Vancomycin population pharmacokinetic models: Uncovering pharmacodynamic divergence amid clinicobiological resemblance

Peggy Gandia, Sahira Chaiben, Nicolas Fabre, Didier Concordet

Received: 2 May 2024 | Revised: 21 September 2024 | Accepted: 25 September 2024

DOI: 10.1002/psp4.13253

ARTICLE

Vancomycin population pharmacokinetic models: Uncovering pharmacodynamic divergence amid clinicobiological resemblance

Peggy Gandia[1,2] | **Sahira Chaiben**[2] | **Nicolas Fabre**[3] | **Didier Concordet**[2]

[1]Pharmacokinetics and Toxicology Laboratory, Federative Institute of Biology, Toulouse University Hospital, Toulouse, France

[2]INTHERES, Université de Toulouse, INRAE, ENVT, Toulouse, France

[3]UMR 152 PharmaDev, University of Toulouse, IRD, UPS, Toulouse, France

Correspondence
Peggy Gandia, Laboratoire de Pharmacocinétique et Toxicologie, Institut Fédératif de Biologie, CHU de Toulouse, 330 avenue de Grande Bretagne – TSA 40031, 31059 Toulouse cedex 9, France.
Email: gandia.p@chu-toulouse.fr

Abstract

Vancomycin is an antibiotic used for severe infections. To ensure microbiological efficacy, a ratio of AUC/MIC ≥400 is recommended. However, there is significant interindividual variability in its pharmacokinetic parameters, necessitating therapeutic drug monitoring to adjust dosing regimens and ensure efficacy while avoiding toxicity. Population pharmacokinetic (PopPK) models enable dose personalization, but the challenge lies in the choice of the model to use among the multitude of models in the literature. We compared 18 PopPK models created from populations with the same sociodemographic and clinicobiological characteristics. Simulations were performed for a 47 years old man, weighing 70 kg, with an albumin level of 35.5 g/L, a creatinine clearance of 100 mL/min, an eGFR of 106 mL/min/1.73 m^2, and receiving an intravenous infusion of 1 g×2/day of VCM over 1 h for 48 h. Simulations of time–concentration profiles revealed differences, leading us to determine the probability of achieving microbiological efficacy (AUC/MIC≥400) with each model. Depending on some models, a dose of 1 g×2/day is required to ensure microbiological efficacy in over 90% of the population, while with the same dose other models do not exceed 10% of the population. To ensure that 90% of the patients are correctly exposed, a dose of vancomycin ranging from 0.9 g×2/day to 2.2 g×2/day is necessary a priori depending on the chosen model. These differences raise an issue in choosing a model for performing therapeutic drug monitoring using a PopPK model with or without Bayesian approach. Thus, it is fundamental to evaluate the impact of these differences on both efficacy/toxicity.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Over 300 PopPK models of vancomycin are available in the literature.

WHAT QUESTION DID THIS STUDY ADDRESS?

Do PopPK models developed with populations sharing similar sociodemographic and clinical–biological characteristics result in comparable a priori dosage?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

For a population with the following characteristics (47 years old man, weighing 70 kg, with an albumin level of 35.5 g/L, a creatinine clearance of 100 mL/min, an eGFR of 106 mL/min/1.73 m^2), a dosing regimen of 1 g × 2/day may not be suitable for this entire population depending on the PopPK model. Indeed, according to the models, the daily dose required to cover 90% of patients varies from 0.9 g × 2/day to 2.2 g × 2/day.

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

This highlights the challenge in selecting appropriate models for determining a priori dosage regimens and for therapeutic drug monitoring using PopPK models.

INTRODUCTION

Vancomycin (VCM) is a glycopeptide antibiotic administered intravenously (IV). It is widely used in hospitals and reserved for severe gram-positive infections resistant to conventional treatments, particularly those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). In most cases, the dosing regimen is 1 g q12h. Its elimination is primarily renal. One of its adverse effects, frequently found in prolonged use (4–8 days of treatment), is nephrotoxicity (in more than 40% of treated patients).[1] Vancomycin has a narrow therapeutic range, meaning the gap between the exposure that determines efficacy and that which determines toxicity is small. Therefore, any deviation in exposure from the therapeutic range leads either to treatment failure or toxicity.

The microbiological efficacy of vancomycin is concentration- and time-dependent,[1] justifying that the optimal pharmacokinetic/pharmacodynamic (PK/PD) criterion to maintain the drug level within the therapeutic window is the ratio of the area under the curve (AUC) to the minimum inhibitory concentration (MIC). For pathogens such as MRSA, this ratio must be equal to or greater than 400 (≥400).[2]

Vancomycin exhibits high interindividual variability in pharmacokinetic parameters. Neely et al. assembled richly sampled vancomycin pharmacokinetic data from three studies comprising 47 adults with various levels of renal function.[3] On the basis of their simulations, even in an ideal population of adults with normal renal function who get the same dosing regimen, vancomycin AUC values varied as much as 30-fold between patients, with associated variability in peak and trough concentrations. Therefore, to ensure microbiological efficacy while limiting toxicity, it is necessary to estimate the patient's vancomycin AUC to individually adjust the dosing regimen when the exposure is not within the therapeutic range.

