SYSTEMATIC REVIEW

REVISED Vancomycin Population Pharmacokinetic Models in Non- Critically Ill Adults Patients: a scoping review

[version 2; peer review: 2 approved]

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Abstract

Background

Vancomycin is an effective first-line therapy primarily in methicillin-resistant Staphylococcus aureus (MRSA) infection and Clostridium difficile, however, it has been shown that its effectiveness and the reduction of nephrotoxicity depend on maintaining adequate therapeutic levels. Population pharmacokinetic (PopPk) models attempt to parameterize the behavior of plasma concentrations in different target populations and scenarios such as renal replacement therapy, to successful therapeutic outcome and avoid these side effects.

Methods

A scoping review was conducted following the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR), through a search in PubMed, LILACS, OVID Medline, Scopus, Web of Science, SAGE Journals, Google Scholar and previous known registers of PopPk models in non-critically ill adult patients, published between 1998 and 2024.

Results

A total of 190 papers were fully screened, of which were included 36 studies conducted in different populations; 12 in general population, 23 in special populations (surgical, with impaired renal function,

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	1	2
version 2 (revision) 06 Mar 2025	✓ view	✓ view
version 1 13 Dec 2022	? view	? view

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obese, elderly, with cancer and cystic fibrosis), and 1 in mixed population (general and with cancer). The main parameters in the models were renal clearance and volume of distribution. The principal covariables that affected the models were creatinine clearance and weight. All studies used internal evaluation and 4 of them used an external group.

Discussion

The technology for the development and implementation of PopPk models requires experts in clinical pharmacology and is limited to university and research centers. The software is mostly expensive and, in most cases, the pharmacokinetic models and the heterogeneity in the parameters and evaluation methods depend on which compartmental model, parameters, covariates and software have been used.

Conclusions

These models require validation in the clinical context and conducting experiments to adapt them for precision dosing in different subpopulations.

Keywords
Population pharmacokinetic, vancomycin; non-critically patients.

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REVISED **Amendments from Version 1**

The new version of the manuscript has been revised according to the reviewers' requests. Most of the changes were based on the comments from Reviewer 2, who requested modifications from the abstract to the discussion, as well as a full revision of the English language. These changes led to substantial modifications in the manuscript, including the inclusion of additional studies, increasing the total from 17 to 36. Consequently, both the presentation of the results and the discussion were expanded to incorporate the new findings while maintaining the content from version 1.

The title was modified in form but not in substance, as the order of the words was rearranged to place "scoping review" at the end. The abstract was partially revised following a suggestion from the reviewer.

A modification has also been made to the authorship. Specifically, two new authors, Manuel Mena and Juan-Francisco Guevara, were included. They conducted an additional literature search to update the number of studies included up to November 2024, as requested by one of the reviewers. Additionally, these new authors performed the data analysis and contributed to the writing of version 2 of the manuscript. No authors were removed.

Tables 2 and 3 have been expanded to include the newly incorporated studies, bringing the total to 36.

Any further responses from the reviewers can be found at the end of the article

Introduction

Vancomycin is a tricycle glycopeptide antibiotic derived from *Streptomyces orientalis*, first used in 1958; by inhibiting the synthesis of the wall, it achieves a high bactericidal power against methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-susceptible *Staphylococcus aureus* (MSSA), streptococci, enterococci and *Clostridium difficile*.[1,2] Pharmacokinetic and pharmacodynamic studies of vancomycin suggest that prior trough monitoring is associated with increased nephrotoxicity, with rates between 5% and 43%, related to high doses or high levels of exposure, mainly in special populations such as elderly and critically ill patients.[3,4] Therefore, the current dosing and monitoring recommendations of the revised consensus guideline and review by ASHP/PIDS/SIDP/IDSA establish an AUC/MIC ratio of 400–600 h^{-1} (assuming a MIC of 1 mg/L) to achieve clinical efficacy and ensure safety for patients treated for serious MRSA infections.[5]

Although therapeutic drug monitoring (TDM) for vancomycin remains controversial, it has been shown to significantly increase the rate of clinical efficacy and decrease the rate of nephrotoxicity.[5] TDM of Vancomycin is essential for the development of PopPK models by the use of Bayesian software for AUC estimation and model-informed precision dosing (MIPD), which has been improved outcomes in patients with culture-proven gram-positive infections just with a single concentration monitoring.[6] The PopPK modeling plays a crucial role in optimizing drug dosing regimens, particularly for drugs with a narrow therapeutic index (NTI). NTI drugs, where small changes in drug concentration can result in significant therapeutic consequences, require precise dosing to maximize efficacy and minimize toxicity.[7] PoPK models enable the integration of various physiological, biochemical, and drug-specific factors to predict drug behavior in different patient populations. By simulating a range of dosing scenarios, these models allow for the identification of optimal dosing strategies that balance therapeutic benefit with safety, ensuring that NTI drugs achieve their intended clinical outcomes while avoiding adverse effects. This modeling approach is essential for personalizing therapy, reducing the risk of underdosing or overdosing, and improving patient outcomes.[8]

PopPK is an emerging discipline developed from the combination of classical pharmacokinetic compartment model and statistical principles, which helps to achieve the preliminary prediction of parameters.[9] Despite having been described more than 30 years ago, PopPK models are not widely used due to mathematical complexity, the variety of the study population and limited access to software.[10] This review aims to summarize the main models, software, parameters and covariates in non-critical adult patients that can be used in future applications for MIPD.

Methods

We developed and performed a scoping review of existing reports about PopPK models of vancomycin in adult population out of intensive care. The research protocol was reviewed and approved by the research subcommittee of School of Medicine of Universidad de La Sabana. The review follows the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) and the Johanna Briggs Institute.[11,12] Reporting checklist extended data E1.

The primary review question was formulated using the population, concept, context framework, as "What are the published vancomycin population pharmacokinetic models with non-critically ill hospitalized adult patients?". Search criteria were established to include studies with: (1) original vancomycin PopPK models, (2) adult patients, and

Table 1. Search constructs.

Database	Search terms
PubMed	(("vancomycin"[All Fields]) AND ("population pharmacokinetic"[All Fields])) NOT ("critically ill"[All Fields])
OVID Medline	((population pharmacokinetic* and vancomycin and adult*) not critically).m_titl.
LILACS	((population pharmacokinetic) AND (vancomycin) AND (adult)) AND NOT (children) AND NOT (neonate) AND NOT (pediatric) AND NOT (critically) AND NOT (intensive care) AND (mj: ("Vancomycin"))
Web of Science	(((((TI=(vancomycin)) AND TI=(population pharmacokinetic)) NOT TI=(critically ill)) NOT TI=(neonates)) NOT TI=(pediatric)) NOT TI=(infants)
SAGE Journals	[Title population pharmacokinetic] AND [Title vancomycin]
Scopus	TITLE (population AND Pharmacokinetic) AND TITLE (vancomycin) AND ALL (adult) AND NOT ALL (critically AND ill) AND NOT ALL (pediatric) AND NOT ALL (children) AND NOT ALL (neonates) AND NOT ALL (infants)
Google Scholar	allintitle: population pharmacokinetic vancomycin adult-critically

(3) non-critical ill patients; articles were excluded if they: (1) are the wrong publication type, (2) patients are hospitalized in the intensive care or burn unit, (3) do not define equations or parameters, and (4) have a broad range of patients, including critically ill patients. The search was conducted on November 2, 2024, in PubMed, LILACS, OVID Medline, Scopus, Web of Science, SAGE Journals, and Google Scholar, including reports published after January 1998 and some previously known reports in other similar publications. Search terms submitted to each database are presented in Table 1. Only articles published in English, Spanish, or Portuguese were included in the search. The founded references were uploaded into Rayyan (http://rayyan.qcri.org; Headquarter: Cambridge, Massachusetts, U.S.A.), which is a free web and mobile app, that helps expedite the initial screening of abstracts and titles using a process of semi-automation while incorporating a high level of usability.[13] First the detected duplicates in data summary was eliminated by preliminary revision, then the reports were screened and selected for the full text screening to check over the inclusion and exclusion criteria.

Results

We identified 180 records in databases and 10 registers previous included in others publications.[14] After removing duplicates, 155 records remained for screening; 100 were eliminated due to exclusion criteria and 55 reports were assessed for eligibility for full text review; finally, 36 studies were included for this review (Figure 1).

In order to organize the information, they were divided into 8 groups of patients, general (12),[15–26] surgical (5),[27–31] with impairment kidney function (7),[32–38] obese (3),[39–41] geriatrics (4),[42–45] with cancer (4),[15,46–48] patients with cystic fibrosis (1)[49] and trauma patients (1).[50] Studies published from 1998 to 2024 were found, the mean study by year was 2.3 with an standard deviation (SD) of 1.6 and the years with the highest number of publications were, 2018 (6), 2020 (5), 2019 (4) and 2024 (4). Predominantly, publications of Asian, Middle Eastern, North American and European origin were found; the countries with the highest number of publications were China (9), Japan (6), South Korea (5) and the United States of America (USA) (5). Regarding the design of the study, 27 (75%) were retrospective and 9 (25%) were prospective; the mean of sample size was 217 and SD of sample size was 434,4 (biased by the study of Pai and DeBacker[36] with 2640 patients). 22 (61.1%) of the models were one-compartment and 14 (38.9%) were two-compartment.

