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Optimisation de l'usage de la vancomycine en néonatalogie à l'aide de modèles pharmacocinétiques de population

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Optimisation de l'usage de la vancomycine en néonatalogie à l'aide de modèles pharmacocinétiques de population

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Résumé

Une révision des lignes directrices consensuelles, proposant un changement de modalités significatif vers le calcul de l'aire sous la courbe pendant 24 heures au détriment du creux pour assurer le suivi thérapeutique pharmacologique de la vancomycine, a été publiée en mars 2020. Ce nouveau paramètre s'obtient à l'aide de prélèvements sanguins limités en combinaison avec un modèle pharmacocinétique de population prédictif, de préférence. Ainsi, le présent mémoire détaille l'évaluation externe de modèles néonataux antérieurs, renseignant leurs performances prédictives en vue d'optimiser l'usage de la vancomycine dans la population québécoise.

Une revue de la littérature a permis l'identification de 28 modèles néonataux qui ont été retranscrits et évalués à l'aide de bases de données externes incluant une soixantaine de patients du Centre hospitalier universitaire Sainte-Justine (Montréal) et du Centre mère-enfant Soleil du Centre hospitalier universitaire de Québec-Université Laval. De nombreux nomogrammes de doses initiales de vancomycine ont enfin été testés par des simulations de Monte-Carlo à l'aide des modèles démontrés les plus prédictifs dans chaque centre.

La performance prédictive varie sensiblement entre les deux centres, permettant tout de même d'identifier 5 et 11 modèles prédictifs pour Montréal et Québec, respectivement. Au final, trois modèles ont mené aux recommandations de différentes doses initiales, soit une dose unique simplifiée à Montréal versus un nomogramme plus standard à Québec.

Ce mémoire met en évidence la faisabilité d'évaluations externes des modèles néonataux de vancomycine ainsi que l'importance de leurs réalisations dans chaque centre d'intérêt.

Mots-clés: Vancomycine, néonatalogie, suivi thérapeutique pharmacologique, pharmacocinétique de population, évaluation externe

Abstract

A revised consensus guideline, proposing a significative change in vancomycin therapeutic drug monitoring modalities by moving from trough concentration to the calculation of the area under the concentration-time curve over 24 hours, was emitted in March 2020. The latter could potentially allow for limited sampling design if used together with population pharmacokinetic models, as preferably recommended. Hence, this master's thesis details the external evaluation of already developed neonatal models, informing their predictive performance to optimize the use of vancomycin in Quebec patients.

A literature review was conducted to identify 28 neonatal models, which were transcribed and assessed via external datasets including approximately sixty patients from the Centre hospitalier universitaire Sainte-Justine (Montreal) as well as the Centre mère-enfant Soleil du Centre hospitalier universitaire de Québec-Université Laval. Ultimately, several initial dosing nomograms were evaluated via Monte Carlo simulations using the most predictive models in each center.

The predictive performance varies considerably between both centers, still enabling the identification of 5 and 11 predictive models in Montreal and Quebec, respectively. Diverse models led to the suggestion of different initial vancomycin doses, with a unique dose in Montreal compared with a more standard nomogram in Quebec.

This master's thesis demonstrates the feasibility of an external evaluation in vancomycin neonatal models and the importance of its realization in each center of interest prior to their clinical implementation.

Keywords: Vancomycin, neonatology, therapeutic drug monitoring, population pharmacokinetics, external evaluation

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Liste des sigles et abréviations

ACEIs : Inhibiteurs de l'enzyme de conversion de l'angiotensine, de l'anglais *Angiotensin Converting Enzyme Inhibitors*

AKI : Insuffisance rénale aiguë, de l'anglais *Acute Kidney Injury*

ARBs : Antagonistes des récepteurs de l'angiotensine II, de l'anglais *Angiotensin II Receptor Blockers*

ASC_{24h}/AUC_{24h} : Aire sous la courbe pendant 24 heures

ASHP : American Society of Health-System Pharmacists

BCP : Distribution postérieure bayésienne, de l'anglais *Bayesian Conditional Posterior*

CHUSJ : Centre hospitalier universitaire Sainte-Justine

CL : Clairance

CMES : Centre mère-enfant Soleil du Centre hospitalier universitaire de Québec-Université Laval

CMI/MIC : Concentration minimale inhibitrice

C_{ipred} : Concentration prédite au niveau individuel

C_{obs} : Concentration observée en clinique

CoNS : Staphylocoques à coagulase négative, de l'anglais *Coagulase-Negative Staphylococci*

COX-2 : Cyclooxygénase 2

C_{pred} : Concentration prédite au niveau de population

CW : Poids au moment du traitement, de l'anglais *Current Weight*

EP/PE : Erreur de prédiction

F_{20} : Proportion d'erreurs de prédiction incluses entre $\pm 20\%$

F_{30} : Proportion d'erreurs de prédiction incluses entre $\pm 30\%$

FO(CE) : *First-Order (Conditional Estimation)*

GA : Âge gestationnel, de l'anglais *Gestational Age*

GA28 : Variable dichotomique prenant la valeur 1 si l'âge gestationnel > 28 semaines ou 0 si l'âge gestationnel ≤ 28 semaines

I : Interaction

IA : Intelligence artificielle

IDSA : Infectious Diseases Society of America

IQR : Écart interquartile, de l'anglais *Interquartile Range*

IV : Intraveineuse

KDIGO : Kidney Disease Improving Global Outcomes

k_{el} : Constante d'élimination

L : Dose de charge, de l'anglais *Loading Dose*

LLOQ : Limite inférieure de quantification, de l'anglais *Lower Limit of Quantification*

LOCF : Dernière observation reportée, de l'anglais *Last Observation Carried Forward*

M : Dose d'entretien, de l'anglais *Maintenance Dose*

MIPD : Dosage de précision basé sur un modèle, de l'anglais *Model-Informed Precision Dosing*

MDAPE : Médiane des erreurs de prédiction en valeur absolue

MDPE : Médiane des erreurs de prédiction

NA : Non applicable

NCOX : Inhibiteurs non sélectifs de la cyclooxygénase 2, de l'anglais N*onselective Cyclooxygenase-2 Inhibitors*

NSAIDs : Médicaments anti-inflammatoires non stéroïdiens, de l'anglais *Nonsteroidal Anti-Inflammatory Drugs*

NPDE : *Normalized Prediction Distribution Errors*

OMS : Organisation mondiale de la Santé

(pc)VPC : *(Prediction-corrected) Visual Predictive Check*

PD : Pharmacodynamique

PIDS : Pediatric Infectious Diseases Society

PK : Pharmacocinétique

PMA : Âge post-menstruel, de l'anglais *Postmenstrual Age*

PNA : Âge chronologique, de l'anglais *Postnatal Age*

PopPK : Pharmacocinétique de population

Q : Clairance intercompartimentale

R^2 : Coefficient de détermination

SAEM : *Stochastic Approximation Expectation Maximisation*

SARM/MRSA : *Staphylococcus aureus* résistant à la méthicilline

SCr : Créatinine sérique, de l'anglais *Serum Creatinine*

SD : Écart type, de l'anglais *Standard Deviation*

SGA : Petit poids à la naissance selon l'âge gestationnel, de l'anglais *Small for Gestational Age*

SIDP : Society of Infectious Diseases Pharmacists

STP/TDM : Suivi thérapeutique pharmacologique

V_d : Volume de distribution

V_{ss} : Volume de distribution à l'état d'équilibre

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Avant-propos

Les travaux réalisés dans le cadre de ce mémoire découlent des ajustements proposés au sein de la révision des lignes directrices consensuelles concernant le suivi thérapeutique pharmacologique de la vancomycine en mars 2020. L'exécution d'une évaluation externe a été préférée au développement de nouveaux modèles néonataux dû à leur abondance et la récurrence des covariables retenues comme pertinentes, soit le poids (à la naissance et surtout au moment du traitement), l'âge (chronologique et souvent post-menstruel) ainsi que le niveau de créatinine sérique qui influent la valeur de clairance dans plus de la moitié des modèles évalués.

Chapitre 1 - Introduction

Ce chapitre introductif propose certains éléments permettant de mieux contextualiser le travail réalisé au fil des dernières années à partir des notions sous-jacentes. Il convient de mentionner ici que les informations sont présentées de façon concise et complémentaire, dans la mesure du possible, à ce qui se trouve déjà au sein des deux articles inclus dans le mémoire de maîtrise.

1.1. La résistance aux antibiotiques

1.1.1. Une ère antibiotique précaire

L'utilisation de molécules antibiotiques, suivant la découverte fortuite de la pénicilline par Sir Alexander Fleming en 1928 et sa commercialisation à l'aube des années 1940 (1), est souvent créditée comme un facteur d'importance contribuant à la hausse de l'espérance de vie humaine (2). De fait, le traitement d'infections bactériennes permet une réduction significative de la mortalité, les décès attribuables aux maladies infectieuses chutant de 797/100 000 en 1900 à 36/100 000 en 1980 aux États-Unis (3). Cependant, les bénéfices antibiotiques actuels sont menacés par une croissance alarmante de bactéries résistantes (2). La résistance aux antibiotiques est intimement liée à un usage inadéquat de l'arsenal thérapeutique, menant au développement de divers mécanismes tels que la dégradation enzymatique de l'anti-infectieux, l'altération des protéines cibles chez la bactérie ou bien des changements de perméabilité membranaire rendant les traitements inefficaces (4,5). Dès lors, l'Organisation mondiale de la Santé (OMS) admet la résistance aux antibiotiques comme source de préoccupation majeure pour la santé publique (6). Bien que l'éducation et la prévention demeurent des mesures importantes privilégiées par l'OMS, la prochaine section opposera quelques solutions pharmacologiques pour remédier au problème de la résistance aux antibiotiques: l'usage rationnel des traitements versus le développement de nouvelles molécules (6).