The published population pharmacokinetic (PopPK) models consistent with the sociodemographic and clinicobiological characteristics of a patient can be used to estimate the patient's dosage regimen. The challenge lies in the large number of PopPK models documented in the literature. The first screening step involves rejecting models developed using populations that differ from the target population in terms of sociodemographic and clinicobiological characteristics (e.g., normal kidney function vs. dialysis). The second screening step involves excluding models that lack essential components for model quality evaluation (e.g., no error model described, absence of covariates in the final model despite individual random >30%, no RSE or RSE >30% for population parameters, absence of VPC/NPDE). Following these steps, it is reasonable to expect that the retained models will yield consistent results.

The objective of this work was to determine if the PopPK models of vancomycin created in similar populations lead, for a same PK/PD target, to the same a priori dosing regimen.

MATERIALS AND METHODS

Selection of population pharmacokinetic models

Searching for publications on PopPK models for vancomycin on reputable database platforms such as PubMed and Google Scholar using the terms "vancomycin" and "population pharmacokinetic" yielded a considerable number of articles, 713 and 39,100 respectively, posing a challenge in distinguishing between articles focused on PK vancomycin and those that were completely unrelated to the topic or did not provide a PopPK model for vancomycin. To address this, a set of inclusion and exclusion criteria were established. Articles research was performed using the following set of keywords: "vancomycin population pharmacokinetic(s)" or "vancomycin model(l)ing," and excluding the following words "pregnant," "pregnancy,"

"p(a)ediatric(s)," "pediatry," "neonate(s)," "neonatal," "newborn(s)," "infant(s)," "children," "h(a)emodiafiltration," "hemodialysis," "peritoneal," "replacement," "transplant," "transplantation," "critically," "intensive," "extracorporeal," "ECMO," "trauma," "sepsis," "burn," "cystic fibrosis," "obese." These keywords were selected to ensure the strict inclusion of adult populations with normal renal function (i.e., no renal insufficiency or glomerular hyperfiltration) (Figure 1). Moreover, a PopPK model was rejected if information on interindividual and residual variability was lacking. The search for articles ranged from January 2009 to February 2024. This 25-year period encompasses the vast majority of PopPK articles published on vancomycin. Indeed, while numerous articles have been published on vancomycin before 2009, only five focus on PopPK models, and access is limited to their abstracts.

Simulation of kinetic profiles and probability of achieving adequate exposure

For each of the selected models, we conducted in R Studio 1000 Monte Carlo simulations representing 1000 kinetic profiles of virtual individuals using the individual random effects η where $\eta \sim \mathbb{N}(0, \Omega)$. These simulations were performed for a 47 years old man, weighing 70 kg, with an albumin level of 35.5 g/L, a creatinine clearance (ClCreat) of 100 mL/min, and an eGFR of 106 mL/min/1.73 m^2. The individual received an intravenous infusion of 1 g of VCM over 1 h q12h for 48 h, as it is a standard dosing regimen.

Then, for each model, the probability of target attainment P((AUC/MIC)≥X), so-called probability of target attainment (PTA), was determined, with (i) AUC area under the concentration–time curve at steady-state, (ii) MIC the minimum inhibitory concentration, and (iii) X the possible values of this ratio (ranging from 0 to 1000 due to possible values in human clinical practice). PTAs were performed at a steady state as kinetic simulations were conducted for a virtual patient with normal renal function. In this case, the terminal half-life of vancomycin ranges between 3.7 and 5.3 h, resulting in a steady state achieved within 24 h.[4] This short delay is considered negligible. In cases where the terminal half-life is increased, a loading dose is typically administered to achieve an exposure similar to that at steady state.

Given that MRSA represents the primary infection treated with vancomycin as per prevailing guidelines, we focused on the MRSA MICs distribution from the EUCAST website. The analysis of the MRSA MIC distribution shows that 83% of MICs are equal to 1 mg/L and