The most commonly used software was NONMEM in 28 studies (77.8%), followed by Monolix 5 (13.9%), Phoenix 2 (5.6%) and R environment with Pmetrics package 1 (2.8%), therefore, 32 (88.9%) of the studies performed a primary analysis and development of the model with Nonlinear mixed-effects modeling (NLME), followed by 3 (8.3%) that used stochastic approximation expectation maximization (SAEM) and 2 (2.8%) performed with nonparametric adaptive grid (NPAG); the most used secondary analyses were first-order conditional estimation (FOCE), first-order conditional estimation with interaction (FOCEI) and first-order conditional estimation with extended least square method (FOCE-ELS) with 19 (52.8%) studies, in addition to objective function value (OFV) with 17 (47.2%) studies and generalized additive model (GAM) with 1 study (7.7%). Almost all models reported internal evaluations, 35 (97.2%) studies, 25 (86.2%) of which reported bootstrap simulations and the methods generally used were goodness-of-fit plots model (GOF), visual predictive checks (VPC), prediction- and variability-corrected VPC (pvcVPC) and numerical predictive

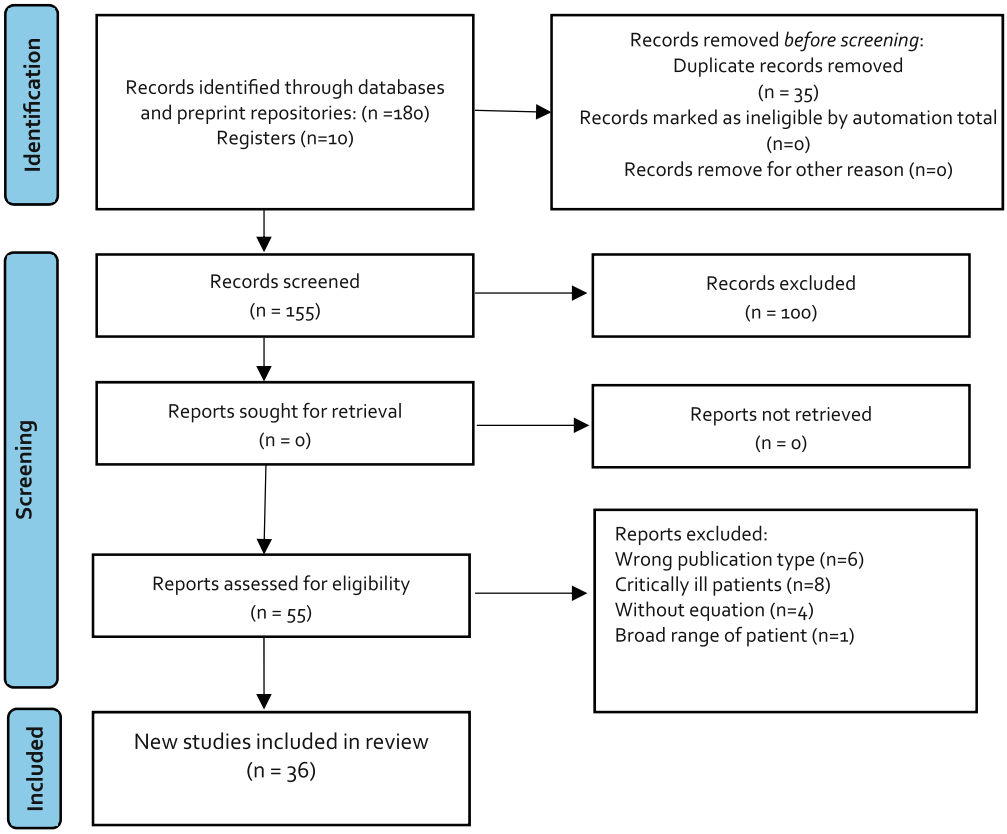

Figure 1. Flowchart of studies selected.

check (NPC); only 4 studies reported external evaluations.[19,21,47,50] A summary of demographics and PopPK modeling methods for all the included studies is presented in Table 2.

The combined mean and combined SD of age did not differ much from the combined means and SD by groups, being for all 59.74 years and 17.24 years respectively; as for the total body weight (TBW) the obese group presented a combined mean of 131.62 kg with a combined SD of 31.59 kg, while the total of the groups had a combined mean of 76.98 kg and a combined SD of 21.25 kg; for the estimated glomerular filtration rate (eGFR) greater heterogeneity was found, since in the group with impaired kidney function the combined means and SD were 59.55 ml/min and 44.54 ml/min respectively, while in the total the combined mean of the eGFR was 80.42 ml/min and the combined SD was 54.07 ml/min (see Extended data E2 Additional results tables).

Most of the equations presented by the PopPK models are in the form in which the expressions for clearance (CL), distribution volumes (V_i), intercompartmental clearance (Q) and elimination transfer rate constants (k_{12}, k_{21}), are equal to the estimates of the population mean of each study (CLpop, $V_i$pop, Qpop, k_{12}pop, k_{21}pop) or typical values (TVCL, TVV_i, TVQ, TVk_{12}, TVk_{21}), which as in the case of CL are generally affected proportionally or additively by covariates, in greater proportion by the renal clearance (CL_{CR}) or the estimated glomerular filtration rate (eGFR) by Cockroft-Gault, although the studies by Chung et al.[17] and Ling et al.[42] uses cystatin C to affect the TVCL or the study by Medellín-Garibay[50] and Wei et al.[31] they associate furosemide or mannitol respectively as factors that alter eGFR, for these models serum creatinine or CLCR are also included as covariates. Furosemide was not directly used to estimate the glomerular filtration rate (GFR). Instead, it was administered as part of a furosemide stress test, which has been proposed as a functional marker of renal reserve. This test assesses renal response to a standardized dose of furosemide and has been used to predict acute kidney injury (AKI) progression in critically ill patients. However, in the context of the referenced study, cystatin C was the primary biomarker used for GFR estimation.

To a lesser extent, total body weight (TBW) or age are reported as covariates for TVCL, other models include clinical conditions such as the use of hemodialysis (HD),[16,35] continuous renal replacement therapy (CRRT)[16] or intermittent renal replacement therapy (IRRT)[37]; there are models such as that of Kim et al.[29] that includes as covariates being a

Table 2. Summary of population group characteristics and modeling methods by year.

	Year	Study	Country	Study design	Population	Sample size, (male/ female)	Age (years), mean (SD) (range)	TBW (kg), mean (SD) (range)	eGFR (mL/min), mean CL_{CR} (SD) (range)	Compartments	Software	Analysis	Evaluation
GENERAL	1998	Yasuhara et al.[26]	Japan	Retrospective	Patients infected with MRSA	190 (131/59)	64.3 (13.8)	52.3 (9.6)	77.1 (50.9)	Two compartments	NONMEM® version IV	NLME FOCE	Internal: GOF
	2009	Yamamoto et al.[25]	Japan	Retrospective	Adult patients with a suspected or documented infection caused by gram positive bacteria and healthy subjects	100 (64/36) 6 (6/0)	65.4 (25.8-99.7) 21.7 (20-25)	52.6 (28.7-97) 60.3 (55.2-64.2)	89.3 (10.4)	Two compartments	NONMEM® version 5.1	NLME FOCE	Internal: Bootstrap
	2010	Tanaka et al.[23]	Japan	Prospective	Patients infected with MRSA	164 (104/60)	74 (17-95)	53 (10)	65 (14-261)	One compartment	NONMEM® version 5	NLME	Internal
	2012	Purwonugroho et al.[22]	Thailand	Prospective	Adult patients	212 (112/100)	66.62 (18.38)	57.64 (11.62)	35.07 (29.83)	Two compartments	NONMEM® version 7	NLME	Internal
	2013	Chung et al.[17]	South Korea	Prospective	Adult patients with normal serum creatinine	678 (400/278)	56 (18-96)	62.3 (27-140)	NR	One compartment	NONMEM® version 7.1	NLME OFV	Internal: Bootstrap (n=2000), GOF, NPC
	2013	Deng et al.[18]	China	Retrospective	Adult patients	72 (19/53)	54.07 (18.36)	61.12 (10.70)	82.09 (36.19)	One compartment	NONMEM® version 7.2	NLME	Internal: Bootstrap (n=2000), VPC
	2014	Lim et al.[20]	South Korea	Prospective	Patients infected with MRSA	20 (15/5)	59.3 (12.9)	63.1 (15.7)	96.6 (31.1)	Two compartments	NONMEM®	NLME FOCE	Internal
	2018	Ji et al.[19]	China	Retrospective	Patients who received continuous infusion of vancomycin and were not on renal replacement therapy	160 (106/54)	78 (42-95)	65 (38-90)	70.667 (42.74)	One compartment	NONMEM® version 7.3	NLME FOCEI OFV	Internal: Bootstrap (n=1000), NPDE; External (n= 58)
	2018	Usman et al.[24]	Germany	Retrospective	Adult patients	144 (93/51)	62 (16-88)	79.5 (40-177)	89.8 (11.3-313.6)	One compartment	NONMEM® version 7.2	NLME FOCEI	Internal: Bootstrap (n=1000)
	2019	Liu et al.[21]	China	Prospective	Adult patients	200 (128/72)	47.4 (15.42)	61.3 (12.06)	123.75 (59.96)	One compartment	NONMEM® version 7.3	NLME	Internal: Bootstrap (n=1000), GOF, VPC; External (n=74)
	2019	Bae et al.[16]	South Korea	Retrospective	Adult patients	220 (139/81)	63 (21-98)	61.6 (30-126.7)	77.0 (4.57-279)	Two compartments	NONMEM® version 7.4	NLME FOCE	Internal: Bootstrap (n=1000), pvcVPC
	2020	Alqahtani et al.[15]	Saudi Arabia	Retrospective	Adult patients older than 18 years old with cancer and non-cancer	74 (44/30)	55.1 (15.9)	75.5 (19.7)	102 (58.8)	One compartment	Monolix® version 4.4	SAEM	Internal: GOF, pvcVPC