1.1.2. Des solutions pharmacologiques

L'optimisation de l'usage de traitements existants se veut une option préférable parmi les solutions envisagées pour freiner la propagation de la résistance aux antibiotiques vue sa faisabilité à court terme. De fait, l'optimisation de l'usage des antibiotiques se traduit par la sélection du bon médicament à la bonne dose. Maints paramètres sont considérés dans le choix d'un traitement idéal comme la bactérie à traiter, soit Gram positif ou négatif, sa sensibilité qui est reflétée par la concentration minimale inhibitrice (CMI), les propriétés pharmacocinétiques (PK)/pharmacodynamiques (PD) des divers antibiotiques, en plus de caractéristiques propres aux patients telles qu'une intolérance, le poids, l'âge, la fonction hépatique ou rénale et autres. Tandis que le traitement idéal dépend principalement des deux premiers éléments ci-avant, les deux derniers guident davantage le choix de la dose et la fréquence d'administration, ayant un impact important sur l'efficacité et l'innocuité. À l'opposé, le développement de traitements pharmacologiques novateurs nécessite des investissements financiers, matériels et temporels majeurs, avec des estimations de coût surpassant le milliard de dollars américains (7) de même que l'effort concerté de plusieurs scientifiques sur plus d'une décennie (8) avant la mise en marché du nouvel antibiotique. De plus, cette option est entravée par le peu d'incitatif économique pour les compagnies pharmaceutiques car les prescriptions antibiotiques sont de courte durée et sporadiques (8), le nombre restreint de cibles (la synthèse de la membrane cellulaire, des protéines ou des acides nucléiques) dû à la nature unicellulaire des bactéries (9), et la transmission de résistance (7,8).

1.1.3. Une progression redoutable

Un traitement antibiotique inefficace favorise l'émergence de mutations de même que le transfert horizontal de gènes, permettant l'échange de matériel génétique entre diverses bactéries et contribuant ainsi à la transmission de mécanismes de résistance (10). Par voie de sélection naturelle, les pathogènes sensibles sont éliminés pendant que les résistants survivent et prolifèrent, combinant parfois plusieurs mécanismes de résistance (10). Une bactérie notoire est le *Staphylococcus aureus* résistant à la méthicilline (SARM), cause de

plusieurs infections nosocomiales, spécialement au tournant du dernier siècle où 86% des cas de SARM au Canada étaient acquis en milieu hospitalier et leurs proportions parmi les infections à *Staphylococcus aureus* sont passées de 0,51% en 1995 à 1,62% en 1999 (11). Au Québec uniquement, les cas de SARM, incluant les infections et les colonisations, ont augmenté de 0,2/1000 à 4,9/1000 admissions sur la même période (11).

1.2. La vancomycine

1.2.1. Une utilisation restreinte

La vancomycine constitue un traitement de première intention contre le SARM, mais aussi d'autres bactéries à Gram positif (12,13). Il s'agit d'un glycopeptide possédant une activité bactéricide résultant de sa liaison au complexe D-Alanyl-D-Alanine du peptidoglycane qui empêche une synthèse conforme de la membrane cellulaire bactérienne (12,13). De fait, la cible au sein du peptidoglycane limite l'utilisation de la vancomycine dans le traitement de pathogènes à Gram négatif car leur membrane externe formée de bicouches lipidiques et lipopolysaccharides freine la progression de l'antibiotique (14). Une différenciation des parois cellulaires de bactéries à Gram positif ou négatif est illustrée à la **Figure 1** (15).

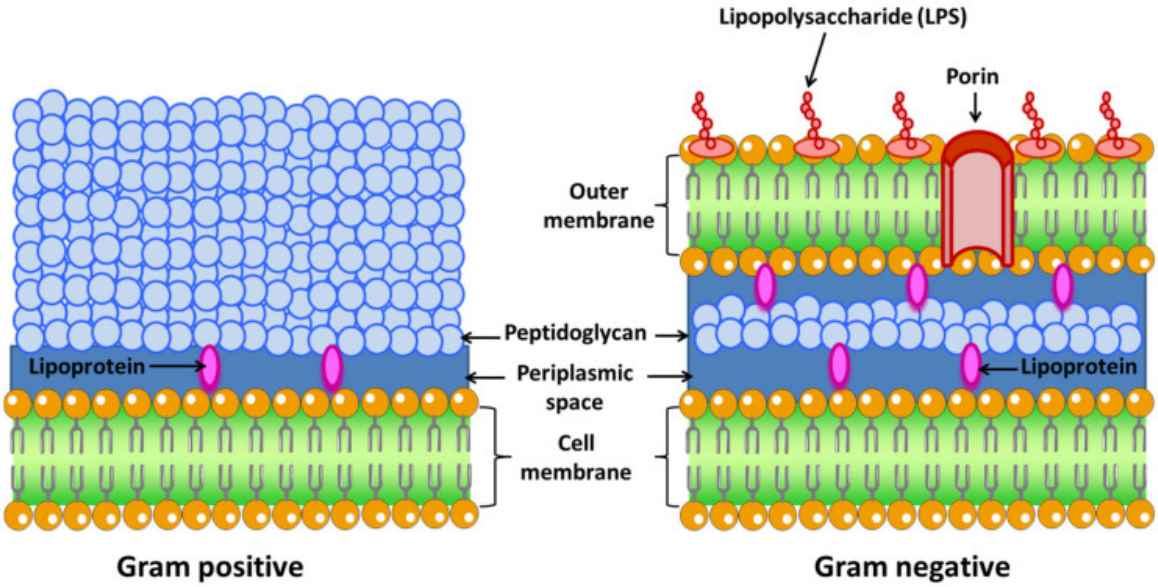

Figure 1. – Parois cellulaires bactériennes en fonction du Gram (tirée de la référence 15)

Par ailleurs, il convient de mentionner que quelques rares souches de SARM présentent dorénavant différents degrés de résistance à la vancomycine, rendant l'optimisation de son usage d'autant plus urgente (13). En dépit de son efficacité à enrayer des infections à Gram positif, la vancomycine est peu utilisée à l'extérieur du milieu hospitalier en raison de sa faible biodisponibilité, limitant son utilisation par voie orale en faveur de perfusion intraveineuse (IV), et de son profil de toxicité défavorable (12,13,16).

1.2.2. Des effets indésirables inquiétants

Les principaux effets secondaires associés à la vancomycine sont l'hypersensibilité, soit un rougissement du visage typiquement contrôlé par une perfusion sur une heure ou plus, l'ototoxicité et surtout la néphrotoxicité, pouvant résulter en une perte auditive ou même une insuffisance rénale (13,16). L'administration concomitante de médicaments affichant des profils de toxicité similaires (les aminosides) et de fortes doses sont étroitement liées à l'incidence de toxicité, bien qu'une meilleure purification de l'antibiotique ait permis de rendre son usage plus sécuritaire qu'originellement (13,16). En réalité, les proportions de néphrotoxicité attribuables à la vancomycine en monothérapie sont rapportées entre 7% et 16%, alors qu'elles atteignent jusqu'à 35% en combinaison avec un aminoside (17).

1.2.3. Le suivi thérapeutique pharmacologique

Les cliniciens se retrouvent donc dans une situation délicate puisqu'une concentration de vancomycine trop élevée augmente les risques de toxicité et qu'au contraire des niveaux sous-thérapeutiques peuvent accélérer le développement de résistance aux antibiotiques tout en étant moins susceptible de guérir l'infection (18). De plus, la vancomycine possède un index thérapeutique étroit, c'est-à-dire que la différence entre une concentration trop faible et trop élevée est mince (18). Ainsi, plusieurs cliniciens ont instauré diverses formes de suivi thérapeutique pharmacologique (STP) visant à promouvoir un traitement efficace et sécuritaire (18). Toutefois, celles-ci manquaient de consensus; les uns prétendants que deux prélèvements sanguins devaient être réalisés (19), les autres soutenants qu'un seul était suffisant (20,21) et les plus sceptiques remettant leurs pertinences en question (22).

1.3. Les premières lignes directrices

1.3.1. À la recherche d'un consensus

Le problème a été adressé en 2009 lorsqu'un comité formé de trois sociétés américaines, soit l'American Society of Health-System Pharmacists (ASHP), l'Infectious Diseases Society of America (IDSA) de même que la Society of Infectious Diseases Pharmacists (SIDP), s'est concerté en vue d'émettre les premières lignes directrices consensuelles encadrant le STP de la vancomycine chez l'adulte (23). La recommandation en émanant délaisse la mesure de la concentration au pic, réalisée juste après la perfusion IV, pour n'effectuer qu'un seul prélèvement sanguin au creux, pris juste avant la 4^{e} perfusion IV de vancomycine, suivant la stabilisation des niveaux avec l'atteinte de l'état d'équilibre (23).

1.3.2. Les cibles de creux

Les concentrations sanguines cibles varient en fonction du type d'infection (23). Dans tous les cas, elles devraient être maintenues au-dessus de 10 mg/L pour assurer l'efficacité du traitement et limiter le développement de résistance (23). Une concentration de 15 mg/L est généralement suffisante à l'atteinte d'un ratio d'aire sous la courbe pendant 24 heures (ASC_{24h})/CMI = 400 mg x h/L, quoiqu'un maximum de 20 mg/L puisse être visé dans le cas de certaines infections complexes (23). La **Figure 2** illustre bien ces cibles, avec l'intervalle thérapeutique (10 à 20 mg/L) coloré en vert et la zone sous-thérapeutique (< 10 mg/L) en orange ou toxique (> 20 mg/L) en rouge. Cette recommandation a aussi été entérinée en vue de mieux guider le traitement de quelques infections pédiatriques sévères, malgré un manque d'évidences probantes (24).