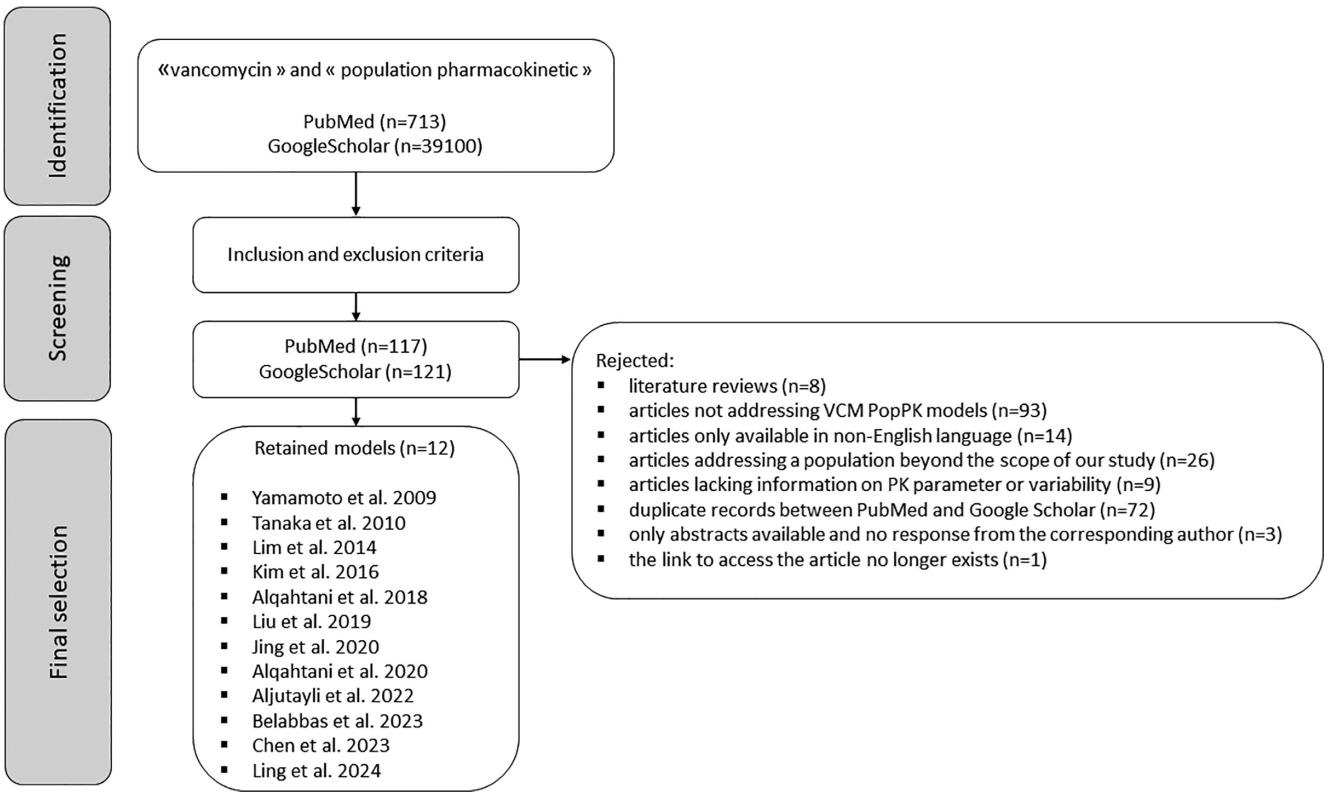

FIGURE 1 Flowchart of the model selection.

13% greater than 1 mg/L. As clinicians do not prescribe vancomycin when MIC is greater than 1 mg/L, we only considered the MIC equal to 1 mg/L.[5]

RESULTS

Population pharmacokinetic models

Using inclusion and exclusion criteria led to 117 and 121 articles for PubMed and Google Scholar, respectively (Figure 1). Among the 238 articles, 226 were excluded for the following reasons: literature reviews; articles not addressing PopPK models of vancomycin; articles inaccessible or only available in non-English language; articles addressing a population beyond the scope of our study; articles lacking information on PK parameter or variability; duplicate records between PubMed and Google Scholar. The remaining 12 articles (i.e., 18 PopPK models) are described in Table 1.

Figure 2a,b depicts two examples of Monte Carlo simulations for individuals aged 47 years, weighing 70 kg, with an albumin level of 35.5 g/L, a creatinine clearance (ClCreat) of 100 mL/min, and an eGFR of 106 mL/min/1.73 m^2, receiving 1 g of VCM over 1 h q12h for 48 h. At steady state, with Belabbas's and Lim's model, VCM trough median concentration is 14.4 and 9 mg/L, and the concentration increases to 22.4 and 33.7 mg/L after 1 h of infusion, respectively. Codes (R) for Monte Carlo simulations and the corresponding figures are available for 22 models in supplemental files (Material S1; Figure S1). Contrary to the PTA (18 PopPK models were retained), a total of 22 PopPK models were retained as clearance and volume of distribution were systematically used for Monte Carlo simulations.

The PTA of 18 PopPK models from the 12 retained articles is plotted in Figure 3. For the same dosing regimen, the probability of achieving adequate exposure $\left(\frac{AUC}{MIC} \geq 400\right)$ ranges from 8.7% to 94.2% (Table 2). Only 2 models (#4 and #15) out of 18 provide coverage for more than 90% of patients for this dosing regimen. Codes (R) are available in a supplemental file (Material S2).

DISCUSSION

The aim of this study was to evaluate the interchangeability of 18 PopPK of vancomycin constructed from similar populations.

Simple comparison of kinetic profiles (Figure 2a,b) revealed differing maximal (C_{max}) and minimal (trough) concentrations among these models. A primary factor contributing to this discrepancy is the number of compartments (mono, bi, tri) characterizing each model. This compartment count is influenced by the analytical performance (i.e., lower limit of quantification "LLOQ") of the method used to assay VCM. More clearly, for the oldest publications, models were built with concentrations measured with assays presenting high LLOQ, rendering impossible the detection of the eventual remaining PK phases. As a consequence, the last documented PK phase is considered the elimination phase. From 25 years, analytical performances of VCM assays have been improved leading to a better description of the VCM PK. A secondary factor contributing to the number of compartments is the number of blood samples available for each patient. For the models built with routine data, a low number of concentrations is available per individual, in general C_{max} and trough concentration. This limits the number of parameters that can be estimated in the model and consequently the number of compartments that can be included in the final model.

However, having distinct kinetic profiles does not invariably lead to different exposures. Thus, if kinetic profiles differ but exposures (AUCs) are similar, microbiological efficacy, characterized by the AUC/CMI ratio ≥400, is expected in this population. This prompted us to conduct PTA.