Table 2. *Continued*

	Year	Study	Country	Study design	Population	Sample size, (male/female)	Age (years), mean (SD) (range)	TBW (kg), mean (SD) (range)	eGFR (mL/min), mean CL_{CR} (SD) (range)	Compartments	Software	Analysis	Evaluation
SURGICAL	2016	Kim et al.[29]	South Korea	Retrospective	Neurosurgical and non-neurosurgical patients	30 (14/16) 37 (20/17)	50.6 (15.0) 61.6 (15.7)	63.2 (11.6) 61.0 (12.7)	113.6 (48.3) 79.0 (44)	One compartment	NONMEM®	NLME FOCE OFV	Internal: Bootstrap (n=2000), VPC
	2018	Alqahtani et al.[27]	Saudi Arabia	Prospective	Patients who underwent cardiac surgical	28 (17/11)	51.7 (15.9)	79.6 (17)	83.5 (29.3)	Two compartments	Monolix® version 4.4	SAEM	Internal: GOF, VPC
	2020	Jing et al.[28]	China	Retrospective	Patients from the neurosurgery department, aged ≥18 years, receiving vancomycin therapy for ≥72 hours	222 (96/126)	46.95 (12.71)	60.22 (11.77)	115.8 (44.64)	One compartment	NONMEM® version 7.4.3	NLME FOCEI OFV	Internal: Bootstrap (n=2000), GOF, NPDE
	2021	Munir et al.[30]	Pakistan	Prospective	Patients admitted to the surgical unit	58 (39/19)	54 (25-86)	75 (53-129)	101.15 (15.9-177.2)	One compartment	NONMEM® version 7.4.4	NLME FOCEI OFV	Internal: Bootstrap (n=1000), GOF, VPC
	2022	Wei et al.[31]	China	Retrospective	Postoperative neurosurgical patients	560 (370/190)	52.41 (15.11)	69.74 (13.05)	112.74 (30.91)	One compartment	Phoenix NLME® version 8.3	NLME FOCE-ELS	Internal: Bootstrap (n=5000), GOF, VPC
IMPAIRMENT KIDNEY FUNCTION	1998	Schaedeli et al.[37]	Switzerland	Retrospective	Patients undergoing long term hemodialysis who received vancomycin for infection therapy or prophylaxis	26 (16/10)	62 (15.2)	64.7 (13.6)	4.5 (4.3)	Two compartments	NONMEM®	NLME FOCE	Internal
	2018	Zaric et al.[38]	Serbia	Retrospective	Patients with normal renal function and with mild to moderate chronic renal failure	32 (21/11) 78 (46/32)	59.15 (14.46) 67.00 (10.74)	81.37 (10.11) 78.52 (16.64)	54.38 (17.70)	Two compartments	NONMEM® version 7.3	NLME FOCE	Internal: Bootstrap (n=200), GOF
	2019	Kim DJ et al.[33]	South Korea	Retrospective	Patients with vancomycin treatment for various infections, and at least two serum concentration measurements	99 (59/40)	64.8 (12.6)	59.7 (10.98)	54.49 (36.25)	Two compartments	NONMEM® version 7.4	NLME OFV	Internal: Bootstrap (n=1000), GOF
	2020	Ma et al.[34]	China	Retrospective	Patients who received vancomycin as prophylactic medication following kidney transplant operation	56 (35/21)	43.72 (9.92)	58.27 (8.47)	41.95 (25.46)	One compartment	NONMEM® version 7.4	NLME FOCE OFV	Internal: GOF
	2020	Pai and DeBacker[36]	USA	Retrospective	Patients with stable and unstable kidney disease	2640 (1689/950)	59 (16)	93.9 (28.1)	63 (39)	One compartment	Monolix® 2019R2	SAEM	Internal: Bootstrap (n=1000), NPDE
	2023	Oda et al.[35]	Japan	Retrospective Prospective	Patients (age ≥ 18 years) who had received intermittent hemodialysis therapy for end-stage kidney disease	28 (8/20)	61 (14.5)	57.8 (13.2)	9.6 (4.7)	Two compartments	NONMEM® version 7.3; R version 4.1.2	NLME OFV	Internal: Bootstrap, GOF, pvcVPC
	2024	Ahmed et al.[32]	Sudan	Retrospective	Adult patients with renal impairment	99 (66/33)	65 (50-75)	NR	12.7 (5.52-25.78)	One compartment	Monolix® 2020R1	NLME SAEM	Internal: Bootstrap (n=1000), NPDE, GOF, VPC

Table 2. *Continued*

	Year	Study	Country	Study design	Population	Sample size, (male/ female)	Age (years), mean (SD) (range)	TBW (kg), mean (SD) (range)	eGFR (mL/min), mean CL_{CR} (SD) (range)	Compartments	Software	Analysis	Evaluation
OBESE	2015	Adane et al.[39]	USA	Prospective	Extremely obese adult patients (BMI ≥ 40 kg/m2) with suspected or confirmed Staphylococcus aureus infection	31 (19/12)	43 (38.5-53)	147.6 (142.8-178.3)	124.8 (106.0-133.9)	Two compartments	NONMEM® version 7.3	NLME FOCE OFV	Internal
	2018	Crass et al.[40]	USA	Retrospective	Obese (BMI ≥ 30 kg/m2) adult patients aged 18–90 years who underwent peak and trough vancomycin	346 (183/163)	57 (14)	132.5 (32.6)	171 (75)	One compartment	R environment Pmetrics™ package	NPAG	NR
	2024	Polásková et al.[41]	Czech Republic	Retrospective	Obese adult patients (age ≥ 18years; BMI ≥ 30kg/m^2) treated with intravenous vancomycin during intermittent hemodialysis	27 (14/13)	69 (58-72)	102 (91.5-118)	NR	One compartment	Monolix® 2021R2	NLME SAEM OFV	Internal: Bootstrap (n=1000), NPDE, GOF
GERIATRICS	2010	Sanchez et al.[43]	USA	Retrospective	Adult and geriatric patients	141 (NR)	55 (14.58)	73.2 (17.48)	NR	Two compartments	NONMEM® version VI	NLME	Internal: Bootstrap (n=200)
	2019	Zhou et al.[45]	China	Retrospective	Elderly patients (age ≥ 65 years) with HAP or CAP	70 (49/21)	78.3 (6.96)	60.7 (10.2)	56.3 (22.1)	One compartment	NONMEM® version 7.3	NLME FOCEI OFV	Internal: Bootstrap (n=1000), NPDE, GOF
	2020	Zhang et al.[44]	China	Prospective	Elderly patients (age ≥ 65 years) infected	150 (104/46)	73.6 (6.83)	61.7 (1 1.1)	84.1 (25.6)	One compartment	NONMEM® version 7.4	NLME FOCEI OFV	Internal: Bootstrap (n=2000), NPDE
	2024	Ling et al.[42]	China	Retrospective	Inpatients with a diagnosis of MRSA or suspected of having a positive drug resistant bacteria infection	313 (201/112)	72 (65-95)	65 (38-110)	70.98 (16.75-165.39)	One compartment	NONMEM® version 7.3 R version 2.15.1	NLME OFV	Internal: Bootstrap (n=2000), NPDE, GOF
CANCER	2005	Buelga et al.[46]	Spain	Retrospective	Adult (15-year-old) in patients with an underlying hematological malignancy admitted for suspected or documented infection caused by gram-positive bacteria	215 (119/96)	51.5 (15.9)	64.7 (11.3)	89.4 (39.2)	One compartment	NONMEM® version 5.1.1	NLME OFV GAM	Internal
	2018	Okada et al.[47]	Japan	Retrospective	Patients undergoing allo-HSCT who received preventive treatment with vancomycin	75 (49/26)	49 (17-69)	59.4 (39.4-104.5)	113 (47-253)	Two compartments	Phoenix NLME® version 7	NLME FOCE-ELS OFV	Internal: Bootstrap (n=1000), GOF, VPC; external: (20 patients)
	2020	Alqahtani et al.[15]	Saudi Arabia	Retrospective	Adult patients older than 18 years old with cancer and non-cancer.	73 (58/42)	53.8 (15.7)	72.7 (16.2)	102 (58.8)	One compartment	Monolix® version 4.4	SAEM OFV	Internal: GOF, pvcVPC
	2023	Tsuda et al.[48]	Japan	Retrospective	Patients with solid or hematological malignancy	325 (182/143)	67.8 (14.8)	54 (12)	80 (46.7)	One compartment	NONMEM® version 7.4.3	NLME FOCEI OFV	Internal: Bootstrap (n=1000), GOF, pvcVPC

Table 2. *Continued*

	Year	Study	Country	Study design	Population	Sample size, (male/ female)	Age (years), mean (SD) (range)	TBW (kg), mean (SD) (range)	eGFR (mL/min), mean CL_{CR} (SD) (range)	Compartments	Software	Analysis	Evaluation
CYSTIC FIBROSIS	2024	Yellepeddi et al.[49]	USA	Retrospective	Adults with cystic fibrosis	19 (5/14)	31.2 (12.5)	63.6 (17.1)	106.6 (37.9)	One compartment	NONMEM® version 7.5	NLME FOCEI OFV	Internal: Bootstrap (n=1000), GOF, VPC
TRAUMA	2015	Medellín-Garibay et al.[50]	Spain	Retrospective	Adult patients from the Traumatology service with proven or suspected infection	118 (53/65)	74.3 (14)	72.0 (15)	90.5 (51.67)	Two compartments	NONMEM® version 7.2	NLME	Internal: Bootstrap (n=200); External, (n=40)

CL_{CR} = Creatinine clearance calculated by Cockcroft-Gault formula; **eGFR** = estimated glomerular filtration rate; **FOCE** = first-order conditional estimation; **FOCEI** = First-order conditional estimation with interaction; **FOCE-ELS** = first-order conditional estimation with extended least square method; **GAM** = generalized additive model; **GOF** = goodness-of-fit plots model; **MRSA** = methicillin resistant Staphylococcus aureus; **NLME** = Nonlinear mixed-effects modeling; **NPAG** = nonparametric adaptive grid; **NPC** = numerical predictive check; **NPDE** = normalized prediction distribution errors; **NR** = no reported; **OFV** = objective function value; **pvcVPC** = prediction- and variability-corrected VPC; **SAEM** = stochastic approximation expectation maximization; **SD** = standard deviation; **USA** = United States of America; **VPC** = visual predictive checks.

neurosurgical patient, presenting underlying liver cirrhosis or co-administration of nephrotoxic drugs; the most recent model such as that of Tsuda et al.[48] even includes quick SOFA (qSOFA) as a covariate. Other covariates only presented once per model, such as sex,[40] daily dose of vancomycin and AST,[38] albumin[27] and post-craniotomy meningitis.[44]

Regarding distribution volumes, they are most commonly reported as equal to TVVi if expressed in liters (L) or as the relative TVVi by TBW if expressed in L/kg. In some equations, age can also influence these values. The most reported equation patterns for CL, V_i, Q, k12, and k21 are:

$$CL = TVCL \times \left(CL_{CR}/\overline{CL}_{CR}\right)^{\theta_{CL_{CR}}}$$

$$CL = \theta_{CL_{CR}} \times CL_{CR}$$

$$CL = TVCL$$

$$CL = TVCL + \left(\theta_{CL_{CR}} \times CL_{CR}\right)$$

$$CL = TVCL \times \left(TBW/\overline{TBW}\right)^{\theta_{TBW}}$$

$$CL = TVCL \times \left(CL_{CR}/\overline{CL}_{CR}\right)$$

$$CL = TVCL \times \left(CL_{CR}/\overline{CL}_{CR}\right)^{\theta_{CL_{CR}}} \times \left[TBW/\overline{TBW}\right]^{\theta_{TBW}}$$

$$V_i = TVV$$

$$V_i = TVV \times TBW$$

$$Q = TVQ$$

$$k_{12} = TVk_{12}$$

$$k_{21} = TVk_{21}$$

The main features and values of the equations, parameters, population mean (VT) and variability are shown in Table 3. Many of the studies do not explicitly show TV for which we calculate with measures of central tendency for the reported covariates and substituting them in the covariate equations in the final model; although most studies with two-compartment models reported parameters in the form of flow rates (CL and Q), two studies reported model parameters in the form of elimination, transfer rate constants (k_{12}, k_{21}) were presented, in order to make comparisons among studies, the conversion of parameters in the form of flow rates was implemented with the following equation:

$$Q = k_{12} \times V_1$$

To perform an analysis of the TV, the combined means of all studies and also by compartments were calculated; the complete results are found in Supplementary data S2. The TVCL for all studies was 3.02 L/h; by groups the TVCL was 3.76 L/h for the general population, 7.08 L/h for surgical patients, 0.5 L/h for the group with impaired renal function, 5.61 L/h for obese patients, 3.31 L/h for geriatric patients, 4.38 L/h for patients with cancer, 5.52 L/h for cystic fibrosis and 2.6 L/h for trauma patients; when separating the patients without impaired renal function, the TVCL is 4.5 L/h, which differs substantially from that reported in the group with impaired renal function and shows the change with respect to the TVCL of all studies when eliminating those with the lowest clearance.