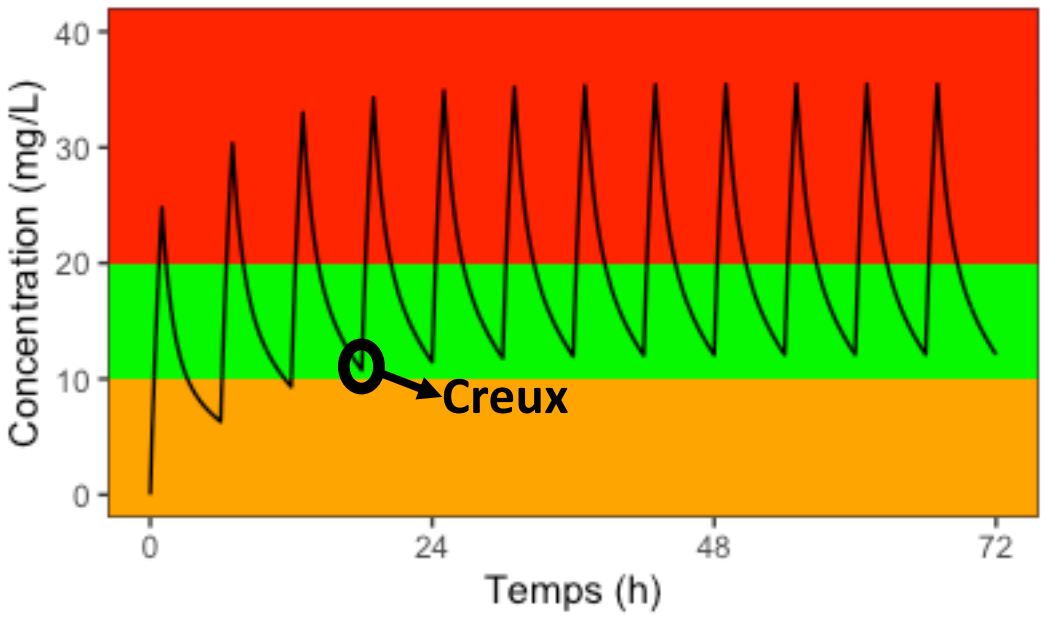

Figure 2. – Illustration des cibles thérapeutiques selon les premières lignes directrices (23)

1.3.3. Pratique, mais utile?

Il convient de mentionner ici que le creux est utilisé comme un marqueur de substitution pratique au calcul de l'ASC_{24h}, qui se veut une mesure de l'exposition à la vancomycine et constitue le paramètre PK/PD représentant le mieux l'activité de cet antibiotique temps-dépendant (23). En effet, le creux reste une valeur ponctuelle renseignant sommairement sur l'exposition réelle (25). En revanche, le calcul de l'ASC_{24h} requiert minimalement deux concentrations sanguines, préférablement un pic et un creux prélevés sur la même dose, et des équations PK de premier ordre tandis qu'un creux est une concentration aisément interprétable sans aucune expertise PK (23,25).

1.4. La pharmacocinétique (PK)

1.4.1. La concentration dans le temps

La pharmacocinétique cherche essentiellement à caractériser le devenir du médicament suivant son administration, de l'absorption (lorsque applicable) jusqu'à l'élimination (26).

Cet objectif est idéalement atteint par l'exécution de plusieurs prélèvements sanguins qui assurent un suivi des concentrations du médicament en fonction du temps, comme dans certaines études PK de phase I conduites chez des volontaires sains (27), mais pas toujours convenable en raison de contraintes éthiques évidentes (26). Pour remédier au problème, diverses approches de modélisation PK ont été introduites, entre autres la pharmacologie quantitative des systèmes, la modélisation pharmacocinétique basée sur la physiologie, ou la pharmacocinétique de population (PopPK) qui nous intéresse plus spécifiquement dans le cadre de cet ouvrage.

1.4.2. L'approche de population

La PopPK est une approche de modélisation non linéaire à effets mixtes dans laquelle les nombreuses concentrations sont issues de plusieurs patients différents, formant ainsi une population évaluée grâce à un logiciel spécialisé tel que NONMEM à titre d'exemple (26). La répartition des concentrations sur une grande quantité de sujets permet une réduction du nombre de prélèvements par patient de même que la considération des composantes de variabilités interindividuelle ou résiduelle (28). La première découle de la variation qui est observée dans la réponse au traitement propre à chaque individu alors que la seconde regroupe toutes les différences inexpliquées par le modèle, provenant d'erreurs liées aux méthodes de quantification entre autres (28). L'agrégation de ces éléments procure une courbe PK type définissant au mieux la population cible où la notion d'effets mixtes réfère d'une part aux effets aléatoires, incluant les composantes de variabilités susmentionnées, et de l'autre les fixes, comportant notamment des covariables cliniquement pertinentes intégrées au modèle en vue de minimiser la fonction objective (28,29).

1.4.3. Un traitement personnalisé

Les covariables qui ont vraisemblablement un impact clinique sur la PK du traitement sont généralement évaluées par un processus en deux étapes menant à la sélection du modèle le plus parcimonieux d'après le critère d'information d'Akaike, qui pénalise un nombre de paramètres important (28). Le modèle final inclut donc un nombre limité de covariables capables d'expliquer et ainsi de réduire la portion aléatoire de variabilité interindividuelle

(29). Néanmoins, l'avantage principal des covariables est l'individualisation des doses en fonction des caractéristiques propres aux patients, autrement dit une forme de médecine personnalisée (29).

1.4.4. Des informations précieuses

La considération de covariables cliniquement pertinentes autres que le poids pour guider le dosage cible mieux les besoins précis d'un patient particulier (29). Prenons le cas de la vancomycine en exemple, l'ajout d'une covariable au modèle qui renseigne sur la fonction rénale du patient est un grand atout sachant que sa nature hydrophile fait en sorte qu'elle soit majoritairement excrétée sous forme inchangée par les reins (13,30). En réalité, une covariable comme la clairance à la créatinine incluse dans l'équation de clairance (CL) d'un modèle PopPK de vancomycine permettrait aux cliniciens traitant des patients avec une insuffisance rénale d'effectuer un ajustement de dose informé plutôt qu'empirique (31).

1.5. La néonatalogie

1.5.1. Des populations spéciales

Maints groupes de patients, reconnus sous l'appellation de populations spéciales, doivent être traités de manière empirique en l'absence de données probantes due à leur exclusion quasi systématique d'essais cliniques randomisés contrôlés (26,32). Les patients souffrant d'insuffisances rénale ou hépatique, les femmes enceintes et les enfants en sont quelques exemples non exhaustifs, où leurs retraits s'expliquent par un impact préjudiciable sur la caractérisation du profil PK des premiers et une plus grande vulnérabilité, synonyme de considérations éthiques accrues, des derniers (32,33). Dans ce mémoire, on s'intéressa plus particulièrement à la population néonatale, un sous-groupe pédiatrique hétérogène (26,33).

1.5.2. Néonatalogie: un sous-groupe pédiatrique

En effet, la population pédiatrique est généralement décomposée en cinq sous-groupes, allant des nouveau-nés prématurés ou à terme, période couvrant environ le premier mois suivant la naissance, jusqu'aux adolescents, entre 12 et 18 ans (33). À titre de clarification, la population néonatale faisant l'objet de cet ouvrage réfère aux patients traités en unité de soins intensifs de néonatalogie, englobant aussi bien des nouveau-nés prématurés que nés à terme en plus de quelques nourrissons, tel qu'illustré à la **Figure 3** ci-après (33,34). Les naissances sont dites prématurées lorsque la période de gestation (GA) est inférieure à 37 semaines, autrement elles sont à terme (34).

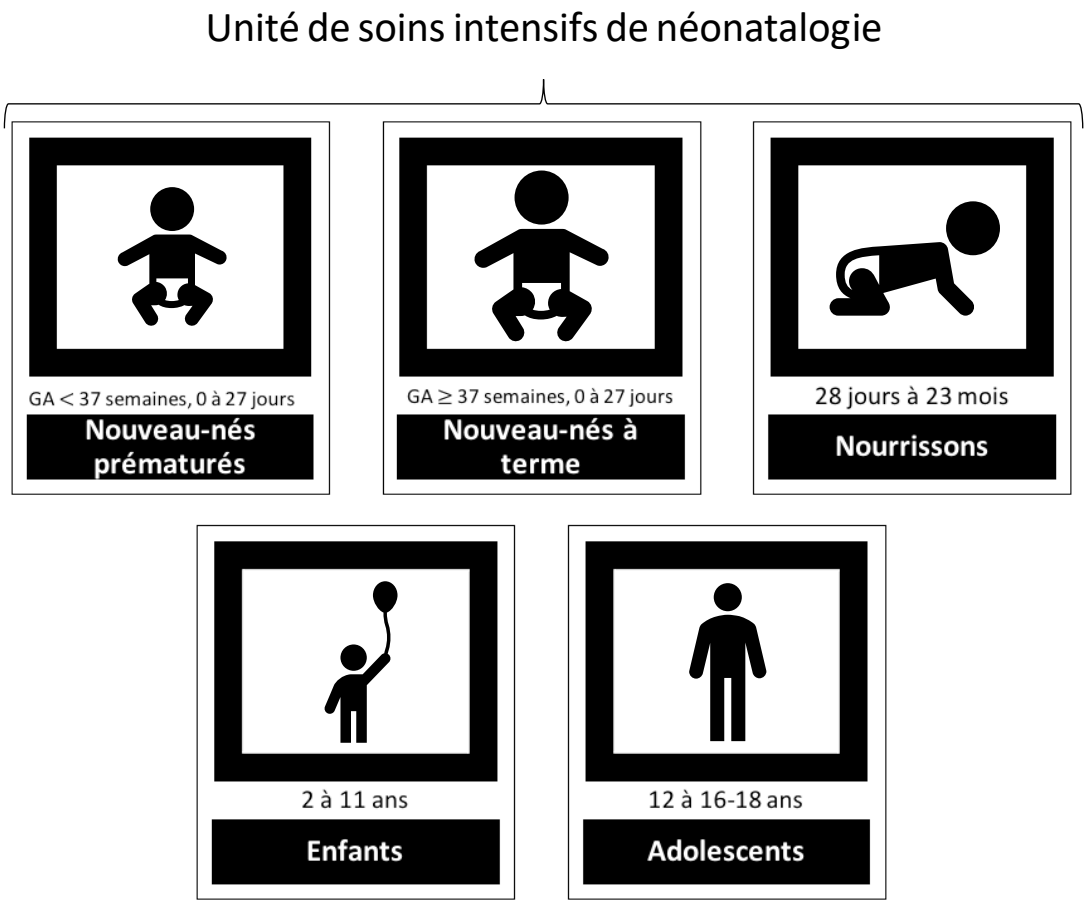

Figure 3. – Classification des sous-groupes pédiatriques en fonction de l'âge (33,34)

D'un point de vue PK, il est primordial de considérer les nouveau-nés à part en raison des processus inachevés de croissance et de maturation. Actuellement, une mise à l'échelle allométrique est appliquée, mais elle demeure insuffisante étant donnée la non-linéarité du développement (35).