PTA analysis indicates that with a dosing regimen of 1 g × 2/day, the proportion of individuals achieving the desired VCM exposure $P\left(\frac{AUC}{MIC} \geq 400\right)$ ranges from 8.7% to 94.2%, for a CMI = 1 mg/L. Some models indicate that the dosing regimen of 1 g × 2/day is ineffective for a significant portion of individuals (PTA < 10%), necessitating dosing regimen adjustment or therapeutic strategy change. Other models indicate that this dosing regimen is effective for the entire population (PTA > 90%). Therefore, depending on the PopPK model, a dosing regimen of 1 g × 2/day may not be suitable for the entire population. Notably, the daily dose required to cover 90% of patients varies, according to the models, from 0.9 g × 2/day to 2.2 g × 2/day. This disparity in doses also raises concerns regarding nephrotoxic.[6] The fact that some models lead to a dosage regimen of 2 g × 2/day to ensure microbiological efficacy, while others recommend 0.9 g × 2/day, implies that a patient could have a priori more than twice the exposure with the former regimen compared with the latter.

The results obtained for models created with apparently similar populations should prompt reflection on the numerous applications for model-informed precision dosing currently available online or developed in some hospitals. These applications offer the user, for a given molecule, either a single model or a panel of models, the choice of which is left to the discretion of the user. However, there is

no guarantee that the models proposed in these applications are compatible with the patient for whom Therapeutic Drug Monitoring (TDM) is considered. External validation trials using real-world data (i.e., measured concentrations in patients undergoing TDM) suggest that this is not the case and that the choice of a model for a given patient is an essential step in the context of individualized adjustment of dosing regimens by Bayesian approach.[7–9]

These results are particularly concerning considering that the populations used to develop these 18 models appear similar based on the clinicobiological data documented in the publications. However, upon closer examination of the model constructions, certain elements warrant discussion:

- Models 1[10] and 2[10] were designed for individuals with CLcreat ≥85 mL/min. In these models, VCM clearance was interpreted as a constant value (3.83 L/h = 63.8 mL/min for model 1 and 3.95 L/h = 65.8 for model 2). This suggests that any patient with CLcreat between 85 and 218.8 mL/min (the maximum CLcreat in the studied population) will have the same constant defining his VCM clearance, regardless of his actual value. On the contrary, the equations provided for patients with CLcreat <85 mL/min (not simulated in our study) vary depending on the specific value of CLcreat. In the latter scenario, it is predictable that VCM clearance will vary with CLcreat. However, for patients with CLcreat >85 mL/min, it is difficult to imagine that all of them, whether they have a normal renal function or are hyperfiltrating, would have the same constant value of VCM clearance.
- Models 6[11] and 8[11] are applicable to patients with neurological impairment, while models 5[11] and 7[11] are suitable for individuals without neurological impairment. Comparison from the available information in the original publication revealed that patients with neurological impairment exhibit higher VCM clearance, associated with lower AUC and PTA values. Models 11,[12] 12,[12] and 16[13] were created for patients with neurological impairment. We observed that the PTA of models 11 and 12 is similar to the PTA of models 6 and 8. However, the PTA of model 16 is significantly higher compared with the other models (ΔPTA between 61.7% and 70.4%). This difference could be explained by the fact that model 16 is a three-compartment model while the other models are one-compartment models. Although the population consists of patients with neurological impairment, the patients used to build model 16 had an extraventricular drain (EVD) while those used to build the other models did not. Since the EVD was not retained as a covariate in the different models and is not expected to affect the renal elimination of VCM, we failed to explain these differences.

Another possible explanation for these discrepancies is the VCM composition injected into the patients. Remind that VCM is a natural compound with a particularly complex structure (C66H75Cl2N9O24, 1449 Da). This glycopeptide is obtained by extraction from the fermentation broth of a bacteria and isolated as a mixture of similarly structured compounds, the main compound of which is vancomycin B. In Europe and the USA, quality control of vancomycin monohydrochloride (VCM), used in therapeutics, involves quantifying vancomycin B and its related products by HPLC. A purity of the peak corresponding to vancomycin B of at least 90 and 91% is required by the US and European Pharmacopeias (EP), respectively.[14,15] EP also requires quantification of the eight specified side-products five degradation products and other components that remain to be identified. It has also been established that only vancomycin B is responsible for the therapeutic properties, its isolation side- and degradation products having no or only weak antibiotic properties.[16,17] In addition, these pharmacopeia methods are criticized by certain authors because the vancomycin B peak quantified by HPLC in these methods is not pure and coeluted with side-products due to the lack of resolution of the chromatographic system used.[17] Similarly, the methods used to quantify VCM in the serum of patients use kits involving direct methods such as fluorescence polarization immunoassay, which are certainly sensitive but lack selectivity toward the real active substance, vancomycin B.

Therefore, these chemical and analytical reasons are perhaps involved in the observed discrepancies pointed out in this work, especially as little is known, in the reference articles examined, about the quality of the VCM (purity in vancomycin B) used to treat patients.

Despite all our efforts, we have not found any reasonable explanations to account for our results for the same administered dose. Neither the chosen PK model, nor the number of blood samples per individual, nor the composition of the VCM are sufficient to explain such variability. We hypothesize that there is an undocumented latent variable. Vancomycin-induced nephrotoxicity (VIN) causes acute kidney injury primarily due to proximal tubular dysfunction.[6] Although vancomycin is mainly eliminated by glomerular filtration, the impact of VIN on its clearance remains unclear. Since serum creatinine levels can lag by about 48–72 h after an injurious event,[18] serum creatinine is likely not sensitive enough to accurately reflect changes in vancomycin clearance.