The TV of the central distribution volume (TVVc) for all studies was 58.24 L, by groups the TVVc was 42.74 L for the general population, 57.93 L surgical, 64.8 L for the group with impaired renal function, 71.01 L obese, 82.3 L geriatric, 47 L with cancer, 31.5 L with cystic fibrosis and 74.4 L for trauma patients; the TVVc without the obese, geriatric and trauma group is 54.78 L, while in the obese, geriatric and trauma group the TVVc was 78 L. The TVCL for single compartment models was 4.38 L/h and TVV was 61.26 L. The TVCL for two compartment models was 2.63 L/h, TVQ was 8.71 L/h, TVV1 and TVV2 were 38.59 L and 96.97 L respectively.

Table 3. **Main features of the published PopPk models.**

	Study				Volume of distribution related expressions: V_i (L)			Population mean (TV)		BSV (ω)		RV (*a*),(*b*)	
		Equations	Parameter	Value	Equations	Parameter	Value	CL (L/h), Q (L/h), k_{ij} (h^{-1})	V_i (L)	CL	V_i	Additive (mg/L)	Proportional
GENERAL	Yasuhara et al.[26]	$CL_{CR} \leq 85$ mL/min: $CL = \theta_1 \times CL_{CR}$ $CL_{CR} > 85$ mL/min: $CL = \theta_2$ $k_{12} = \theta_3$ $k_{21} = \theta_4$	θ_1 θ_2 θ_3 θ_4	0.0478 3.51 0.525 0.213	$V_{ss} = \theta_5$	θ_5	60,7	3.51	60.7	38.5%	V_{ss} = 25.4%	NR	23.7%
	Yamamoto et al.[25]	$CL_{CR} > 85$ mL/min: $CL = \theta_1$ $CL_{CR} \leq 85$ mL/min: $CL = \theta_2 \times CL_{CR} + \theta_3$ $Q = \theta_8$	θ_1 θ_2 θ_3 θ_8	3.83 0.0322 0.32 8.81	$V_1 = \theta_4 \times (1 + (\theta_5 \times STATUS)) \times TBW$ $V_2 = \theta_6 + (STATUS \times \theta_7)$	θ_4 θ_5 θ_6 θ_7	0.206 0.272 39.4 21.2	CL = 3.83 Q = 8.81	V_1 = 28.82 V_2 = 60.6	37.5%	V_1 = 18.2% V_2 = 72.8%	NR	14.3%
	Tanaka et al.[23]	$CL\ (ml/min) = \theta_1 \times eGFR$	θ_1	0.875	$V\ (L/kg) = \theta_2$	θ_2	0.864	2.68	45.79	19.8%	30.7%	12.7	NR
	Purwonugroho et al.[22]	$CL = \theta_1 \times CL_{CR}\ (mL/min)$ $Q = \theta_3$	θ_1 θ_3	0.044 6.950	$V_1 = \theta_2 \times Age$ $V_2 = \theta_4$	θ_2 θ_4	0.542 44.2	CL = 1.56 Q = 6.95	V_1 = 36.11 V_2 = 44.2	35.78%	V_1 = 20.93% V_2 = 57.27%	4.51	NR
	Chung et al.[17]	$CL = 4.9 \times (1 + \theta_1 \times [AGE-57]) \times (1 + \theta_2 \times [TBW - 60.8]) \times (1 + \theta_3 \times [SCr - 0.8]) \times (CystatinC/0.91)^{\theta_4}$ if female, apply $1 + \theta_5$	θ_1 θ_2 θ_3 θ_4 θ_5	-0.0042 0.00997 -0.322 -0.780 -0.150	$V = 46.2 \times (1 + \theta_6 \times [AGE-57]) \times (1 + \theta_7 \times [TBW-60.8])$ if female, apply $1 + \theta_8$	θ_6 θ_7 θ_8	0.00580 0.00661 -0.119	4.90	46.2	26.2%	37.3%	1.40	6.39%
	Deng et al.[18]	$CLCR < 80$ mL/min: $CL = \theta_1 \times CL_{CR}$ $CLCR \geq 80$ mL/min: $CL = \theta_2$	θ_1 θ_2	0.0654 4.9	$V = \theta_3$	θ_3	47.76	4.90	47.76	45.35 %	39.25 %	1.21	30.71%
	Lim et al.[20]	$CL = \theta_1 \times CL_{CR}/100$ $Q = \theta_4$	θ_1 θ_4	3.96 6.99	$V_1 = \theta_2$ $V_2 = \theta_3$	θ_2 θ_3	33.1 48.3	CL = 3.96 Q = 6.99	V_1 = 33.1 V_2 = 48.3	40.1%	35.7%	NR	0.231 (SD)
	Medellín-Garibay et al.[50]	Furosemide = 0: $CL = \theta_1 \times CL_{CR}$ Furosemide = 1: $CL = \theta_5 \times CL_{CR}$ $Q = \theta_3$	θ_1 θ_5 θ_3	0.49 0.34 0.81	If age > 65 years: $V_1\ (L/kg) = \theta_2 \times TBW$ $V_2\ (L/kg) = \theta_4 \times TBW$ If age ≤ 65 years: $V_1\ (L/kg) = \theta_6 \times TBW$	θ_2 θ_4 θ_6	1.07 5.99 0.74	CL = 2.6 (1.85) Q = 0.81	V_1 = 77.4 (53.28) V_2 = 424.8	36.2%	V_1 = 37.1% V_2 = NR	NR	19.3%
	Ji et al.[19]	$CL = \theta_1 \times (1 + \theta_2 \times [CL_{CR} - 80]) \times (75/AGE)^{\theta_3}$	θ_1 θ_2 θ_3	2.829 0.00842 0.8143	$V = \theta_4$	θ_4	52.14	2.829	52.14	32.42%	28.87%	2.64	26.79%
	Usman et al.[24]	$CL = \theta_1 \times (1 + \theta_2 \times [CL_{CR} - \theta_3])$	θ_1 θ_2 θ_3	2.32 0.0018 89.8	$V = \theta_4$	θ_4	19.2	2.32	19.2	20.40%	NR	NR	38.50%
	Liu et al.[21]	$CL = \theta_1 \times (eGFR/105.5)^{\theta_2} \times (AGE/48.5)^{\theta_3} \times (TBW/60)^{\theta_4}$	θ_1 θ_2 θ_3 θ_4	5.07 0.524 -0.309 0.491	$V = \theta_5$	θ_5	46.3	5.07	46.3	20.80%	18.10%	1.28	15.90%
	Bae et al.[16]	$CL = \theta_1 \times (CL_{CR}/72)^{\theta_2}$ $CL_{CRRT} = \theta_3$ $CL_{HD} = \theta_4$ $Q = \theta_6$	θ_1 θ_2 θ_3 θ_6	2.82 0.836 0.716 0.334 11.7	$V_1 = \theta_4$ $V_2 = \theta_5 \times (TBW/60)$	θ_4 θ_5	31.8 75.4	CL = 2.80 Q = 11.7	V_1 = 31.8 V_2 = 75.4	99.20%	V_1 = NR V_2 = 49.20%	NR	0.253 (SD)
	Alqahtani et al.[15]	$CL = \theta_1 \times (CL_{CR}/96.3)^{\theta_2}$	θ_1 θ_2	5.6 0.18	$V = \theta_3$	θ_3	42	5.6	42	20.3%	18.2%	NR	23%

