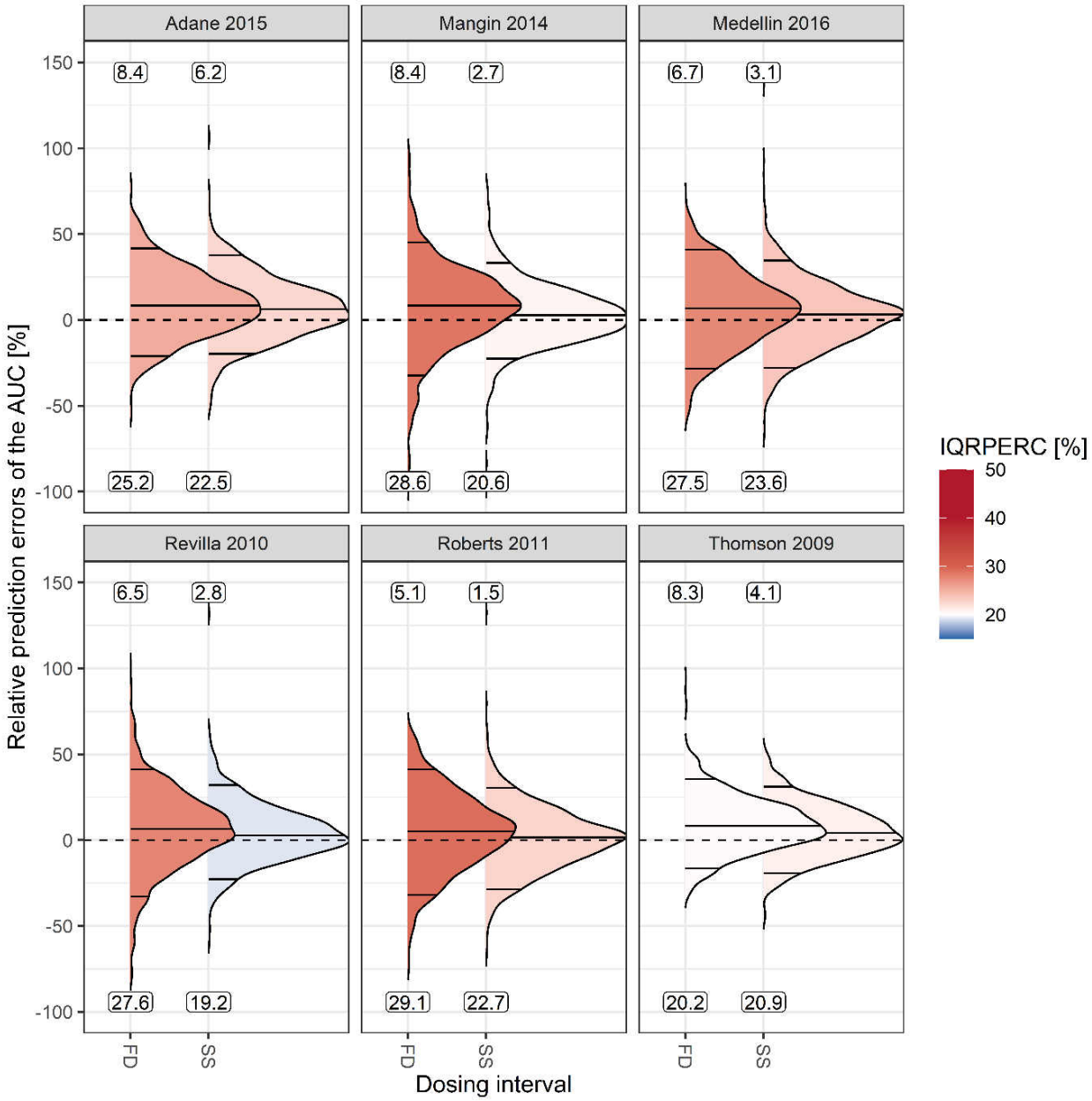


Figure S4: Relative prediction errors (rPE) and performance metrics (upper: median percentage error, lower: interquartile range) of the equation-based approach stratified by the population simulated using the indicated models; FD – first dose; SS – steady-state