TABLE 1 Description of the Pop PK models used for determining the probability of target attainment (PTA): 18 PopPK models were retained as (i) these models are compatible with the sociodemographic and clinicobiological characteristics of the virtual patient used for our study and (ii) only elimination clearance was used to calculate PTA.

Publication	Yamamoto 2009[10]		Tanaka 2010[21]	Lim 2014[20]	Kim 2016[11]				Alqahtani 2018[22]	Liu 2019[23]
Model N°	1	2	3	4	5	6	7	8	9	10
Population	Infected patients and healthy volunteers		–	–	Neurosurgical and non-neurosurgical patients				Patients with open heart surgery	Chinese patients (43% neuro)
N	106		86	20	132				28	200
Age (year)	65.4 ± 15.1 [25.8–99.7]	21.7 ± 2 [20–25]	73 [17–91]	59.3 ± 12.9	Neuro: 50.6 ± 15 Non-Neuro: 61.6 ± 15.7				51.7 ± 15.19 [18–78]	47.40 ± 15.42
Posology	Intermittent infusion over 0.5 to 2 h 1251 ± 446 mg/day Volunteers: infusion over 1 h 500 and 1000 mg		Infusion over 1–2 h 500–1500 mg at dosing intervals 6–48 h	1000 mg over 2 h q12h	1981 ± 219 or 1810 ± 387 mg/day				30 min infusion 1000 mg 2 h before surgery then q12h 12 cases of redosing	250; 500; 750; 1000; 1250; 1500 mg over 1 h Intervals 6; 8; 12; 24 h
GFR (mL/min)	–		59 [16–146]	–	–				–	106.39 ± 38.89
CLcr (mL/min)	79.6 ± 41.8 [15.3–218.8]	89.3 ± 10.4 [76.7–106.5]	74 [14–261]	96.6 ± 31.1	Neuro: 113.6 ± 48.3 Non-neuro: 79.0 ± 44.0				83.5 ± 29.3 [33.4–125]	123.75 ± 59.96
Compartment(s) in the model	2		1	2	1				2	1
COV of the clearance model	CLcr		CysGFR	CLcr	CLcr Neuro				CLcr Albumin	cysGFR Age TBW
Interindividual variability [RSE%]	ωCL = 0.375 [–] ωV1 = 0.182 [–] ωV2 = 0.728 [–] ωQ = 0.192 [–]	ωCL = 0.390 [–] ωV1 = 0.101 [–] ωQ = 0.174 [–] ωV2 = 0.819 [–]	ωCL = 0.196 [–] ωV = 0.300 [–]	ωCL = 0.149 [44.8] ωV1 = 0.120 [52.1] ωV2 = – ωQ = 0.416 [54.8]	ωCL = 0.354 [–] ωV = –				ωCL = 0.218 [16][a] ωV1 = 0.063 [17][a] ωQ = 0.537 [12][a] ωV2 = 0.564 [19][a]	ωCL = 0.208 [8] ωV = 0.181 [30]
Residual error [RSE%]	pro = 0.143 [–] add = –	pro = 0.132 [–] add = –	pro = 0.127 [–] add = –	pro = 0.231 [17.6] add = –	pro = 0.0859 [48.5] add = 1.92 mg/L [23.4]				pro = 0.152 [7] add = 0.055 mg/L [11]	pro = 0.158 [21][a] add = 1.28 mg/L [30]

Note: The symbol "–" indicates that data for the respective parameter are not available in the article.

Abbreviations: add, additive error; BIS-2, GFR calculated from Berlin Initiative Study; COV, covariate of the clearance model; creaGFR, GFR calculated from creatinine; cysGFR, GFR calculated from cystatin C; EPIcys-scr, GFR calculated from both cystatin and creatinine; *N*, number of patients; Neuro, whether the patient has a neurological impairment or not; pro, proportional error (standard error); Scr, serum creatinine; tbw, total body weight; *ω*, interindividual variability (standard error).

[a]If interindividual variability or proportional error is expressed in the article as a coefficient of variation and the value is <0.4, then this same value is used as standard error; otherwise, standard error is determined according to the following formula: se = sqrt(log((CV^2) + 1)). Inter-occasion variability was not explored in any of the 12 selected publications. RSE: relative standard error of the interindividual variability and the residual error.

The unexpected and unexplained differences in microbiological efficacy observed across various population pharmacokinetic (PK POP) models in our study may also occur with other antibiotics and pharmacological classes. To address and minimize these discrepancies, the following strategies should be considered:

(i) Construct models according to established checklists, such as those proposed by the FDA, EMA, or specific PK/PD modeling journals. Pay special attention to inter-occasion variability, which can vary in significance depending on the populations studied. This variability should be thoroughly documented, with a clear