Table 3. *Continued*

	Study				Volume of distribution related expressions: V_i (L)			Population mean (TV)		BSV (ω)		RV (*a*),(*b*)	
		Equations	Parameter	Value	Equations	Parameter	Value	CL (L/h), Q (L/h), k_{ij} (h^{-1})	V_i (L)	CL	V_i	Additive (mg/L)	Proportional
SURGICAL	Kim et al.[29]	CL = [early phase θ_1 or late phase θ_2] × (CL_{CR}/95.8) × $\theta_3^{TO\times I}$ × θ_4^{LC} + θ_5^{NEUR}	θ_1 θ_2 θ_3 θ_4 θ_5	4.36 3.69 0.811 0.511 2.42	V = [early phase θ_6 or late phase θ_7]	θ_6 θ_7	83.7 (107)	4.36 (3.69)	83.7 (107)	0.125 variance	NR	1.92	8.59%
	Alqahtani et al.[27]	CL = θ_1 × (CL_{CR}/83.5)^0.514 × (ALBUMIN/35.5)^0.854 Q = θ_2	θ_1 θ_2	6.13 0.22	$V_1 = \theta_3$ × (TBW/79.6) ^0.466 $V_2 = \theta_4$	θ_3 θ_4	40 3.88	CL = 6.13 Q = 0.22	V_1 = 40 V_2 = 3.88	22.1%	V_1 = 6.34% V_2 = 61.2%	0.055	15.2%
	Jing et al.[28]	CL = [6.4 × (eGFR/128)^θ_1 × (TBW/60) (AGE/47)^θ_3] × e×p^θ_4	θ_1 θ_2 θ_3 θ_4	0.515 0.417 0.267 0.0417	V = θ_4	θ_4	60.1	6.49	60.2	7%	NR	NR	9%
	Munir et al.[30]	By CL_{CR}: CL = 1 + θ_1 × (CL_{CR} − 101.15) By TBW: CL = 1 − θ_2 × (TBW − 75)	θ_1 θ_2	0.0046 0.011	V = θ_3	θ_3	22.6	2.45	22.6	11.3%	22.8%	3.07	NR
	Wei et al.[31]	CL = 7.98 × (eGFR/115.2)^θ_1 × (TBW/70)^θ_2 × e×p^A with mannitol, A = 0.13; otherwise, A = 0	θ_1 θ_2	0.8 0.3	V = θ_3	θ_3	60.2	7.98	60.2	48.19%	NR	2.73	13.06%
RENAL	Schaedeli et al.[37]	CL_{CR} ≥ 2 mL/min: CL = θ_1+ θ_2 × CL_{CR} CL_{CR} < 2 mL/min: CL = θ_1 CLDv = θ_3 × CLD_{BUN} $k_{12} = \theta_5$ $k_{21} = \theta_6$	θ_1 θ_2 θ_3 θ_5 θ_6	2.25 0.585 0.336 0.872 0.162	$V_c = \theta_4$ × TBW $V_{ss} = \theta_5$ × TBW	θ_4 θ_5	0.164 1.05	CL = 2.25 k_{12} = 0.872 k_{21} = 0.162	V_{ss} = 67.93	CLCR < 2 mL/min: CI = 90% CLCR ≥ 2 mL/min: CI = 32%	22%	NR	13%
	Zaric et al.[38]	Normal renal function: CL = θ_1 + θ_3 × FIB Impaired renal function: CL = θ_2 + θ_4 × DD + 0.00194 × AST	θ_1 θ_2 θ_3 θ_4 θ_5	0.0727 0.284 0.205 0.000596 0.00194	Normal renal function: $V_1 = \theta_6$ Impaired renal function: $V_1 = \theta_7$	θ_6 θ_7	7.47 29.9	0.284	29.9	0.059 variance 0.135 variance	NR	0.05 variance 0.045 variance	NR
	Kim DJ et al.[33]	CL = θ_1 × [(θ_2/ $eGFR_{base}$) + ($eGFR_{at\ time}$/$eGFR_{median}$)] Q = θ_5	θ_1 θ_2 θ_5	2.21 0.921 3.06	$V_1 = \theta_3$ $V_2 = \theta_4$	θ_3 θ_4	32.6 45.8	CL = 2.21 Q = 3.06	V_1 = 32.6 V_2 = 45.8	5.3%	V_1 = NR V_2 = 32%	1.95	14.3%
	Ma et al.[34]	CL = θ_1 × [(TBW/59.95)^θ_2] × [(eGFR/36.67)^θ_3]	θ_1 θ_2 θ_3	2.08 0.698 1.07	V = θ_4 × [(TBW/59.95) ^θ_5]	θ_4 θ_5	63.2 0.934	2.08	63.2	21.5%	NR	NR	24.2%
	Pai and DeBacker[36]	CL = e×p(θ_1 + θ_2 × (eGFR/100)) - θ_3	θ_1 θ_2 θ_3	1.03 0.737 -1.63	V = θ_4	θ_4	66.4	0.334	66.4	(0.44, 0.85) IQR	(60.5, 98.2) IQR	0.76	NR
	Oda et al.[35]	CL = θ_1 × (TBW/70)^0.75 × e×p (η_{CL}) + unbound fraction × KoA-predicted CL_{HD} if (during HD) 1 else 0 $k_{12} = \theta_3$ $k_{21} = \theta_4$ × e×p (η_{k21}) $\eta_{(CL,K21)}$ is a random variable number depending on the mean of zero with a variance of $\omega^2_{(CL,k21)}$	θ_1 θ_3 θ_4	0.316 0.525 0.213	$V_{SS} = \theta_2$ × TBW × e×p (η_{Vss}) η_{Vss} is a random variable number depending on the mean of zero with a variance of ω^2_{Vss}	θ_2	1.160	CL = 0.316 k_{12} = 0.525 k_{21} = 0.213	V_{SS} = 67.05	0.365 variance	0.302 variance	0.064 variance	NR
	Ahmed et al.[32]	CL = θ_1 × TZ_R^θ_2 × e×p (η_{CL}) η_{CL} is a random variable number depending on the mean of zero with a variance of ω^2_{CL}	θ_1 θ_2	2.02 40.49	V = θ_2 × e×p (η_V) η_V is a random variable number depending on the mean of zero with a variance of ω^2_V	θ_2	65	2.02	65	0.46 (SD)	0.39 (SD)	NR	0.28 (SD)

Table 3. *Continued*

	Study				Volume of distribution related expressions: V_i (L)			Population mean (TV)		BSV (ω)		RV (*a*),(*b*)	
		Equations	Parameter	Value	Equations	Parameter	Value	CL (L/h), Q (L/h), k_{ij} (h^{-1})	V_i (L)	CL	V_i	Additive (mg/L)	Proportional
OBESE	Adane et al.[39]	$CL = \theta_2 \times (CL_{CR}/125)$	θ_2	6.54	$V = \theta_1 \times TBW$	θ_1	0.51	6.54	75.43	26.70 %	23.90 %	NR	18.9%
	Crass et al.[40]	$CL = \theta_1 - \theta_2 \times AGE - \theta_3 \times (SCr) + \theta_4 \times SEX + \theta_5 \times TBW^{0.75}$	θ_1 θ_2 θ_3 θ_4 θ_5	8.688 0.075 1.988 1.245 0.073	$V = \theta_6$	θ_6	73.969	5.9	74.1	39.94%	33.20%	NR	NR
	Polásková et al.[41]	$CL = \theta_1$	θ_1	0.83	$V = \theta_2 \times e \times p\text{^}(\theta_3 \times LBM)$	θ_2 θ_3	26.39 0.015	0.83	26.39	0.39 (SD)	0.39 (SD)	NR	0.13 (SD)
GERIATRICS	Sanchez et al.[43]	$CL = \theta_1 + \theta_5 \times CL_{CR}$ $Q = \theta_4 \times TBW$	θ_1 θ_5 θ_4	0.157 0.563 0.111	$V_1 = \theta_2 \times TBW$ $V_2 = \theta_3 \times AGE/53.5$	θ_2 θ_3	0.283 32.2	CL = 2.21 Q = 8.12	V_1 = 20.71 V_2 = 44.5	24.49 %	V_1 = NR V_2 = 6.8 %	NR	24.9%
	Zhou et al.[45]	$CL = \theta_1 \times (CL_{CR}/56.28)\text{^}\theta_2$	θ_1 θ_2	2.45 0.542	$V = \theta_3$	θ_3	154	2.45	154	17.53%	34.90%	NR	6.57%
	Zhang et al.[44]	$CL = \theta_1 \times (eGFR/80)\text{^}\theta_2 \times (1 + \theta_3 \times PCM)$	θ_1 θ_2 θ_3	3.74 1.03 0.41	$V = \theta_4$	θ_4	118	3.74	118	44.26%	54.99%	0.184 (log scale)	NR
	Ling et al.[42]	eGFR by CKD-EPIcys-scr: $CL = 3.79 \times (eGFR/64.82)\text{^}\theta_1 \times (TBW/65)\text{^}\theta_3$ eGFR by BIS-2: $CL = 3.71 \times (eGFR/59.53)\text{^}\theta_2 \times (TBW/65)\text{^}\theta_3$	θ_1 θ_2 θ_3	1.06 1.11 0.575	$V = \theta_4$	θ_4	76.9	3.79	76.9	23.6%	NR	0.7	23.2%
CANCER	Buelga et al.[46]	$CL = \theta_1 \times CL_{CR}$	θ_1	1.08	$V = \theta_2 \times TBW$	θ_2	0.98	5.79	63.40	28.16%	37.15%	3.52	NR
	Okada et al.[47]	$CL = \theta_2 \times (CL_{CR}/113)\text{^}\theta_6$ $Q = \theta_4$	θ_2 θ_6 θ_4	4.25 0.70 1.95	$V_1 = \theta_1 \times (TBW/59.4)\text{^}\theta_5$ $V_2 = \theta_3$	θ_1 θ_5 θ_3	39.2 0.78 56.1	CL = 4.25 Q = 1.95	V_1 = 39.2 V_2 = 56.1	25.2%	V_1 = 14.2% V_2 = 66.9%	NR	17.2%
	Alqahtani et al.[15]	$CL = \theta_1 \times (CL_{CR}/99.9)\text{^}\theta_2$	θ_1 θ_2	7.4 0.21	$V = \theta_3$	θ_3	45	7.4	45	15.9%	13.8%	NR	12.5%
	Tsuda et al.[48]	$CL = \theta_1 \times (CL_{CR}/4.2)\text{^}\theta_2 \times f$qSOFA fqSOFA is 1 when qSOFA scores of 0 and it is 0 when qSOFA scores are 1 or greater	θ_1 θ_2	2.8 0.8	$V = 0.17 \times AGE + 0.22 \times TBW + 15$	NR	NR	2.8	38.40	28%	NR	NR	23.2%
CYSTIC FIBROSIS	Yellepeddi et al.[49]	$CL = \theta_1 \times (TBW/52.6)\text{^}\theta_2$	θ_1 θ_2	5.52 0.5	$V = \theta_3$	θ_3	31.5	5.52	31.5	23%	NR	NR	0.0413 variance
TRAUMA	Medellín-Garibay et al.[50]	Furosemide = 0: $CL = \theta_1 \times CL_{CR}$ Furosemide = 1: $CL = \theta_5 \times CL_{CR}$ $Q = \theta_3$	θ_1 θ_5 θ_3	0.49 0.34 0.81	If age > 65 years: V_1 (L/kg) = $\theta_2 \times TBW$ V_2 (L/kg) = $\theta_4 \times TBW$ If age ≤ 65 years: V_1 (L/kg) = $\theta_6 \times TBW$	θ_2 θ_4 θ_6	1.07 5.99 0.74	CL = 2.6 (1.85) Q = 0.81	V_1 = 77.4 (53.28) V_2 = 424.8	36.2%	V_1 = 37.1% V_2 = NR	NR	19.3%

AST = aspartate aminotransferase (IU/L); **BIS-2** = Berlin Initiative Study 2; **BSV** = between-subject variability; **BUN** = blood urea nitrogen; **CKD-EPIcys-scr** = Chronic Kidney Disease Epidemiology Collaboration for cystatin C and creatinine; **CL** = Clearance; **CL_{CR}** = creatinine clearance calculated by Cockcroft-Gault formula; **CL_{HD}** = hemodialysis clearance; **CL_{CRRT}** = CL in patients with continuous renal replacement therapy; CL in patients with hemodialysis; **CLD_{BUN}** = in vivo urea dyalisis clearance; **CLDv** = vancomycin dialysis filter clearance; **DD** = daily dose (mg/day); **eGFR** = estimated glomerular filtration rate; **FIB** = Fibrinogen; **HD** = hemodialysis; **IQR** = Interquartile Range; **KoA** = dialyzer mass transfer-area coefficient; **LC** = underlying liver cirrhosis; **LBM** = lean body mass; **NR** = no reported; **NEUR** = neurosurgical patient; **PCM** = post-craniotomy meningitis; **RV** = residual variability; **SD** = standard deviation; **SCr** = serum creatinine; **STATUS** = Value 1 for patients with gram-positive infections; **TBW** = total body weight; **TOXI** = co-administration of nephrotoxic drug; **TV** = typical value; **Vc** = central volume; **Vd** = volume of distribution; **Vp** = plasma volume; **Vss** = steady-state volume of distribution.