1.5.3. Des impacts PK à considérer

Nous avons vu auparavant que l'élimination de la vancomycine dépend principalement de la fonction rénale (13,30), et celle-ci est encore immature à la naissance (35). La réalité est d'autant plus critique chez les nouveau-nés prématurés alors que le débit de filtration glomérulaire peut souvent atteindre des valeurs aussi faibles que 0,6-0,8 mL/min/1,73m^2, comparativement à 2-4 mL/min/1,73m^2 pour les poupons à terme ou 120 mL/min/1,73m^2 pour un adulte sain (35). Il est donc naturel que la CL de la vancomycine soit grandement réduite par rapport aux valeurs ordinairement rapportées chez l'adulte (36). D'autre part, la proportion d'eau corporelle plus élevée de même que les niveaux réduits de protéines plasmatiques facilitent une meilleure distribution de la vancomycine vue son affinité pour l'eau et la hausse de sa fraction libre, malgré des taux de liaison à l'albumine inférieurs à 50% (35,37). À l'inverse de l'impact sur la CL de la vancomycine, le volume de distribution (V_d) est donc plus élevé en néonatalogie que chez l'adulte (36). Finalement, il convient de mentionner que d'autres spécificités PK de nature pathologique pourraient bien s'ajouter à cette liste de changements physiologiques (38). D'ailleurs, une grande susceptibilité aux infections est observable chez les nouveau-nés en raison de l'immaturité de leur système immunitaire (39).

1.5.4. Un outil d'aide à la décision

Les particularités physiologiques inhérentes à la population néonatale suffisent à modifier le profil PK d'un médicament comme la vancomycine, d'autant qu'une grande variabilité est observable au sein même de ce sous-groupe pédiatrique singulier (36). Tel que discuté précédemment dans la section **1.4.3**, l'ajout de covariables comme la créatinine sérique (SCr) ou l'âge post-menstruel (PMA), par une équation de Hill informant sur la maturation rénale, permet d'expliquer une portion de variabilité et personnaliser le traitement selon

les besoins spécifiques des nouveau-nés (40). Au final, ces différences PK se reflètent sur tous les paramètres de STP, que ce soit des concentrations sanguines prélevées au creux ou des mesures d'exposition comme l'ASC_{24h}.

1.6. Une révision des lignes directrices

1.6.1. Utile, mais pratique?

Environ une décennie après l'adoption des premières lignes directrices, l'accumulation de nouvelles preuves discréditant l'utilisation du creux comme marqueur de substitution et critiquant des cibles (15 à 20 mg/L pour infections sévères) trop élevées potentialisant les risques de néphrotoxicité ont poussé les sociétés susmentionnées, la Pediatric Infectious Diseases Society (PIDS) en outre, à modifier leur recommandation (25,41). Effectivement, la vancomycine dispose d'une grande variabilité interindividuelle, de sorte qu'une même valeur de creux peut résulter en un large éventail d'ASC_{24h}, comme on peut le constater à la **Figure 4** où le coefficient de détermination (R^2) entre les paramètres de STP est de ,409 uniquement suite à des simulations de Monte-Carlo (25).

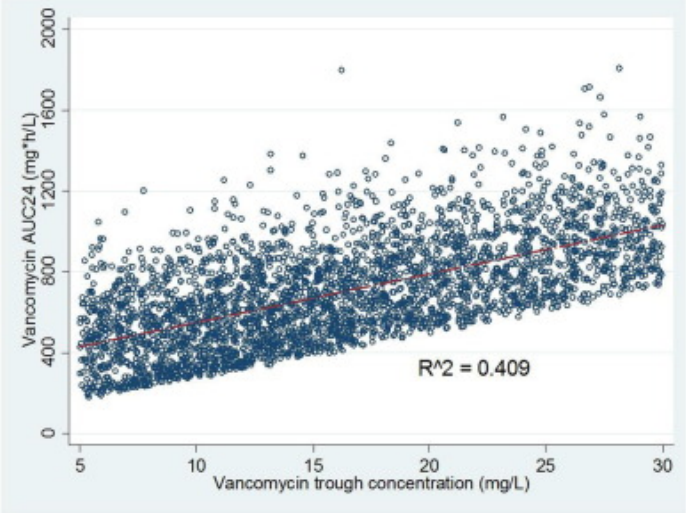

Figure 4. – Comparaison des valeurs d'ASC_{24h} en fonction du creux (tirée de la référence 25)

Un résultat similaire (R^2 = ,5317) soutient aussi cette idée en pédiatrie, tel qu'illustré à la **Figure 5** (42).

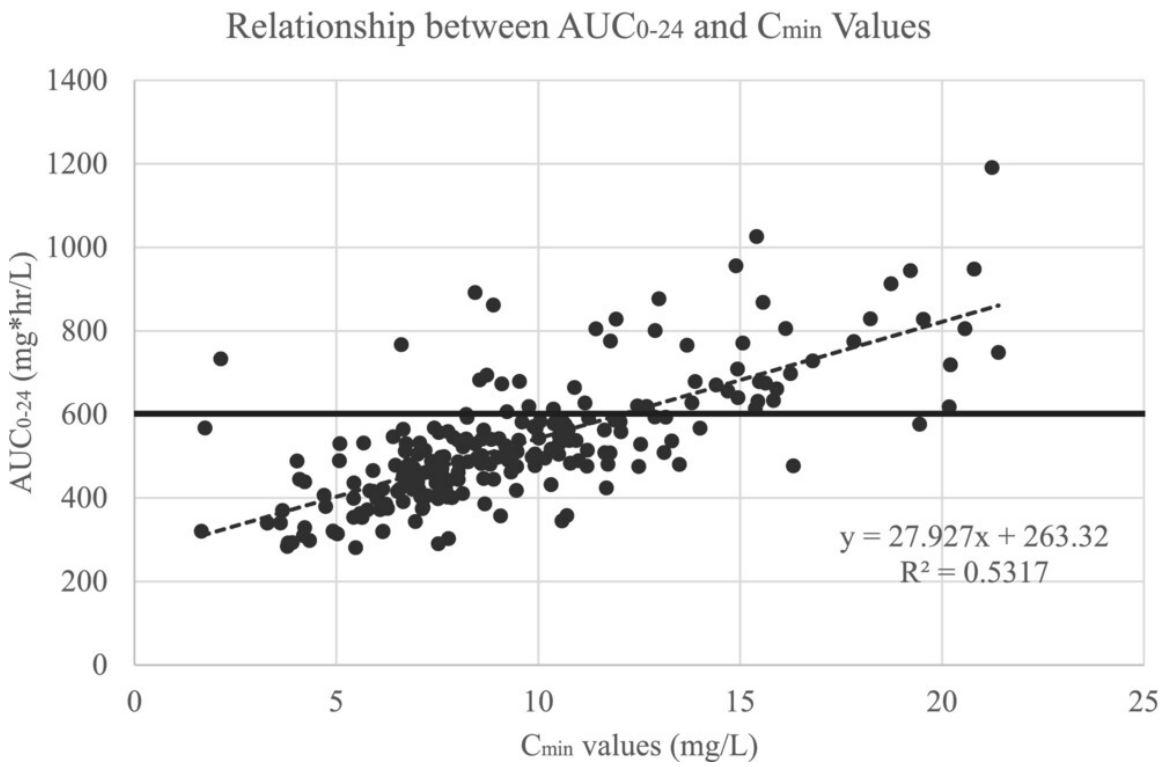

Figure 5. – Comparaison des valeurs d'ASC_{24h} en fonction du creux (tirée de la référence 42)

Désormais, le STP de la vancomycine repose donc sur l'ASC_{24h}/CMI (assumant une CMI = 1 d'après la microdilution en bouillon), cependant sa mise en application ne requiert plus forcément deux dosages grâce aux récentes avancées dans les approches de modélisation PK (25,41). Bien qu'un seul prélèvement soit réalisable, il faut tout de même préciser que l'obtention de deux concentrations sanguines est préférable étant donné le manque de preuves appuyant un tel design de STP (41).

1.6.2. Les cibles d'ASC_{24h}/CMI

Le seuil d'efficacité précédemment rapporté demeure inchangé à 400 mg x h/L, toutefois les seuils de toxicité apparaissent variables selon la population (41). En effet, des valeurs d'ASC_{24h} au-delà de 600 mg x h/L sont à éviter chez l'adulte alors qu'en pédiatrie celles-ci peuvent atteindre jusqu'à 800 mg x h/L, les enfants étant typiquement moins enclins à la néphrotoxicité associée à la vancomycine (41). La **Figure 6** représente l'ASC_{24h} entre 24 et 48 heures. À noter que les cibles sont indépendantes de la façon dont l'ASC_{24h} est calculée, que ce soit à l'aide d'équations PK de premier ordre ou d'un modèle PopPK combiné avec une approche bayésienne.