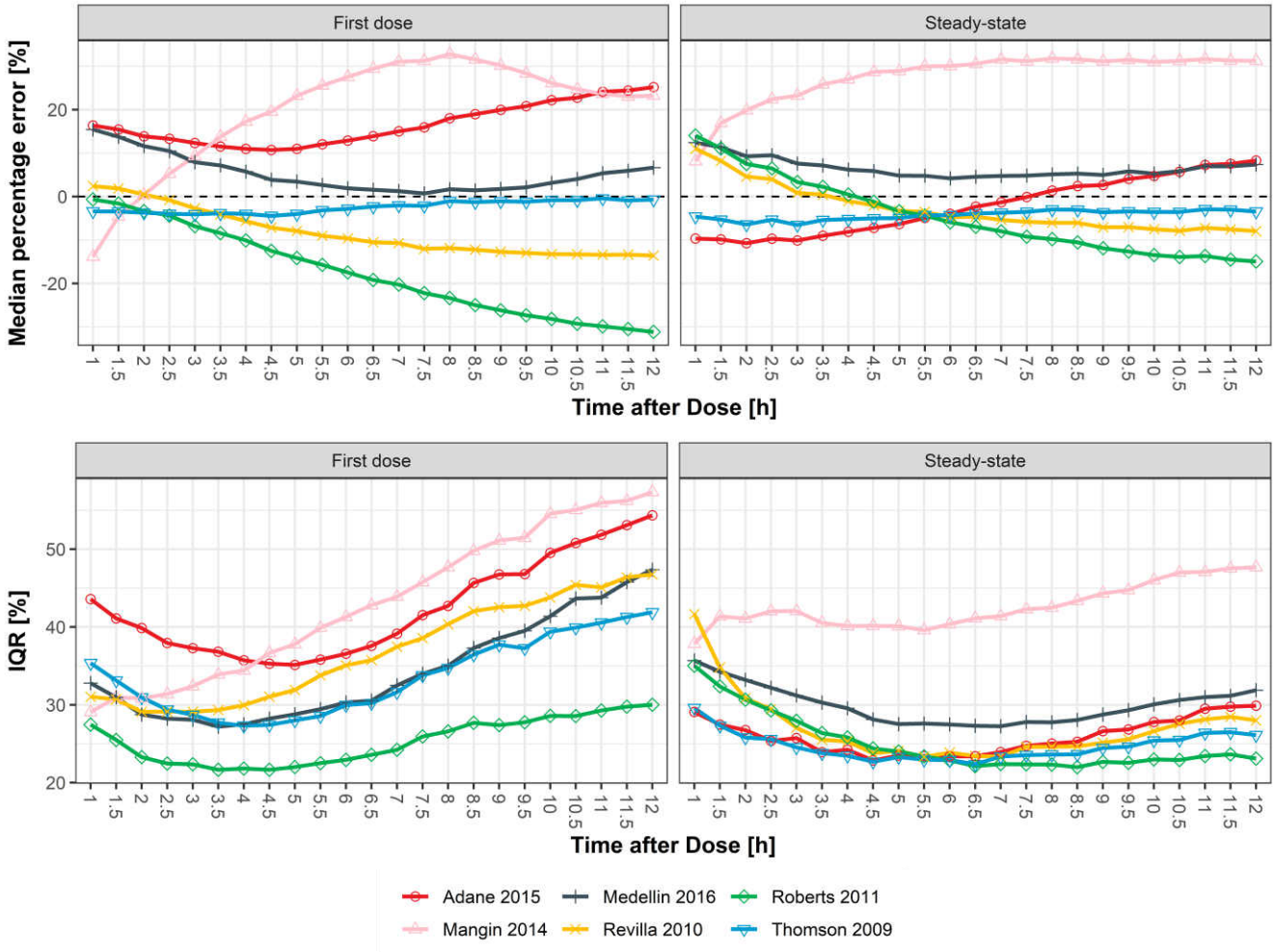


Figure S5: Predictive performance of the six population PK models used to simulate the virtual patients using the single-sample strategies in the total simulation (n=5925). The median percentage error and the interquartile range of the relative prediction errors of the AUC (IQR) are representing accuracy and imprecision, respectively. Time after dose indicates the distinct timepoint of the single sample drawn in the 5925 patients either in the first dosing interval or the fifth (i.e. Steady-state).