Regarding the variability of the TV, the mean between-subject variability coefficients of CL (ωCL) were 31.44% (max: 99.20%; min: 5.30%), of the central distribution volume (ωVc) 27.29% (max: 54.99; min: 6.34%) and peripheral (ωVp) 49.45% (max: 72.80%; min: 6.80%); and finally the means of additive (*a*) and proportional (*b*) errors were 6.67 mg/L (max: 55.00 mg/L; min: 6.34 mg/L) and 27.29% (max: 54.99; min: 0.70%) respectively. The previously mentioned results are summarized in Supplementary data S2.

Discussion

In the precision dosing, the TDM and development of PopPK within the MIPD is relevant to improve efficacy and/or lower toxicity in special populations with high variability, like pediatrics, elderly, those with renal or hepatic impairment and comedicated patients. The translation of this approach personalized medicine requires the implementation of new dosing scenarios, new working paradigms and clinical pharmacology experts and researchers, that are not limited only to the academic area.[51]

NONMEM (ICON, Dublin, Ireland), Monolix (Lixoft, Paris, France) and Phoenix NLME (Certara, Princeton, NJ) are the most widely used nonlinear mixed effects modeling (NLMEM) tools in pharmacometrics. They are commercial offerings with fees substantial licensing costs, and while all have programs aimed at reducing or eliminating licensing costs in educational institutions or low-income countries, the administrative hurdles and associated delays in availability can be cumbersome when conducting analysis and training students and researchers to use these tools in resource-limited settings. Implementation of open-source software based on R and the nlmixr package may be a credible and capable alternative to commercial PK/PD modeling software to fit compartmental of pharmacokinetic/pharmacodynamic (PK/PD) models described by ordinary differential equations (ODEs). Parameter estimation algorithms implemented in nlmixr currently include relatively mature implementations of NLMEM, SAEM, and first-order, first-order with interaction, FOCE, and FOCEI.[52]

About the development of PopPK models we can observe for vancomycin it is expected that CL_{CR} would be the most important covariable in most models and could affect the CL and the prediction of serum vancomycin concentration, it is because vancomycin is excreted 80% to 90% as an unchanged drug in urine[19]; conventionally, the eGFR is calculated by the Cockroft-Gault equation, however, the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), Modification of Diet in Renal Disease (MDRD) and Berlin Initiative Study 2 (BIS-2) equations has been shown to be more accurate, especially in youngest.[53] This is because, although the Cockcroft-Gault equation is widely used in pharmacokinetic studies and drug dosing adjustments, it has several limitations. It was developed in a specific population, primarily adult males, which limits its applicability to other groups, such as elderly individuals, patients with altered body composition (e.g., obesity, cachexia), or critically ill patients. Additionally, since it relies on serum creatinine levels, it is influenced by factors such as muscle mass, diet, and hydration status, potentially leading to inaccurate estimations of renal function. The equation also lacks standardization across different creatinine assay methods, and its accuracy diminishes in patients with very low or highly fluctuating glomerular filtration rates (GFR), such as those with acute kidney injury (AKI). Moreover, the use of actual body weight can introduce further errors, particularly in patients with obesity or fluid overload. Despite these limitations, the Cockcroft-Gault equation remains widely used due to its historical application in drug dosing guidelines and its inclusion in many pharmacokinetic models.

Ling et al. used to covariate the model CKD-EPIcys and BIS-2 eGFR with specific equations for each one.[42] Beyond that, models have always been compared to the CL_{CR}, including the studies like Tanaka et al. which uses cystatin C, those who consider that this may be more accurate and sensitive than creatinine for calculating eGFR, suggesting that it could be a good predictive marker of CL and vancomycin concentrations.[23]

Great difference was found in TV estimates, the population with significantly higher TVCL and TVV are obese and surgical patients; in both, this finding in TVCL are explained by the augmented renal clearance (ARC) in early stage of the surgical approach or in obese by the compensatory vasodilation of the afferent arteriole,[54] also in neurological patients the brain lesions and the loss of autoregulation induced by brain injury may impair the kidney autoregulatory process[29]; in the obese population because the volume of distribution is linked to weight and also to the constants of CL_{CR}, it is expected that both the TVCL and the TVV increase.[39] The trauma and elderly have also the highest TVV (central and peripheral) but lowest TVCL; Variability in trauma patients CL is due to the fact that the elimination of vancomycin depending on tubular secretion and the concomitant administration of other drugs, such as furosemide[50]; the renal function of the elderly gradually decreases with age and the larger volume of distribution may be by the changes in the peripheral circulation usually due to poor nutrition, hypoalbuminemia and internal environmental disorders such as hypokalemia, hyponatremia and metabolic acidosis that increased tissue affinity for vancomycin, and the TVV is high because they are attached to the weight.[45] In patients with impairment kidney function the heterogenicity of the TVCL it is due to changes in the central compartment generated by renal effect of the vancomycin, dialysis and changes in the ultrafiltration rate of

each session, for this reason eGFR estimated by Cockroft-Gault equation is not a reliable marker of renal function.[33,36,37] Patients with above-the-mean vancomycin clearance and volume of distribution typically exhibit pharmacokinetic profiles associated with increased drug elimination and expanded drug distribution. Several factors may contribute to these elevated parameters, including younger age, preserved or augmented renal function, higher body weight, and conditions associated with hyperdynamic circulation, such as sepsis or burns. Higher clearance rates may result in subtherapeutic vancomycin concentrations, potentially reducing efficacy and increasing the risk of treatment failure, particularly in infections caused by less susceptible pathogens. Similarly, an increased volume of distribution may lead to lower peak concentrations, which could impact the drug's time-dependent antibacterial activity. Given these considerations, patients with above-the-mean clearance and volume of distribution may require individualized dosing strategies, such as higher initial doses, more frequent administration, or therapeutic drug monitoring to ensure optimal target attainment while minimizing the risk of underexposure.[55–57]

To end when we look at the variability of the models is striking that for the patients undergoing allogeneic transplantation, the models developed indicate a high variability due to high between-subject variability and the difficulty of maintaining the therapeutic range, due to the characteristics of these patients with extremely low hematocrit levels, increased intravascular volume, and increased renal clearance.[46–48] It is important to note that this review had several limitations. Some of the papers do not specify the clinical and pathological characteristics of the study subjects. The creatinine clearance formulas are different in every article making necessary the classification of every subpopulation before applying the model, the units of measure and the population have great variability. That is the main reason why the comparisons presented are indirect and the generalization of the data that we show must be read carefully.

Conclusions and recommendations for future research

This scoping review highlights the principal information of different PopPK models, which showed heterogeneity in the parameters and methods of analysis and evaluation, even if these methods can be used to guide the dosing regimen in different subpopulations, it is imperative to conduct experiments with local samples to define the best fit in the different subpopulation.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Zenodo: Scoping review on Population pharmacokinetics of vancomycin in non-critically ill. https://doi.org/10.5281/zenodo.14876777[58]

This project contains the following underlying data:

- PkPop Vanco_non critical patients - Extended data E1 PRISMA-ScR checklist.docx
- PkPop Vanco_non critical ill patients - Extended data E2 Additional results tables.pdf
- LICENSE.txt- - Supplementary data S2: Additional results tables.pdf
- LICENSE.txt

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Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 21 March 2025

https://doi.org/10.5256/f1000research.178348.r369835

✔ **Venkata Kashyap Yellepeddi**
Spencer Fox Eccles School of Medicine, Department of Pediatrics, The University of Utah, Salt Lake City, Utah, USA

Authors have addressed all my comments satisfactorily.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Pharmacology, Nanotechnology. Mode-informed drug design, Population PK modeling, Physiologically based pharmacokinetic modeling.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 20 March 2025

https://doi.org/10.5256/f1000research.178348.r369834

✔ **Manal Abouelkheir**
Misr International University, Cairo, Cairo Governorate, Egypt

Thank you to the authors for revising the manuscript and incorporating all the requested modifications. I have no further comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Antibiotics pharmacokinetics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 06 August 2024

https://doi.org/10.5256/f1000research.140830.r234168

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Manal Abouelkheir
Misr International University, Cairo, Cairo Governorate, Egypt

This scoping review is comprehensive and well-structured. It provides valuable insight into PopPK models of vancomycin in non-critically ill patients. It highlights important covariates and model parameters while pointing out the variability and limitations in existing studies. It also offers practical recommendations for future research. Below are some comments to improve the quality of the manuscript.

Abstract:

- Please make the abstract more concise by summarizing the search strategy and inclusion criteria in fewer words in the method, focusing the results on the most critical findings, such as the main covariates and models used, and finally, highlighting the key takeaway points briefly in the conclusion.