Jing 2020[12]		Alqahtani 2020[24]	Aljutayli 2022[25]	Belabbas 2023[19]	Chen 2023[13]	Ling 2024[26]	
11	12	13	14	15	16	17	18
Neurosurgical patients		Cancer and noncancer patients	Different infections	Hematological malignancies with neutropenia and augmented renal clearance	External ventricular drainage w/ or w/o primary CNS infection	Elderly Chinese patients	
222		147	116	148	14	313	
46.95 ± 12.71		55.10 ± 15.90	67.80 ± 11.00	53.6 ± 16 [20–82]	59.7 ± 11.8	72 [65–95]	
–		1 h infusion b.i.d 2160 mg/day	15 mg/kg b.i.d	–	Intermittent and/or continuous infusion w/ or w/o initial loading dose	1790 ± 530 mg/day	
128.8 ± 35.63	115.8 ± 44.64	–	–	110 ± 43.8 /1.73 m^2	–	64.99/1.73 m^2 [11.01–120.94]	59.74/1.73 m^2 [14.04–123.21]
–		103 ± 59.3	–	122 ± 52.8	142 ± 57	–	
1		1	1	1	3	1	
creaGFR cysGFR Age TBW		CLcr	CLcr	CLcr	CLcr	EPIcys-scr, BIS-2	
ωCL = 0.210 [7] ωV = –	ωCL = 0.204 [7] ωV = –	ωCL = 0.201 [19][a] ωV = 0.181 [20][a]	ωCL = 0.332 [11.2][a] ωV = 0.488 [16.8][a]	ωCL = 0.250 [7.6][a] ωV = 0.450 [14.2][a]	ωCL = 0.295 [18.7] ωV1 = – ωQ1 = – ωV2 = 0.543 [25.1] ωQ2 = 0.198 [20.8] ωV3 = 0.942 [20.8]	ωCL = 0.236 [–] ωV = –	ωCL = 0.237 [–] ωV = –
pro = 0.063 [9] add = –	pro = 0.065 [9] add = –	pro = 0.23 [12] add = –	pro = 0.14 [29.9][a] add = 3.04 mg/L [19.7]	pro = – add = 4.92 mg/L [9.8]	pro = 0.158 [15.5][a] add = –	pro = 0.232 [–] add = 0.7 mg/L [–]	pro = 0.227 [–] add = 0.95 mg/L [–]

definition of what constitutes an 'occasion' (e.g., variability over 24 h, 1 week, 1 month, 1 year, etc.).

(ii) Implement genotyping for drug transport proteins (e.g., P-gp, OCT) and relevant elimination pathways that exhibit genetic polymorphism (e.g., CYP2C19, CYP2D6).

(iii) Create a shared database between industry and academic sectors, acknowledging the regulatory challenges that such data sharing may entail.

(iv) Use concentrations measured shortly after treatment initiation as part of therapeutic drug monitoring to select a more appropriate model than the initial

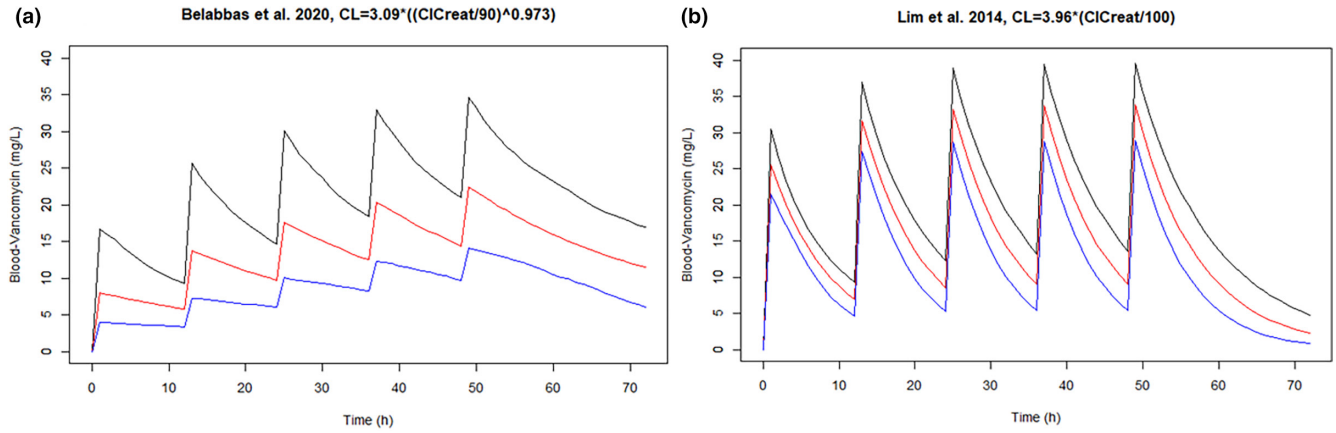

FIGURE 2 (a) Monte Carlo simulations performed with Belabbas's model.[19] Belabbas et al. developed a population pharmacokinetic model with patients with underlying hematological malignancies. For a patient with normal renal function, only creatinine clearance plays a role in estimating vancomycin clearance. Plasma concentrations of vancomycin gradually increase with each administered dose and reach equilibrium by the 5th dose. The black, red, and blue curves represent the 5th, 50th, and 95th percentiles, respectively. (b) Monte Carlo simulations were performed with Lim's model.[20] Lim et al. developed a population pharmacokinetic model with patients with MRSA infection. For a patient with a normal renal function, vancomycin clearance depends solely on creatinine clearance. It is observed that the plasma concentration of vancomycin reaches equilibrium by the 3rd dose. The black, red, and blue curves represent the 5th, 50th, and 95th percentiles, respectively.