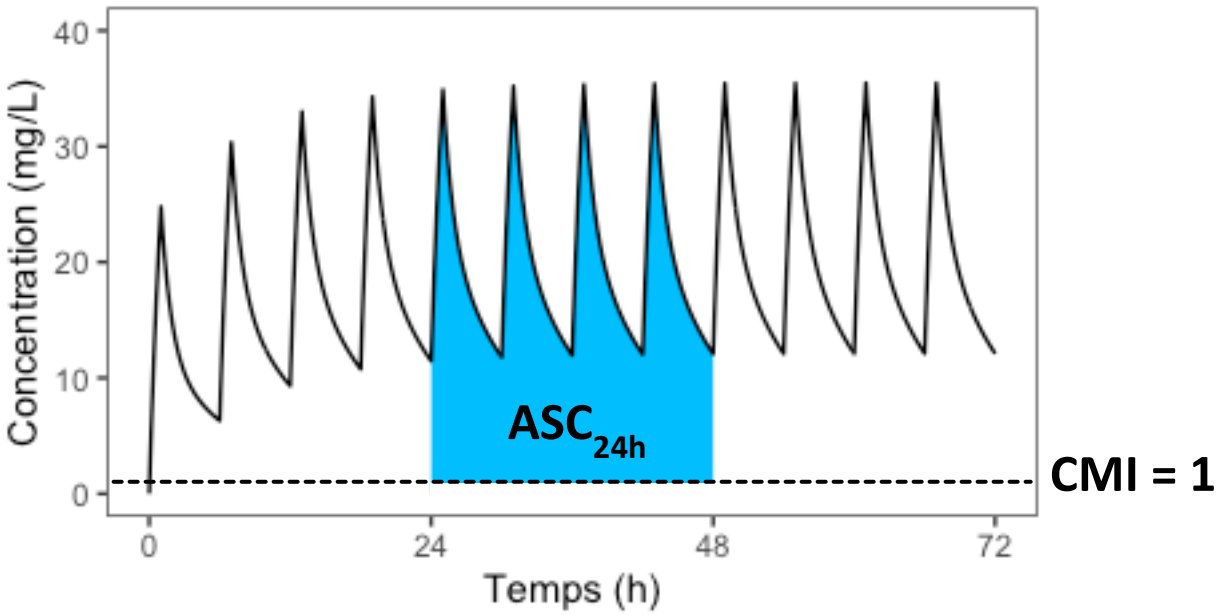

Figure 6. – Illustration de l'aire sous la courbe (ASC_{24h}) à l'aide du profil PK de la **Figure 2**

1.6.3. Plusieurs voies mènent à l'ASC_{24h}

Bien que les équations de premier ordre PK restent une option envisageable, l'application d'une approche bayésienne guidée par un modèle PopPK prédictif est préférable, car elle laisse présager une potentielle baisse du nombre de prélèvements sanguins (25,41). Dans

le cas des équations PK, les concentrations mesurées servent en premier lieu à calculer la constante d'élimination (k_{el}) grâce à l'**Équation 1** suivante:

$$\textbf{Équation 1. –}\ k_{el} = \frac{\ln\left(\frac{C1}{C2}\right)}{t}$$

où C_1 représente une concentration aux alentours du pic, idem pour C_2 au creux alors que t correspond au temps écoulé entre les deux prélèvements (25). On peut ensuite estimer l'aire sous la courbe à l'aide de l'**Équation 2** ci-dessous:

$$\textbf{Équation 2. –}\ ASC = \frac{(C_{pic} + C_{creux}) \times durée\ perfusion}{2} + \frac{C_{pic} - C_{creux}}{k_{el}}$$

où C_{pic} désigne une concentration extrapolée à la fin de la perfusion IV, qui diffère souvent de la concentration au pic mesurée en clinique, et C_{creux} représente la concentration juste avant la prochaine perfusion IV, pouvant potentiellement être extrapolée aussi au besoin (25). À noter que la valeur d'ASC résultante doit finalement être ajustée pour une période de 24 heures en fonction de l'intervalle d'administration, de sorte qu'un facteur de trois doit être appliqué dans le cas de perfusion aux 8 heures, par exemple (25). Cette méthode tend à sous-estimer légèrement l'ASC_{24h}, tel qu'illustré à la Figure 4 de l'article référencé, mais nous l'avons préférée à son analogue surestimant l'exposition (25). Dans l'autre cas, les modèles PopPK évalués grâce à NONMEM procureront les valeurs les plus plausibles des paramètres PK, comme la CL et le V_d pour un modèle à un compartiment, pour chacun des patients en fonction de leurs caractéristiques uniques (25). Enfin, le calcul de l'ASC_{24h} est plus simple avec l'approche bayésienne puisqu'il suffit de diviser la dose quotidienne administrée par la valeur de clairance prédite à l'aide des modèles PopPK (28).

1.6.4. Des avantages bayésiens attrayants

Outre la réduction potentielle des prélèvements sanguins, notablement souhaitable dans certaines populations vulnérables à l'instar des nouveau-nés, l'approche bayésienne offre plusieurs autres avantages par rapport aux équations PK standards (41,43). En fait, l'usage d'un modèle PopPK augmente la flexibilité du STP, permettant l'intégration de covariables cliniquement pertinentes et reflétant leurs changements sur les paramètres PK résultants ainsi que l'affranchissement de l'état d'équilibre contribuant à un ajustement plus rapide

des doses au besoin (25,41,43). Le modèle PopPK représente donc la probabilité a priori, se basant sur des observations antérieures, tandis que toutes les données additionnelles fournies au modèle constituent la probabilité a posteriori (41,43). En effet, le modèle tend à améliorer ses prédictions grâce aux nouvelles valeurs spécifiques au patient pour mieux personnaliser le traitement (41,43). Toutefois, il est primordial de s'assurer que le modèle PopPK soit prédictif au préalable, une population comparable et un échantillonnage riche étant souvent des qualités recherchées, afin d'en bénéficier puisqu'il incarne la fondation même sur laquelle l'ensemble des estimations sont basées (41,43).

1.7. Le projet de recherche

1.7.1. L'évaluation externe opportune

L'évaluation externe des modèles PopPK représente une approche de choix informant sur leurs transférabilités vers d'autres groupes de patients, testant la performance prédictive d'un modèle développé dans une population différente sur une population d'intérêt (44). Malgré leur pertinence, les évaluations externes ne sont que trop rarement réalisées lors du développement de nouveaux modèles PopPK (44). Pourtant, une simple identification de modèles robustes applicables à divers groupes de patients comparables pourrait éviter une surcharge de la littérature et devrait donc être la première étape lorsque la situation si prête (44,45). L'évaluation externe s'effectue généralement en deux parties distinctes, diagnostiquant la performance prédictive grâce au calcul de l'erreur de prédiction (EP) en premier lieu et une analyse graphique basée sur des simulations par la suite (44). Le calcul d'EP est présenté ci-dessous par l'**Équation 3**, la différence relative entre la concentration prédite (C_{pred}) à l'aide du modèle et celle réellement observée (C_{obs}) en clinique.

Équation 3. – $$\boldsymbol{EP}(\%) = \frac{(\boldsymbol{C_{pred} - C_{obs}})}{\boldsymbol{C_{obs}}} \times \mathbf{100}\%$$

Un biais (médiane EP) $\leq \pm 15\%$, une imprécision (médiane |EP|) $\leq 30\%$ et des valeurs de F_{20}/F_{30}, représentant le pourcentage des EP incluses entre $\pm 20/30\%$ respectivement, sont les critères d'acceptabilité préétablis que les modèles se doivent de respecter pour passer

aux analyses graphiques (46). Les graphiques *goodness-of-fit* comparent les C_{pred} aux C_{obs} ou les concentrations prédites au niveau individuel (C_{ipred}) aux C_{obs} tandis que les *Visual Predictive Check* (VPC) et *Normalized Prediction Distribution Errors* (NPDE) joignent des valeurs simulées à l'aide du modèle aux C_{obs}, permettant de corroborer l'adéquation d'un modèle dans la population d'intérêt (44). En prévision d'une intégration de la pratique de STP proposée au sein des dernières lignes directrices (41), la vancomycine représente une excellente candidate à l'évaluation externe considérant l'abondance de modèles PopPK développés dans des populations néonatales et leurs similitudes à l'égard des covariables, intégrant régulièrement le poids, la PMA et la SCr (45,47,48) dans l'équation de CL. Plus d'une trentaine de modèles PopPK néonataux de vancomycine ont déjà été développés à ce jour (45,47,48); on émet donc l'hypothèse qu'au moins l'un d'entre eux devrait avoir une performance prédictive adéquate dans notre population québécoise.

1.7.2. Les objectifs du projet

Cette étude rétrospective observationnelle multicentrique est menée dans les principaux centres de soins mère-enfant de la province de Québec: le Centre hospitalier universitaire Sainte-Justine (CHUSJ) et le Centre mère-enfant Soleil du Centre hospitalier universitaire de Québec-Université Laval (CMES). L'objectif primaire du projet est d'évaluer en externe les modèles PopPK de vancomycine pour spécifier leurs performances prédictives à l'aide de la méthode définie dans la section **1.7.1**. Les modèles ayant la meilleure performance prédictive, à savoir des valeurs de biais et d'imprécision près de 0%, synonyme de valeurs de C_{pred} quasi identiques à C_{obs}, de F_{20}/F_{30} aussi élevées que possibles, minimisant les EP de fortes amplitudes, et des graphiques satisfaisants ont été retenus pour les simulations de Monte-Carlo. À partir d'une population néonatale simulée d'après les caractéristiques spécifiques de celles du CHUSJ et CMES (49), on a évalué de nombreux régimes de doses initiales de vancomycine visant à optimiser l'atteinte des cibles thérapeutiques, aussi bien celles de creux (23) que d'ASC_{24h} (41) compte tenu des doutes subsistants quant aux cibles thérapeutiques idéales en pédiatrie (42,50,51). Ultimement, un nouveau régime de doses initiales reposant sur les simulations effectuées à l'aide du modèle PopPK le plus prédictif

a été proposé, possédant la plus grande proportion d'atteinte des cibles thérapeutiques en autant que les proportions au-dessus des seuils de toxicité demeurent raisonnables.

Chapitre 2 - Optimization of vancomycin initial dosing regimen in neonates using an externally evaluated population pharmacokinetic model

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Ce premier article a été publié le 6 juin 2024 dans le journal Therapeutic Drug Monitoring (10.1097/FTD.0000000000001226). L'objectif primaire est l'évaluation de modèles PopPK dans une population externe du CHUSJ menant au développement d'un nomogramme de doses initiales tandis que l'objectif secondaire est l'établissement d'une corrélation entre les paramètres de STP de la vancomycine et les issues cliniques d'efficacité et de toxicité. Ma contribution sur ce manuscrit s'étend de la collecte des données des patients formant la base de données externe jusqu'à l'écriture du manuscrit, en passant par l'ensemble des analyses statistiques et PK. Pour ce qui est des coauteurs, Marie-Élaine Métras et Amélie Marsot ont conçu l'étude, de concert avec Isabelle Viel-Thériault et Julie Autmizguine qui n'ont pu réviser cet article et qui ne sont donc pas coauteures sur celui-ci, tout en assurant la supervision du projet. Mehdi El Hassani a effectué les simulations de Monte-Carlo, puis j'ai analysé les fichiers résultants. Aysenur Yaliniz a réalisé une revue de littérature initiale en janvier 2022, que j'ai moi-même mise à jour en septembre 2023. Veuillez noter que du matériel supplémentaire a été ajouté selon l'ordre de présentation après les références.