Methods:

- The method has two redundant sentences: “Articles that did not meet inclusion/exclusion criteria were removed. The selected articles were reviewed by two authors (J.-D.V. and D.N.) and compared to inclusion and exclusion criteria.” Please remove one of them.
- The research question “What is the existing evidence related to PopPK models of vancomycin in non-critical hospitalized adult patients?" actually follows the PCC format (Population, Concept, Context) which is generally more appropriate than PICO for scoping reviews. The PICO format (Population, Intervention, Comparison, Outcome) is commonly used for formulating research questions in systematic reviews and clinical research, especially for randomized controlled trials. However, for scoping reviews, which aim to map the existing literature on a particular topic or research area and identify key concepts, gaps, and evidence types, the PICO format might not always be the best fit.
- The authors mentioned that they included studies published between January 1980 and November 2021. But I noticed that some studies are missing, for example: Population Pharmacokinetic Model for Vancomycin Used in Open Heart Surgery: Model-Based Evaluation of Standard Dosing Regimens (https://doi.org/10.1128/aac.00088-18) and Dose Tailoring of Vancomycin Through Population Pharmacokinetic Modeling Among Surgical Patients in Pakistan (https://doi.org/10.3389/fphar.2021.721819). In addition, more studies

are published thereafter, like: Population pharmacokinetic model of vancomycin in postoperative neurosurgical patients (https://doi.org/10.3389/fphar.2022.1005791). I suggest to either including them in the revised version or explaining the reason why you excluded such studies.
- Remove the sentence "The results were categorized and organized into subgroups in Table 2 and Table 3." From the method section and better refer to these tables in the results section in a more descriptive way for the content of each table.

Results:
- The authors mentioned that "after removing the duplicate studies, 134 articles remained for screening and 73 of these articles were selected for review. Finally, we considered 17 articles that met the inclusion/exclusion criteria". The stepwise screening approach needs further clarification. What is the difference between 1st and 2nd screening steps? Could you please further clarify on which base you reduced the number of studies from 134 to 73 and then to 17??
- It is mentioned in the results section that "The study populations were categorized into four groups: (a) renal, (b) obese, (c) older, and (d) cancer patients (Figure 1)" However, Figure 1 shows the flowchart of selected studies, not the patient categorization. Please correct it.
- The results section mentions that "these results are shown in Table 2." A suggested better description for Table 2 would be " A summary of demographics and PopPK modeling methods for all the included studies is presented in Table 2."
- All abbreviations in the tables should be spelled out as a footnote under the tables.
- The results section mentions that "Only 3 studies (17.3%) had external validation (Table 3)." However, information about validity is mentioned in Table 2, not 3.
- It is mentioned in the results section "Table 3 summarizes the results of the 17 studies". Actually table 3 summarizes the models formula, and parameters not the whole results of the 17 studies.
- "Table 3: Characteristics PK models" Please write a more descriptive title for Table 3.
- It is mentioned that "The lowest vancomycin CL value was reported in the study by Ma KF et al., where a typical value of 2.08 L/h was reported. For the patients in this study, a mean value of 2.08mL/min was reported for CLCR." The value 2.08 couldn't be the same for both vancomycin Cl and CLCR. I believe it is a typo for CLCR, please correct it and rephrase the sentence for better readability.
- It is mentioned that "The lowest TVV was 42 L in the subgroup of non-cancer patients in the Alqhatani study and the highest was 66.4 L in the patients with unstable and stable kidney function.7". Reference 7 is the updated vancomycin guideline 2020, not the study that reported this value of TVV. Also, how come the TVV of 66.4 L is the same for patients with stable and unstable kidney function? Do you mean that kidney function has no effect on TVV?
- In the result section, it is mentioned that "Although most studies with two-compartment models reported parameters in the form of flow rates (CL and Q), two studies reported model parameters in the form of elimination, transfer rate constants (k_{10}, k_{12}, k_{21}) were presented." Could you please spell out each abbreviation when it first appears?
- In the result section, it is mentioned that "One article used furosemide and other cystatin C for glomerular filtration rate (GFR) estimation." How furosemide was used for GFR estimation?
- "GFR was the main covariable that affected the models, and this covariate was used to

explain between-individual variability in drug clearance." What about covariates to explain variability in volume of distribution"

Discussion:

- It is mentioned in the discussion section that "Despite the multiple limitations of the Cockcroft Gault equation, most of the articles used it". Could you please elaborate more on the limitations of Cockcroft Gault equation.
- "In the volume parameter, we can notice that the two volumes that are above the mean are those of the geriatric patients and the general group." And then you referred to the Medellin Garibay article, which actually includes trauma patients who are considered a special population, not a general population.
- In the discussion sections the authors commented only on the populations who have above the mean clearance and volume of distribution. Could you please also comment on populations who have below the mean parameters.
- In the discussion section, "For the obese subpopulation, the elimination rate constant (k10=CL/V) could be affected by the patients being overweight and in the geriatric subpopulation by a change in the central compartment volume. A solution to this problem would be to increase the loading dose to achieve a faster steady state and make it easier for them to achieve the target of AUC/MIC > 400 to ensure an adequate bactericidal effect." This paragraph is a bit confusing. You already mentioned in a previous paragraph that obese patients had higher CL and geriatric had higher V, you just repeated the same information but in another word. And does the loading dose would be helpful only with obese and geriatric patients, or with other general populations?
- The order of the paragraphs of the discussion section needs to be revised for better readability. The 3rd and 7th paragraphs talk about vancomycin elimination, renal patients, and equations to estimate renal function. I suggest combining them together. Again, the 8th paragraph can be combined with the 5th one when talking about cancer patients.

General comments:

- The whole manuscript needs proofreading with language and grammatical editing to improve readability.
- Abbreviations should be spelled out when 1st appears.
- Please replace the term "non-critical adults" throughout the text with "non-critical ill adults.".

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term

should be included in the title.)
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Antibiotics pharmacokinetics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 16 Feb 2025

Rosa Helena Bustos

Original comments of the reviewer
Reply by the author(s)
Changes done on page number and line number

This scoping review is comprehensive and well-structured. It provides valuable insight into PopPK models of vancomycin in non-critically ill patients. It highlights important covariates and model parameters while pointing out the variability and limitations in existing studies. It also offers practical recommendations for future research. Below are some comments to improve the quality of the manuscript.

We would like to thank the reviewer for the painstaking review of our document and the suggestions made. We have taken the suggestions to heart and made the appropriate corrections and revision which have thereby strengthened and enriched our manuscript

Abstract

1 Please make the abstract more concise by summarizing the search strategy and inclusion criteria in fewer words in the method, focusing the results on the most critical findings, such as the main covariates and models used, and finally, highlighting the key takeaway points briefly in the conclusion.

Answer: The abstract has been revised and modified, with an emphasis on focusing the results on the most critical findings, such as the main covariates and models used. Key aspects of the study have been highlighted in the conclusion.
Page 1
Line 11-27

Methods

2 The method has two redundant sentences: “Articles that did not meet inclusion/exclusion criteria were removed. The selected articles were reviewed by two authors (J.-D.V. and D.N.) and compared to inclusion and exclusion criteria.” Please remove one of them.

Answer: The methods section has been thoroughly revised and modified.
Page 2
Line 66-85

3 The research question “What is the existing evidence related to PopPK models of vancomycin in non-critical hospitalized adult patients?" actually follows the PCC format (Population, Concept, Context) which is generally more appropriate than PICO for scoping reviews. The PICO format (Population, Intervention, Comparison, Outcome) is commonly used for formulating research questions in systematic reviews and clinical research, especially for randomized controlled trials. However, for scoping reviews, which aim to map the existing literature on a particular topic or research area and identify key concepts, gaps, and evidence types, the PICO format might not always be the best fit.

Answer: The reviewer’s observation is absolutely valid. The methods section has been thoroughly revised and updated."
Page 2
Line 71-73

4 The authors mentioned that they included studies published between January 1980 and November 2021. But I noticed that some studies are missing, for example: Population Pharmacokinetic Model for Vancomycin Used in Open Heart Surgery: Model-Based Evaluation of Standard Dosing Regimens (https://doi.org/10.1128/aac.00088-18) and Dose Tailoring of Vancomycin Through Population Pharmacokinetic Modeling Among Surgical Patients in Pakistan (https://doi.org/10.3389/fphar.2021.721819). In addition, more studies are published thereafter, like: Population pharmacokinetic model of vancomycin in postoperative neurosurgical patients (https://doi.org/10.3389/fphar.2022.1005791). I suggest to either including them in the revised version or explaining the reason why you excluded such studies.

Answer: A new literature search has been ongoing as of November 2024, leading to an increase in the number of included articles from 17 in the initial review to 36 in this revised version submitted to the reviewers. The analysis of these studies has been presented in Tables 2 and 3. Additionally, the articles suggested by the reviewer have been incorporated into the updated literature search
Page 2 Line 76-79
Table 2, Page 6-9
Table 3, Page 10-13

5 Remove the sentence “The results were categorized and organized into subgroups in Table 2 and Table 3.” From the method section and better refer to these tables in the results section in a more descriptive way for the content of each table.

Answer: The results section has been completely revised. The findings from the newly included articles in Tables 2 and 3 have been incorporated, and their description has been presented in this section.
Table 2, Page 6-9
Table 3, Page 10-13

Page 3 Line 92-96
Page 3 Line 122-141
Page 4 Line 142-145

Results

6 The authors mentioned that "after removing the duplicate studies, 134 articles remained for screening and 73 of these articles were selected for review. Finally, we considered 17 articles that met the inclusion/exclusion criteria". The stepwise screening approach needs further clarification. What is the difference between 1st and 2nd screening steps? Could you please further clarify on which base you reduced the number of studies from 134 to 73 and then to 17??

Answer: The study flowchart has been modified to include the newly selected studies. The description of identification, screening, and inclusion has been carefully reviewed.
Figure 1 -Page 3

7 It is mentioned in the results section that "The study populations were categorized into four groups: (a) renal, (b) obese, (c) older, and (d) cancer patients (Figure 1)" However, Figure 1 shows the flowchart of selected studies, not the patient categorization. Please correct it.

Answer: The flowchart has been revised and updated to include the newly identified studies from the expanded search. However, Figure 1 does not display the categorization of the groups. The description of the categorization has been included in the results section.
Page 2
Line 122-125

8 The results section mentions that "these results are shown in Table 2." A suggested better description for Table 2 would be " A summary of demographics and PopPK modeling methods for all the included studies is presented in Table 2."