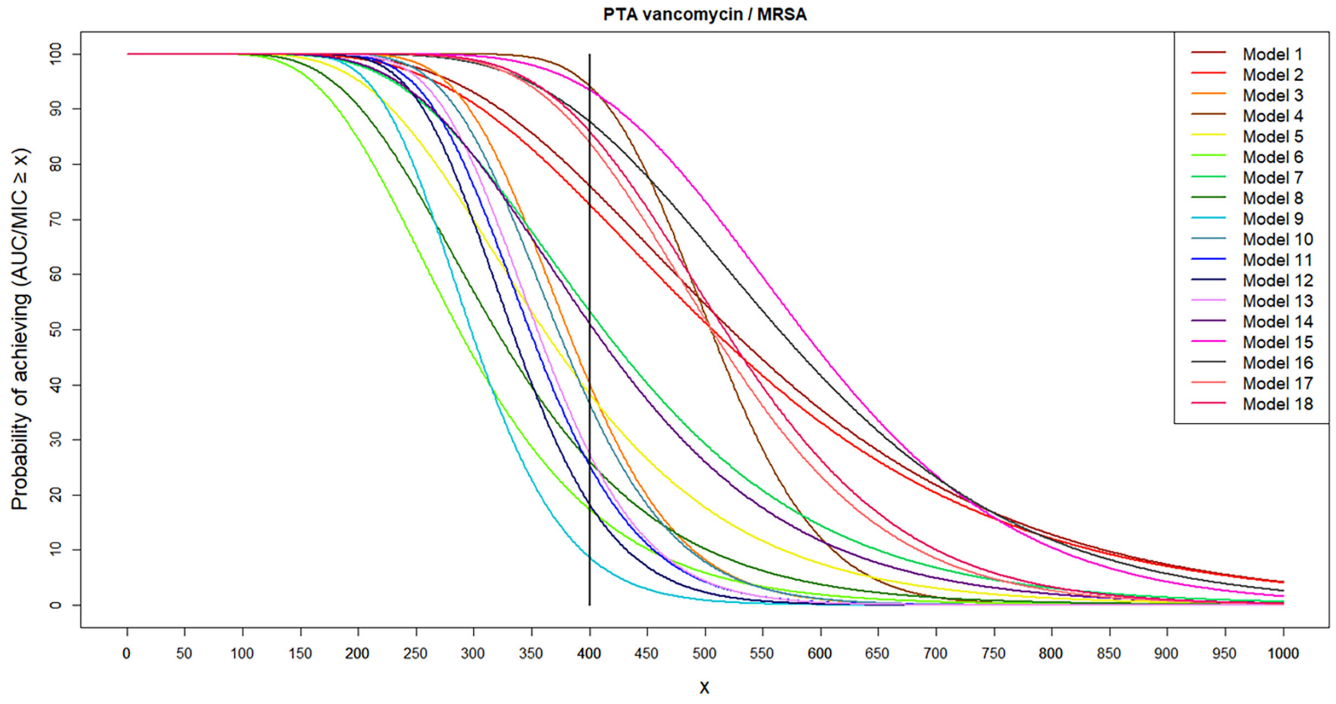

FIGURE 3 Probability of achieving $\left(\frac{\text{AUC}}{\text{MIC}} \geq X\right)$ for X ranging from 0 to 1000 for 18 models. This figure includes 11 one-compartment models, 6 two-compartment models, and only 1 three-compartment model. The vertical black line at $X = 400$ represents the recommended $\frac{\text{AUC}}{\text{MIC}}$ ratio to ensure microbiological efficacy against MRSA infection when CMI = 1 mg/L.

probabilistic one. Establishing a real-time, accessible model repository would be a crucial first step. This initiative could be led by a national or European society, such as SFPT or IATDMCT.

In conclusion, until we achieve interchangeability between models constructed from similar populations, these differences underscore the challenge of selecting a model to recommend the initial dosing regimen. They

TABLE 2 Probability of achieving AUC/CMI ≥400 for 18 PopPK models extracted from the 12 selected publications.

Model	PTA (%)	Model	PTA (%)	Model	PTA (%)
1	76.1	7	53.4	13	27.5
2	72.7	8	26.1	14	51.1
3	40.2	9	8.7	15	93.5
4	94.2	10	36.6	16	87.8
5	38.4	11	25.4	17	84.0
6	17.4	12	18.4	18	86.0

also highlight challenges in TDM, whether using a PopPK model with or without Bayesian approach. Therefore, considerable efforts are required systematically identify the appropriate model for each patient undergoing TDM.

AUTHOR CONTRIBUTIONS

P.G., S.C., N.F. and D.C. wrote the manuscript; P.G. and D.C. designed the research; P.G., S.C. and D.C. performed the research; P.G., S.C. and D.C. analyzed the data.

FUNDING INFORMATION

This study was supported by internal funding.

CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

The data presented in this study are available from the corresponding authors (Pr Peggy Gandia) upon reasonable request.