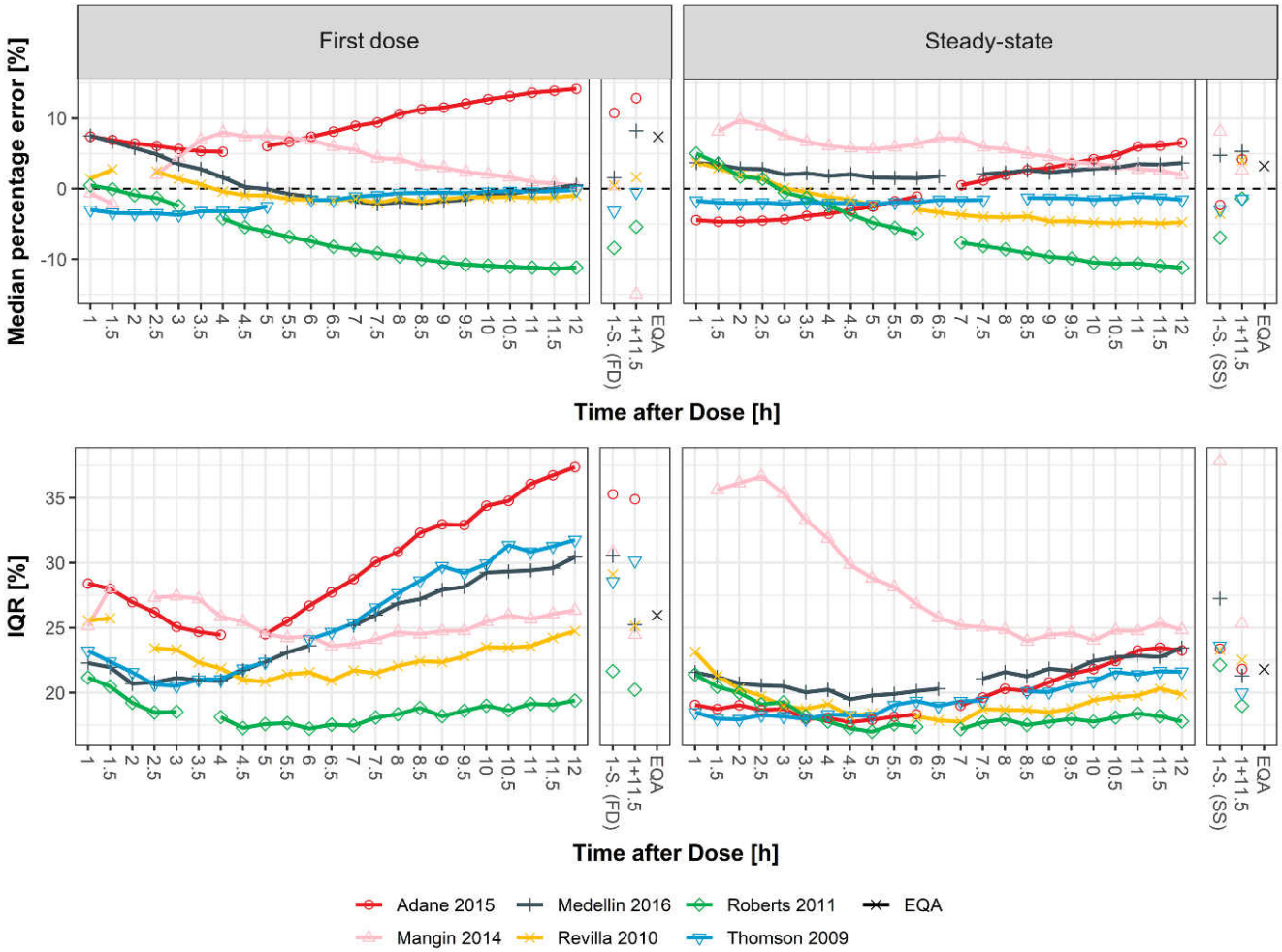


Figure S6: Predictive performance of the six population PK models used to simulate the virtual patients using the optimized first sample and a second sample drawn in between 1-12 hours post start of infusion. Time after dose indicates the timepoint of the second sample drawn in the 5925 patients either 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. 1-S. – displays the performance metrics of the optimal single-sample strategy of the six models (see Table S3); 1+11.5 – represents the performance metrics of the gold-standard "peak-trough" sampling strategies in the six approaches; EQA – the black crosses display the performance metrics of the equation-based approach as a reference; IQR – interquartile range of the relative prediction errors of the AUC

Supplementary references

1. Pai, M. P., Neely, M., Rodvold, K. A. & Lodise, T. P. Innovative approaches to optimizing the delivery of vancomycin in individual patients. *Adv. Drug Deliv. Rev.* **77**, 50–57 (2014).

2. Broeker, A. *et al.* Towards precision dosing of vancomycin: a systematic evaluation of pharmacometric models for Bayesian forecasting. *Clin. Microbiol. Infect.* **25**, 1286.e1-1286.e7 (2019).

3. Cunio, C. B. *et al.* Towards precision dosing of vancomycin in critically ill patients: an evaluation of the predictive performance of pharmacometric models in ICU patients. *Clin. Microbiol. Infect.* **27**, 783.e7-783.e14 (2021).

8 Hazardous materials

Not applicable.

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10 Eidesstattliche Versicherung

Hiermit versichere ich an Eides statt, die vorliegende Dissertation selbst verfasst und keine anderen als die angegebenen Hilfsmittel benutzt zu haben. Die eingereichte schriftliche Fassung entspricht der auf dem elektronischen Speichermedium. Ich versichere, dass diese Dissertation nicht in einem früheren Promotionsverfahren eingereicht wurde.

Hamburg, den _____

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David William Uster