Answer: The description of Table 2, as suggested by the reviewer, has been included in the text.
Page 4 Line 144-145

9 All abbreviations in the tables should be spelled out as a footnote under the tables.

Answer: The abbreviations in the table have been spelled out under the tables.
Table 2 Page 9
Table 3 Page 13

10 The results section mentions that "Only 3 studies (17.3%) had external validation (Table 3)." However, information about validity is mentioned in Table 2, not 3.

Answer: The results section has been revised and modified according to the reviewer's

suggestion
Page 3 Line 92-96
Page 3 Line 122-141
Page 4 Line 142-145

11 It is mentioned in the results section “Table 3 summarizes the results of the 17 studies”. Actually table 3 summarizes the models formula, and parameters not the whole results of the 17 studies.

Answer: The number of included articles has increased from 17 in the initial review to 36 in this revised version, which has been submitted to the reviewers. All 36 studies have been included in Tables 2 and 3. *Note: The study by Alqahtani et al. (2020) has been included in two categories: General and Cancer.*
Table 2, Page 6-9
Table 3, Page 10-13

12 “Table 3: Characteristics PK models” Please write a more descriptive title for Table 3.

Answer: The name of table 3 has been modified.
Table 3 Page 10

13 It is mentioned that “The lowest vancomycin CL value was reported in the study by Ma KF et al., where a typical value of 2.08 L/h was reported. For the patients in this study, a mean value of 2.08mL/min was reported for CLCR.” The value 2.08 couldn’t be the same for both vancomycin Cl and CLCR. I believe it is a typo for CLCR, please correct it and rephrase the sentence for better readability.

Answer: The results section has been completely modified due to the increased number of studies included in the paper. However, after reviewing the reviewer's suggestion, the value of 2.08 L/h was confirmed to correspond to the CL value, as presented in Table 3.
Result section
Table 3 Page 10-13

14 It is mentioned that “The lowest TVV was 42 L in the subgroup of non-cancer patients in the Alqhatani study and the highest was 66.4 L in the patients with unstable and stable kidney function.7”. Reference 7 is the updated vancomycin guideline 2020, not the study that reported this value of TVV. Also, how come the TVV of 66.4 L is the same for patients with stable and unstable kidney function? Do you mean that kidney function has no effect on TVV?

Answer: The TVV values have been reviewed. The description of the TVV values for each category has been modified according to the newly included studies.
Page 5
Line 202-208

15 In the result section, it is mentioned that “Although most studies with two-compartment

models reported parameters in the form of flow rates (CL and Q), two studies reported model parameters in the form of elimination, transfer rate constants (k10, k12, k21) were presented." Could you please spell out each abbreviation when it first appears?

Answer: The abbreviations have been reviewed throughout the text and spelled out upon their first appearance.
All document

16 In the result section, it is mentioned that "One article used furosemide and other cystatin C for glomerular filtration rate (GFR) estimation." How furosemide was used for GFR estimation?
The paragraph has been revised and modified.

Answer: Furosemide was not directly used to estimate the glomerular filtration rate (GFR). Instead, it was administered as part of a furosemide stress test, which has been proposed as a functional marker of renal reserve. This test assesses renal response to a standardized dose of furosemide and has been used to predict acute kidney injury (AKI) progression in critically ill patients. However, in the context of the referenced study, cystatin C was the primary biomarker used for GFR estimation.
Page 4
Line 162-167

17 "GFR was the main covariable that affected the models, and this covariate was used to explain between-individual variability in drug clearance." What about covariates to explain variability in volume of distribution"
The paragraph has been revised and modified.

Answer: In our analysis, variability in the volume of distribution (Vd) was primarily assessed in relation to physiological and clinical covariates. While GFR significantly influenced drug clearance, other factors such as body weight, age, and serum albumin levels were evaluated as potential covariates for Vd. Among these, body weight showed the strongest correlation with Vd, which is consistent with its role in determining drug distribution, particularly for hydrophilic compounds like vancomycin.

Table 3
Pag 10-13

Discussion

18 It is mentioned in the discussion section that "Despite the multiple limitations of the Cockcroft Gault equation, most of the articles used it". Could you please elaborate more on the limitations of Cockcroft Gault equation.

Answer: A paragraph in the discussion section has been added.
The Cockcroft-Gault equation, despite its widespread use in pharmacokinetic studies and drug dosing adjustments, has several limitations. It was developed in a specific population, primarily adult males, which limits its applicability to other groups such as elderly

individuals, patients with altered body composition (e.g., obesity, cachexia), or critically ill patients. Additionally, since it relies on serum creatinine levels, it is influenced by factors such as muscle mass, diet, and hydration status, potentially leading to inaccurate estimations of renal function. The equation also lacks standardization across different creatinine assay methods, and its accuracy diminishes in patients with very low or highly fluctuating glomerular filtration rates (GFR), such as those with acute kidney injury (AKI). Moreover, the use of actual body weight can introduce further errors, particularly in patients with obesity or fluid overload. Despite these limitations, Cockcroft-Gault remains widely used due to its historical application in drug dosing guidelines and its inclusion in many pharmacokinetic models.
Page 14
Line 271-281

19 “In the volume parameter, we can notice that the two volumes that are above the mean are those of the geriatric patients and the general group.” And then you referred to the Medellin Garibay article, which actually includes trauma patients who are considered a special population, not a general population.

Answer: We acknowledge the inconsistency in our statement regarding the classification of the population in the Medellín-Garibay study. While we initially referred to it as a "general group," we recognize that this study specifically includes trauma patients, who are considered a special population due to their distinct physiological and pharmacokinetic characteristics. The paragraph has been revised and modified.

Table 2 and Table 3

20 In the discussion sections the authors commented only on the populations who have above the mean clearance and volume of distribution. Could you please also comment on populations who have below the mean parameters.

Answer: The discussion section has been revised and a new paragraph added according to the reviewer's suggestion.

Patients with above-the-mean vancomycin clearance and volume of distribution typically exhibit pharmacokinetic profiles associated with increased drug elimination and expanded drug distribution. Several factors may contribute to these elevated parameters, including younger age, preserved or augmented renal function, higher body weight, and conditions associated with hyperdynamic circulation, such as sepsis or burns. Higher clearance rates may result in subtherapeutic vancomycin concentrations, potentially reducing efficacy and increasing the risk of treatment failure, particularly in infections caused by less susceptible pathogens. Similarly, an increased volume of distribution may lead to lower peak concentrations, which could impact the drug’s time-dependent antibacterial activity. Given these considerations, patients with above-the-mean clearance and volume of distribution may require individualized dosing strategies, such as higher initial doses, more frequent administration, or therapeutic drug monitoring to ensure optimal target attainment while minimizing the risk of underexposure.
Page 15

Line 303-313

21 In the discussion section, “For the obese subpopulation, the elimination rate constant (k10=CL/V) could be affected by the patients being overweight and in the geriatric subpopulation by a change in the central compartment volume. A solution to this problem would be to increase the loading dose to achieve a faster steady state and make it easier for them to achieve the target of AUC/MIC > 400 to ensure an adequate bactericidal effect.” This paragraph is a bit confusing. You already mentioned in a previous paragraph that obese patients had higher CL and geriatric had higher V, you just repeated the same information but in another word. And does the loading dose would be helpful only with obese and geriatric patients, or with other general populations?

Answer: The order of the paragraphs of the discussion section needs to be revised for better readability. The 3rd and 7th paragraphs talk about vancomycin elimination, renal patients, and equations to estimate renal function. I suggest combining them together. Again, the 8th paragraph can be combined with the 5th one when talking about cancer patients.
Due to changes in the discussion section following the inclusion of new studies, we are unable to merge these paragraphs. However, a new paragraph has been written in the discussion section specifically addressing the findings related to elimination.
Pag 14-15
Line 287-303

General comments

21 The whole manuscript needs proofreading with language and grammatical editing to improve readability.

Answer: The manuscript has been fully reviewed, focusing on language and grammatical editing to enhance readability and ensure clarity, coherence, and precision in the text.
All document

22 Abbreviations should be spelled out when 1st appears.

Answer: The abbreviations have been reviewed throughout the text and spelled out upon their first appearance.
All document

23 Please replace the term “non-critical adults” throughout the text with “non-critical ill adults.”.

Answer: The entire document has been reviewed, and the term "non-critical adults" has been included
All document

Competing Interests: No competing interests were disclosed.

Reviewer Report 18 July 2024

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The manuscript reports the scoping review of the PoPK models of vancomycin. The review includes details about model information, covariates assessed, and PK parameters reported. Below are some of the comments that would improve the quality of this scoping review:

1. In the introduction, paragraph 2 must be rewritten. In its current form, its incoherent and incomplete. Please add more details with citations about the importance of PoPK modeling in finding optimal drug dosing regimens for narrow therapeutic index drugs. The sentence "Sex had no influence
in the variability of PK parameters" is totally out of place remove it.
2. Please add the details of Rayyan software, such as manufacturer and country of origin.
3. Please extend the search to the year 2024 and update the current list with new articles.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Pharmacology, Nanotechnology. Mode-informed drug design, Population PK modeling, Physiologically based pharmacokinetic modeling.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 16 Feb 2025

Rosa Helena Bustos

We would like to thank the reviewer for the painstaking review of our document and the suggestions made. We have taken the suggestions to heart and made the appropriate corrections and revision which have thereby strengthened and enriched our manuscript

1 In the introduction, paragraph 2 must be rewritten. In its current form, its incoherent and incomplete. Please add more details with citations about the importance of PoPK modeling in finding optimal drug dosing regimens for narrow therapeutic index drugs. The sentence "Sex had no influence.

Answer: The entire introduction has been revised and updated. The reviewer's suggestions have been incorporated, with greater emphasis placed on the importance of PopPK modeling in optimizing drug dosing regimens for narrow therapeutic index drugs
Page 1
Line 47-53

2 Please add the details of Rayyan software, such as manufacturer and country of origin.

Answer: The details of Rayyan have been included.
Page 2
Line 80-83

3 Please extend the search to the year 2024 and update the current list with new articles.

Answer: A new literature search was conducted as of November 2024. The number of included articles has increased from 17 in the initial review to 36 in this revised version, which has been submitted to the reviewers. Tables 1 and 2 present the analysis of these studies.
Page 2
Line 76-79
Table 2, Page 6-9
Table 3, Page 10-13

Competing Interests: No competing interests were disclosed.