2.1. Abstract

Background

Vancomycin therapeutic monitoring guidelines were revised in March 2020, and a population pharmacokinetics-guided Bayesian approach to estimate the 24-hour area under the concentration-time curve to the minimum inhibitory concentration ratio has since been recommended instead of trough concentrations. To comply with these latest guidelines, we evaluated published population pharmacokinetic models of vancomycin using an external dataset of neonatal patients and selected the most predictive model to develop a new initial dosing regimen.

Methods

The models were identified from the literature and tested using a retrospective dataset of Canadian neonates. Their predictive performance was assessed using prediction- and simulation-based diagnostics. Monte Carlo simulations were performed to develop the initial dosing regimen with the highest probability of therapeutic target attainment.

Results

A total of 144 vancomycin concentrations were derived from 63 neonates in the external population. Five of the 28 models retained for evaluation were found predictive with a bias of $\leq \pm 15\%$ and an imprecision of $\leq 30\%$. Overall, the Grimsley and Thomson model performed best, with a bias of -0.8% and an imprecision of 20.9%; therefore, it was applied in the simulations. A novel initial dosing regimen of 15 mg/kg followed by 11 mg/kg every 8 hours should favor therapeutic target attainment.

Conclusions

A predictive population pharmacokinetic model of vancomycin was identified after an external evaluation and used to recommend a novel initial dosing regimen. The

implementation of these model-based tools may guide physicians in selecting the most appropriate initial vancomycin dose, leading to improved clinical outcomes.

Keywords

Vancomycin, neonatology, therapeutic drug monitoring, external evaluation, and population pharmacokinetic

2.2. Introduction

Vancomycin is a glycopeptide antibiotic possessing a bactericidal activity against Gram-positive germs such as methicillin-resistant *Staphylococcus aureus* (MRSA), for which it is indicated as a first-line treatment.[1] Despite abundant literature and clinical use spanning over half a century,[2] vancomycin optimal dosage remains a challenge because of its narrow therapeutic index coupled with high interindividual pharmacokinetic (PK) variability.[3] This variability is amplified in newborns because of their rapid growth and ongoing maturation.[4] For example, renal maturation is incomplete in most preterm neonates,[4] thereby reducing vancomycin clearance (CL) because it is primarily excreted unchanged in urine.[5] Other physiological peculiarities include a higher percentage of body water and lower albumin concentrations, affecting the volume of distribution (V_d) and CL of vancomycin.[4] All these newborn-specific PK changes exclude any pathological considerations that could further increase variability.[6] Therapeutic drug monitoring (TDM) has become a standard clinical practice given the risks of toxicity on one side or lack of effectiveness and greater susceptibility to antibiotic resistance on the other, linked to supratherapeutic or subtherapeutic vancomycin concentrations, respectively.[7] During the data collection period, TDM procedures established at the pediatric hospital of interest referred to the first consensus guidelines published by a committee acting on behalf of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists, which suggested

that vancomycin monitoring should be done by sampling trough concentrations at steady-state.[7]

In the meantime, sufficient evidence has accumulated over the past decade to encourage the aforementioned committee, together with the Pediatric Infectious Diseases Society, to issue an updated version of their guidelines in an effort to minimize vancomycin-related nephrotoxicity, also known as acute kidney injury (AKI).[8] Incidentally, it marked the first time a guideline was emitted for pediatric patients despite relatively scarce data and such uncertainty about clinical outcomes that the therapeutic target is assumed to be the same as adults in the absence of more conclusive information.[8] Of note, trough concentration target between 10 and 20 mg/L, depending on infection severity, was initially used as a suitable surrogate for the 24-hour area under the concentration-time curve (AUC_{24h}) target of 400-600 mg x h/L over minimum inhibitory concentration (MIC assumed to be $\leq$ 1 mg/L), which is commonly recognized as the best predictor of vancomycin therapeutic activity.[7-9] To clinically implement these revised guidelines, the recommendation favored the use of an AUC-guided Bayesian approach based on population pharmacokinetic (PopPK) models that are able to estimate AUC_{24h} faster and with limited sampling[8]; nevertheless, a suitable model must be chosen carefully to ensure reliable predictions.[10]

Fortunately, a considerable number of vancomycin PopPK models have already been described in neonatology and identified through literature reviews.[3,11,12] We hypothesized that one model might prove useful in accurately predicting the PK profiles of our external population without the need to develop any additional model,[3] especially because weight, serum creatinine (SCr), and postmenstrual age (PMA) were recurring covariates. Hence, we assessed the predictive performance of these PopPK models to propose a new initial vancomycin dosing regimen for neonates based on the best-performing model, which could also provide a valuable option for model-informed precision dosing to guide physicians in clinical settings. Second, effectiveness and toxicity

were compared using the AUC_{24h} or vancomycin trough concentrations in our external dataset.

2.3. Materials and Methods

2.3.1. Literature Review and Model Selection

Identification of admissible vancomycin PopPK models was facilitated by recent literature reviews up to August 17, 2020[3,11,12] and then extended to September 2023 using the terms “vancomycin AND pharmacokinetic” OR “vancomycin AND pharmacokinetic AND population” OR “vancomycin AND pharmacokinetic AND model(ling)” OR “vancomycin AND pharmacokinetic AND nonlinear mixed effect model” OR “vancomycin AND pharmacokinetic AND (NONMEM OR WinNonMix OR ADAPT OR P-PHARM OR NLMIXED)” in the PubMed database search strategy. Their reference lists were examined to identify as many PopPK models as possible. Models were included if (1) a PopPK approach was applied to vancomycin, (2) the model was developed in a neonatal population consisting of preterm or term newborns or young infants, or (3) the publication was written in English. Conversely, studies were excluded if (1) any of the incorporated covariates were not documented in the hospital’s clinical routine, (2) the model could not be fully transcribed for evaluation, or (3) it used a modeling strategy other than the nonlinear mixed-effects method, such as noncompartmental and nonparametric approaches.

2.3.2. Patients

This retrospective observational study was conducted at the Centre Hospitalier Universitaire Sainte-Justine (CHUSJ) in accordance with the Declaration of Helsinki. The research protocol was approved by the Institutional (2021-3329 CHUSJ) and Academic (CERC-21-033-R UdeM) Ethics Committees. Eligible patients were recruited from the pharmacy’s electronic database if they met the following inclusion criteria: neonates (including preterm and term newborns or young infants in the neonatal intensive care

unit) treated with intravenous vancomycin for more than 48 hours between January 1, 2019, and December 31, 2020. Each treatment was considered individually when a patient had multiple occurrences. In addition, the 48-hour threshold was intended to exclude patients receiving empiric vancomycin therapy because trough sample collection is typically not performed in these cases.[13] In fact, the absence of measured vancomycin concentrations or other significant covariates along with noncomputerized medical records were listed as exclusion criteria; none concerning pathogens because they are often unknown at the start of antibiotic therapy. In the event of missing continuous data, values were imputed using the last observation carried forward (LOCF) method, taking into account biological and physiological plausibilities.

2.3.3. Data Collection

After patient recruitment, all the following relevant information was extracted from patient's clinical records: birth date/weight, gestational age (GA), sex, admission date/diagnosis, current weight and SCr levels throughout treatment, date/time/dose/duration of vancomycin infusion, date/time of blood collection together with the measured concentration, concurrent administration of additional antibiotics, or recognized nephrotoxins. A complete list of the nephrotoxins can be found in **Supplemental Digital Content - Table S1**. A few models included drugs as covariates, so exposure to dopamine[14] and spironolactone[15] was also recorded; amoxicillin/clavulanate,[15] ceftriaxone,[16] amikacin, and nonselective cyclooxygenase (NCOX) inhibitors[17-19] were already accounted for within the list mentioned above of concurrent treatments. A further 2[17,20] had a small-for-gestational age (SGA) covariate, in which newborns were categorized according to their birth weight using the referenced European table.[21] Postnatal age (PNA) was calculated as the difference between the date of treatment and birth, whereas PMA was the sum of PNA and GA. Newborns were considered premature if born before 37 weeks of gestation.[22]

2.3.4. Effectiveness and Toxicity Outcomes

Changes in SCr levels were monitored throughout vancomycin treatment to assess toxicity; AKI was defined as a 50% increase from its baseline value in accordance with the KDIGO guideline.[23] In contrast, treatment was determined to be effective when vancomycin was discontinued after a negative blood culture without being substituted for comparable antibiotics (ie, linezolid and daptomycin) or reinitiated within 48 hours of treatment completion.

2.3.5. Vancomycin and Bioanalytical Methods

Vancomycin was administered intravenously over a 60-minute infusion. The neonatal dosage regimen currently used at CHUSJ recommends a loading dose of 15 mg/kg, preceding maintenance doses of 10 mg/kg, with administration intervals of 6, 8, and 12 hours, depending on PMA and PNA.[13,24] The initial dosing nomogram is divided into 6 subgroups, which are detailed in **Supplemental Digital Content - Table S2.** Vancomycin samples were collected before the fourth administration, and blood concentrations were measured using a chemiluminescent microparticle immunoassay on an ARCHITECT iVancomycin (Abbott Core Laboratory, Abbott Park, IL). SCr levels were analyzed only at the physician's request using the Jaffe method on an ARCHITECT c8000 (Abbott Core Laboratory). The respective lower limit of quantification (LLOQ) for blood levels of vancomycin and SCr was 3 mg/L and 8 µmol/L. Finally, the infectious pathogens were identified by microbiologists, and their MICs were determined using the E-test for MRSA.

2.3.6. External Evaluation

Models of interest were transcribed for evaluation using NONMEM software (Version 7.5; ICON Development Solutions, Ellicott City, MD). Applying MAXEVAL=0 to the $ESTIMATION record yields Bayesian estimates with parameter values (THETA) and variabilities (OMEGA and SIGMA) identical to those found in the original articles. The external CHUSJ dataset was then applied to test each model individually, and NONMEM

predicted vancomycin concentrations any time a trough was recorded. The predictive performance of the PopPK models was first assessed using prediction-based diagnostics, and only the best models were retained for simulation-based diagnostics.