ORCID

Peggy Gandia https://orcid.org/0000-0002-4385-7894
Nicolas Fabre https://orcid.org/0000-0001-5896-5700
Didier Concordet https://orcid.org/0000-0003-3916-577X

REFERENCES

1. Filippone EJ, Kraft WK, Farber JL. The nephrotoxicity of vancomycin. *Clin Pharmacol Ther*. 2017;102:459-469.
2. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82-98.
3. Neely MN, Youn G, Jones B, et al. Are vancomycin trough concentrations adequate for optimal dosing? *Antimicrob Agents Chemother*. 2014;58:309-316.
4. Boeckh M, Lode H, Borner K, Höffken G, Wagner J, Koeppe P. Pharmacokinetics and serum bactericidal activity of vancomycin alone and in combination with ceftazidime in healthy volunteers. *Antimicrob Agents Chemother*. 1988;32:92-95.
5. Haque NZ, Zuniga LC, Peyrani P, et al. Relationship of vancomycin minimum inhibitory concentration to mortality in patients with methicillin-resistant *Staphylococcus aureus* hospital-acquired, ventilator-associated, or health-care-associated pneumonia. *Chest*. 2010;138:1356-1362.
6. Bamgbola O. Review of vancomycin-induced renal toxicity: an update. *Ther Adv Endocrinol Metab*. 2016;7:136-147.
7. El Hassani M, Marsot A. External evaluation of population pharmacokinetic models for precision dosing: current state and knowledge gaps. *Clin Pharmacokinet*. 2023;62:533-540.
8. Alrahahleh D, Thoma Y, Van Daele R, et al. Bayesian vancomycin model selection for therapeutic drug monitoring in neonates. *Clin Pharmacokinet*. 2024;63:367-380.
9. Baklouti S, Comets E, Gandia P, Concordet D. Multivariate exact discrepancy: a new tool for PK/PD model evaluation. *Clin Pharmacokinet*. 2023;62:1599-1609.
10. Yamamoto M, Kuzuya T, Baba H, Yamada K, Nabeshima T. Population pharmacokinetic analysis of vancomycin in patients with gram-positive infections and the influence of infectious disease type. *J Clin Pharm Ther*. 2009;34:473-483.
11. Kim AJ, Lee J-Y, Choi SA, Shin WG. Comparison of the pharmacokinetics of vancomycin in neurosurgical and non-neurosurgical patients. *Int J Antimicrob Agents*. 2016;48:381-387.
12. Jing L, Liu TT, Guo Q, Chen M, Lu JJ, Lv CL. Development and comparison of population pharmacokinetic models of vancomycin in neurosurgical patients based on two different renal function markers. *J Clin Pharm Ther*. 2020;45:88-96.
13. Chen Z, Taubert M, Chen C, et al. Plasma and cerebrospinal fluid population pharmacokinetics of vancomycin in patients with external ventricular drain. *Antimicrob Agents Chemother*. 2023;67:e0024123.
14. US Pharmacopeia (USP). https://www.usp.org. Accessed July 02, 2024.
15. European Pharmacopoeia Online. https://pheur.edqm.eu/home. Accessed July 02, 2024.
16. Nagarajan R. Antibacterial activities and modes of action of vancomycin and related glycopeptides. *Antimicrob Agents Chemother*. 1991;35:605-609.
17. Diana J, Visky D, Roets E, Hoogmartens J. Development and validation of an improved method for the analysis of vancomycin by liquid chromatography selectivity of reversed-phase columns towards vancomycin components. *J Chromatogr A*. 2003;996:115-131.
18. Mehta RL, Kellum JA, Shah SV, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31.
19. Belabbas T, Yamada T, Egashira N, et al. Population pharmacokinetic model and dosing optimization of vancomycin in

hematologic malignancies with neutropenia and augmented renal clearance. *J Infect Chemother*. 2023;29:391-400.
20. Lim H-S, Chong YP, Noh Y-H, Jung J-A, Kim YS. Exploration of optimal dosing regimens of vancomycin in patients infected with methicillin-resistant *Staphylococcus aureus* by modeling and simulation. *J Clin Pharm Ther*. 2014;39:196-203.
21. Tanaka A, Aiba T, Otsuka T, et al. Population pharmacokinetic analysis of vancomycin using serum cystatin C as a marker of renal function. *Antimicrob Agents Chemother*. 2010;54:778-782.
22. Alqahtani S, Abouelkheir M, Alsultan A, et al. Optimizing amikacin dosage in pediatrics based on population pharmacokinetic/pharmacodynamic modeling. *Pediatr Drugs*. 2018;20:265-272.
23. Liu T-T, Pang H-M, Jing L, et al. A population pharmacokinetic model of vancomycin for dose individualization based on serum cystatin C as a marker of renal function. *J Pharm Pharmacol*. 2019;71:945-955.
24. Alqahtani S, Almatrafi A, Bin Aydan N, et al. Optimization of vancomycin dosing regimen in cancer patients using pharmacokinetic/pharmacodynamic modeling. *Pharmacotherapy*. 2020;40:1192-1200.
25. Aljutayli A, Thirion DJG, Bonnefois G, Nekka F. Pharmacokinetic equations versus Bayesian guided vancomycin monitoring: pharmacokinetic model and model-informed precision dosing trial simulations. *Clin Transl Sci*. 2022;15:942-953.
26. Ling J, Yang X, Dong L, Jiang Y, Zou S, Hu N. Utility of cystatin C and serum creatinine-based glomerular filtration rate equations in predicting vancomycin clearance: a population pharmacokinetics analysis in elderly Chinese patients. *Biopharm Drug Dispos*. 2024;45:58-68.

SUPPORTING INFORMATION

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

How to cite this article: Gandia P, Chaiben S, Fabre N, Concordet D. Vancomycin population pharmacokinetic models: Uncovering pharmacodynamic divergence amid clinicobiological resemblance. *CPT Pharmacometrics Syst Pharmacol*. 2024;00:1-10. doi:10.1002/psp4.13253