2.3.6.1. Prediction-Based Diagnostics

The relative prediction error (PE%/IPE%) was calculated for each combination of population/individual predictions (C_{pred}/C_{ipred}) and corresponding observed vancomycin concentrations (C_{obs}) using the following equations:

$$\boldsymbol{PE}(\%) = \frac{\left(\boldsymbol{C_{pred}} - \boldsymbol{C_{obs}}\right)}{\boldsymbol{C_{obs}}} \times \mathbf{100}\%$$

$$\boldsymbol{IPE}(\%) = \frac{\left(\boldsymbol{C_{ipred}} - \boldsymbol{C_{obs}}\right)}{\boldsymbol{C_{obs}}} \times \mathbf{100}\%$$

The median value (MDPE) and median absolute value (MDAPE) of the PE% were considered to indicate the bias and imprecision of the PopPK models, respectively. The PE% distribution was further assessed using the percentage of values included between $\pm$20% (F_{20}) and $\pm$30% (F_{30}). To be suitable on a population basis and be a candidate for a priori dosing, a model needed to have at least an MDPE $\leq \pm$15%, MDAPE $\leq$30%, values of F_{20} >35%, and F_{30} >50%.[25] Whenever a model was found appropriate, goodness-of-fit plots allowed a visual comparison between observed and predicted concentrations.

2.3.6.2. Simulation-Based Diagnostics

Prediction-corrected visual predictive check (pcVPC) and normalized prediction distribution errors (NPDE) were plotted solely for adequate models, using R (Version 4.1.1; https://www.r-project.org/) with the vpc and npde packages, respectively. Both simulation-based diagnostics were performed after 1000 simulations of the dataset. The prediction confidence intervals were set at 90% for pcVPC. The NPDE should follow a normal distribution with a mean of 0 and variance of 1.[26]

2.3.7. Monte Carlo Simulations

Only the best-performing model was retained for Monte Carlo simulations. From the current initial dosing nomogram, various combinations of loading doses from 15 to 20 mg/kg, along with maintenance doses from 10 to 15 mg/kg, all in 1 mg/kg increments and over a 60-minute infusion, at administration intervals of 6, 8, and 12 hours, were tested on more than 1000 simulated patients. The proportion of patients in each subgroup and their characteristics were based on our external dataset. Simulated concentrations below the LLOQ of 3 mg/L were imputed at 1.5 mg/L. The AUC_{24h} was calculated on the second day (ie, 24-48 hours) as the ratio of total daily dose (mg) to model individual-predicted clearance (L/h) and with the first-order equation underpredicting AUC_{24h} formulated by **Pai et *al.***,[27] requiring at least a peak and a trough sample to determine the elimination rate constant, as a practicable alternative.[27] The regimen leading to the highest percentage of AUC_{24h} values between 400 and 600 mg x h/L with a limited number exceeding 600 mg x h/L was selected.

2.3.8. Statistical Analysis

Descriptive statistical analyses were carried out on R to determine mean $\pm$ SD and median [interquartile range (IQR)] or (range), before comparing neonatal population characteristics of all PopPK models to those of our external CHUSJ database by 2-sided tests with a significance level set at 5%. For continuous data, the Shapiro-Wilk test was conducted to assess the normality of the distribution. If the characteristics were found to be normally distributed, values were compared using Student *t* test; otherwise, the Mann-Whitney *U* test was performed. Likewise, the effectiveness and toxicity outcomes of the AUC_{24h} and trough concentrations were compared. Categorical variables were analyzed using the χ^2 test.

2.4. Results

2.4.1. Review of Published PopPK Models

Forty-seven vancomycin PopPK models were identified, but just 28 were retained for evaluation.[14-20,28-48] The remaining 19 were removed because of the inclusion of undocumented covariates such as cystatin C,[47] use of positive pressure artificial ventilation and inotropes/vasoactive agents (besides dopamine), [49,50] length/creatinine clearance,[51-53] volume of infusion,[54] urine output,[55] and race[56] along with incomplete information or nonparametric modeling approaches.[57-66] Of the models assessed, 20[14,15,17-20,28-41] (71.4%) were discovered in previous literature reviews,[3,11,12] whereas 8[16,42-48] (28.6%) were subsequently added. **Supplemental Digital Content - Table S3** provides a summary of all the neonatal vancomycin PopPK models tested. These mainly were developed on Asian[16,20,29,34,35,39,40,42,44,46,48] (39.3%) or European[15,17-19,30,32,33,38,41,47] (35.7%) newborns, 5[14,18,19,28,44] (17.9%) had a 2-compartment structure, 5[14,15,33,34,39] were assessed with the default first-order estimation method, systematically applying the POSTHOC option to provide individual-specific estimates,[67] and only 3[37,42,45] (10.7%) used Monolix or Pumas rather than NONMEM. Some frequently observed covariates were weight (92.9%, 2 included birth weight instead[18,19]), SCr (67.9%), PMA (57.1%, up to 75.0% if PNA is also taken into account[18,19,28,39,41]) on CL and weight (96.4%) on V_d; typical values ranged from 0.023 to 0.273 L/h/kg and 0.29 to 1.38 L/kg, respectively.

2.4.2. External Neonatal Population

CHUSJ external population included 63 patients (77 treatment episodes) in whom 144 vancomycin concentrations, mainly through (94.4%), were quantified with a median (IQR) of 12.6 (9.0-15.9) mg/L. The median GA was only 27 weeks, which is consistent with the fact that 50 neonates (79.4%) were born prematurely; however, only 13 neonates (20.6%) were SGA. The main characteristics of the CHUSJ external population are summarized in **Table 1**. After performing the Shapiro-Wilk test, it was determined that continuous

covariates were not normally distributed. Comparisons were made using the Mann-Whitney *U* test.

2.4.3. External Evaluation

The predictive performance varied considerably among the models. Bias and imprecision on a population and individual basis, along with the F_{20} and F_{30} values, are reported in **Table 2** for all PopPK models. Those published by **Capparelli et *al.***,[28] **Chen et *al.***,[29] **Chung and Seto**,[43] **Germovsek et *al.***,[32] and **Grimsley and Thomson**[33] were deemed adequate because of their ability to predict vancomycin concentrations in the external dataset accurately; their biases and imprecisions ranging from -6.9 to 8.5% and 20.9 to 28.2%, respectively. Nonetheless, **Grimsley and Thomson**[33] outperformed the others with a bias of -0.8%, an imprecision of 20.9%, 49.3% of F_{20} and 63.2% of F_{30}. The characteristics of their populations were compared with those of CHUSJ in **Table 1**. Newborns from the **Grimsley and Thomson**[33] model were comparable, as evidenced by the absence of statistical differences. Interestingly, some statistically significant differences were found within the populations of the other suitable models, although this did not prevent them from achieving satisfactory predictive performance. A comparison of the population characteristics for the 23 inadequate PopPK models is also available in **Supplemental Digital Content - Table S4**. For the predictive models, goodness-of-fit, pcVPC, and NPDE graphs were plotted in **Figure 1**; overall, variability in the data was adequately predicted.

Table 1. – Characteristics of CHUSJ External Neonatal Population Compared With Those of Adequate Models

Characteristics (Units)	**Type of value**	**CHUSJ**	**Capparelli et *al.*[28]**	**Chen et *al.*[29]**	**Chung and Seto[43]**	**Germovsek et *al.*[32]**	**Grimsley and Thomson[33]**
Number of patients (M/F)	Numbers	63 (37/26)	374 (172/202)†	213 (NA)	442 (259/183)†	54 (NA)	59 (38/21)†
Gestational age (weeks)	Mean ± SD	29.4 ± 5.6	33.5 ± 6.0**	NA	NA	NA	NA
	Median (IQR) or [range]	27 [22-41]	33.5 (28-40)**	36.9 [25-42]**	28.43 (25.29-34.86)	29.0 [23.7-41.9]	29 [25-41]
Postnatal age (days)	Mean ± SD	27.2 ± 25.5	70 ± 100**	NA	NA	NA	NA
	Median (IQR) or [range]	18.7 [2.9-137.8]	27 (15-74)	26 [6-59]	21.00 (9.00-41.49)	30 [1-156]*	19 [2-76]
Postmenstrual age (weeks)	Mean ± SD	33.2 ± 6.5	NA	NA	NA	NA	NA
	Median (IQR) or [range]	31.9 [25.0-50.6]	NA	39.8 [28-47.9]**	34.35 (30.17-38.54)	NA	32 [26-45]
Weight (kg)	Mean ± SD	2.0 ± 1.2	2.82 ± 2.33**	NA	NA	NA	NA
	Median (IQR) or [range]	1.5 [0.7-4.7]	2.00 (1.04-3.60)	2.73 [0.88-5.10]**	1.73 (1.02-2.50)	NA	1.52 [0.57-4.23]

Table 1. – (Cont.)

Birth weight (kg)	Mean ± SD	1.5 ± 1.0	NA	NA	NA	NA	NA
	Median (IQR) or [range]	0.9 [0.5-4.2]	NA	2.53 [0.70-4.70]**	1.04 (0.73-2.15)	NA	NA
Serum creatinine (µmol/L)	Mean ± SD	49.2 ± 15.2	NA	NA	NA	NA	NA
	Median (IQR) or [range]	45.3 [29.6-92.3]	NA	NA	29.00 (21.00-43.00)**	31 [18-98]**	49 [18-172]
Serum creatinine (mg/dL)	Mean ± SD	0.6 ± 0.2	0.7 ± 0.5**	NA	NA	NA	NA
	Median (IQR) or [range]	0.5 [0.3-1.0]	0.6 (0.4-0.9)*	0.28 [0.11-0.72]**	NA	NA	NA
Number of blood samples	Number	144	1103	330	666	183†	347

*$P < 0.05$; **$P < 0.001$ - †Values derived from available information found in the original publication - NA: Not Applicable

Table 2. – Predictive Performance of Assessed Neonatal PopPK Models of Vancomycin

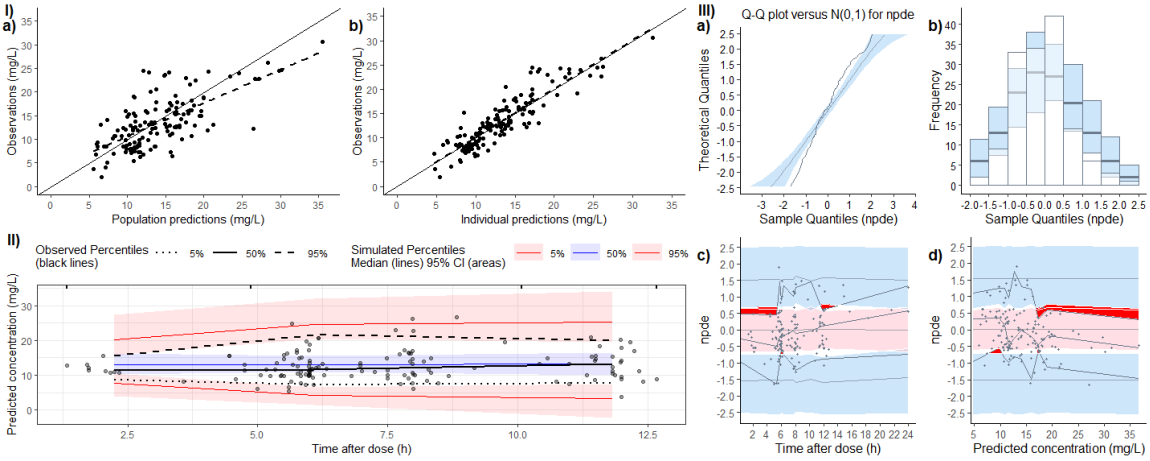
Original publication	Population level				Individual level	
	Bias (%)	Imprecision (%)	F_{20} (%)	F_{30} (%)	Bias (%)	Imprecision (%)
Allegaert et *al.*[17]	-22.7	29.5	35.4	50.0	0.0	2.2
Alsultan et *al.*[42]	24.0	32.1	32.6	47.2	-1.5	14.6
Capparelli et *al.*[28]	**8.5**	**22.9**	**43.1**	**61.1**	**-0.7**	**12.2**
Chen et *al.*[29]	**5.3**	**27.7**	**36.1**	**55.6**	**-1.0**	**11.5**
Chung and Seto[43]	**-6.9**	**22.1**	**45.1**	**66.7**	**-1.8**	**14.4**
Cristea et *al.*[18]	13.5	29.8	31.9	50.7	-3.8	12.8
Dao et *al.*[30]	107.2	107.2	7.6	9.7	34.7	34.7
De Cock et *al.*[19]	1.0	30.9	34.7	49.3	-4.3	12.9
Frymoyer et *al.*[31]	-25.5	29.8	34.0	50.7	-7.3	16.4
Germovsek et *al.*[32]	**6.6**	**28.2**	**40.3**	**54.9**	**-2.2**	**11.3**
Grimsley and Thomson[33]	**-0.8**	**20.9**	**49.3**	**63.2**	**0.4**	**14.7**
Hui et *al.*[44]	58.9	58.9	18.1	27.8	12.6	15.6
Jarugula et *al.*[45]	29.6	29.6	30.6	50.0	18.2	21.4
Jung et *al.*[46]	19.3	31.9	34.0	47.9	0.2	3.3
Kimura et *al.*[34]	47.0	47.0	22.9	33.3	13.8	17.3

Table 2. – (Cont.)

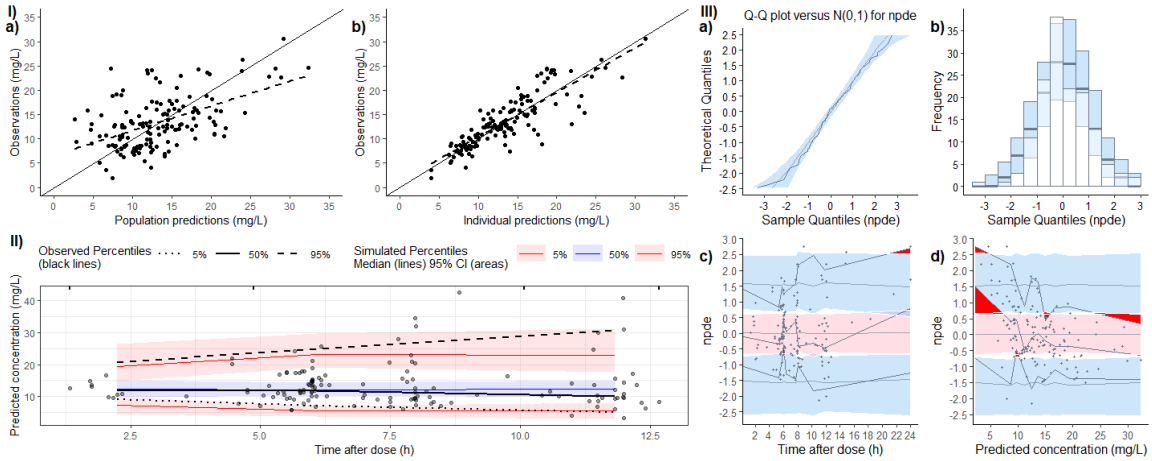
Leroux et *al.*[47]	-32.2	35.0	26.4	41.7	-10.3	15.3
Li et *al.*[16]	-21.6	28.5	34.0	51.4	-13.3	17.1
Li et *al.*[35]	34.6	39.9	21.5	33.3	-0.3	16.5
Lo et *al.*[20]	74.2	74.2	14.6	21.5	7.4	14.5
Marqués-Miñana et *al.*[15]	18.7	33.9	31.9	43.8	0.1	6.3
Mehrotra et *al.*[36]	36.0	36.0	30.6	41.7	7.5	13.6
Mulubwa et *al.*[37]	6.2	47.3	19.4	31.3	-5.2	30.5
Oudin et *al.*[38]	19.5	28.3	38.2	52.8	7.3	13.5
Sasano et *al.*[48]	114.5	114.5	8.3	11.8	7.1	18.8
Seay et *al.*[14,*]	49.5	53.3	18.4	28.4	5.9	10.6
Sheng et *al.*[39]	-46.2	47.7	15.3	26.4	-14.5	24.8
Tseng et *al.*[40]	120.5	120.5	8.3	11.1	10.7	15.9
Zhao et *al.*[41]	35.9	38.5	26.4	39.6	7.0	14.3

Suitable models are highlighted in bold - *1 patient (3 concentrations) was excluded to obtain individual-specific estimates

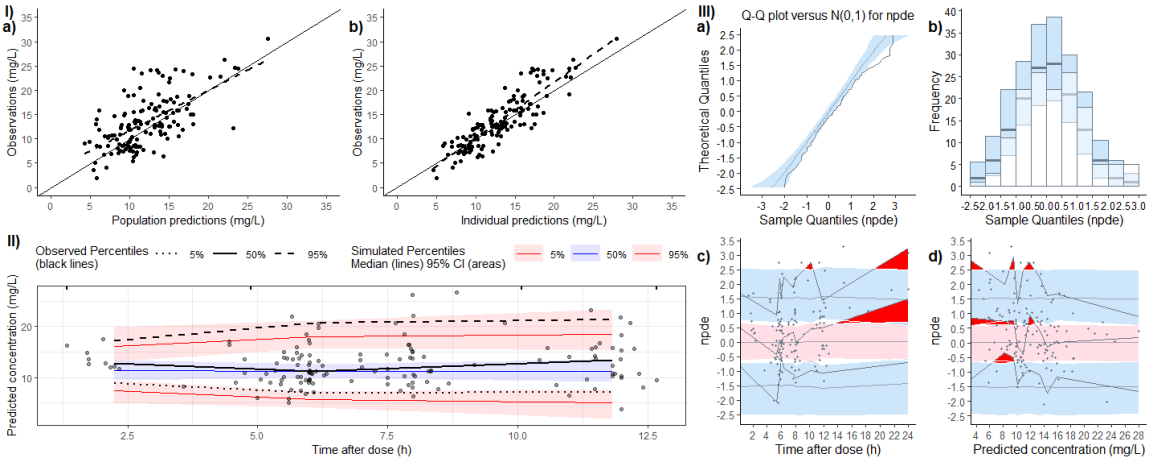
1) Capparelli et *al.*[28]



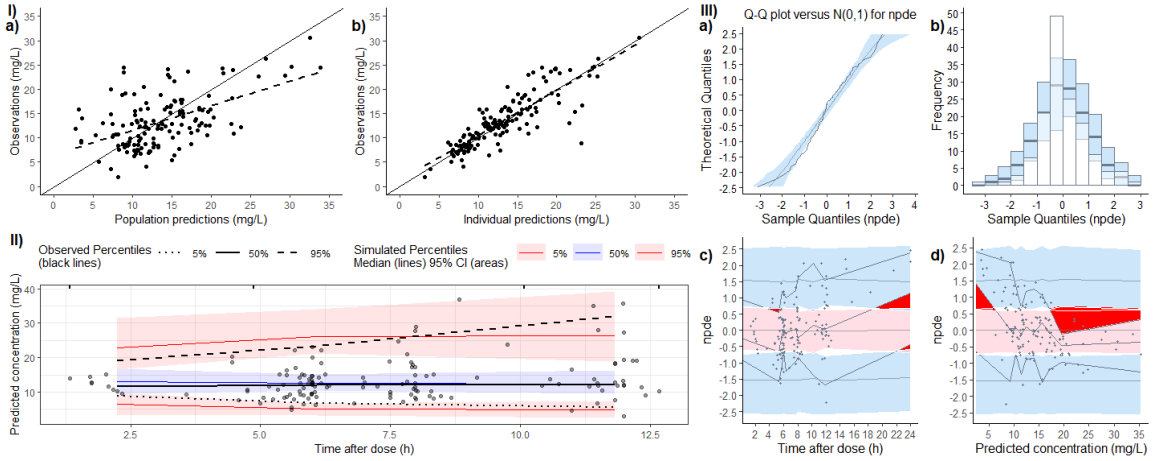
2) Chen et *al.*[29]



3) Chung and Seto[43]



4) Germovsek et *al.*[32]



5) Grimsley and Thomson[33]

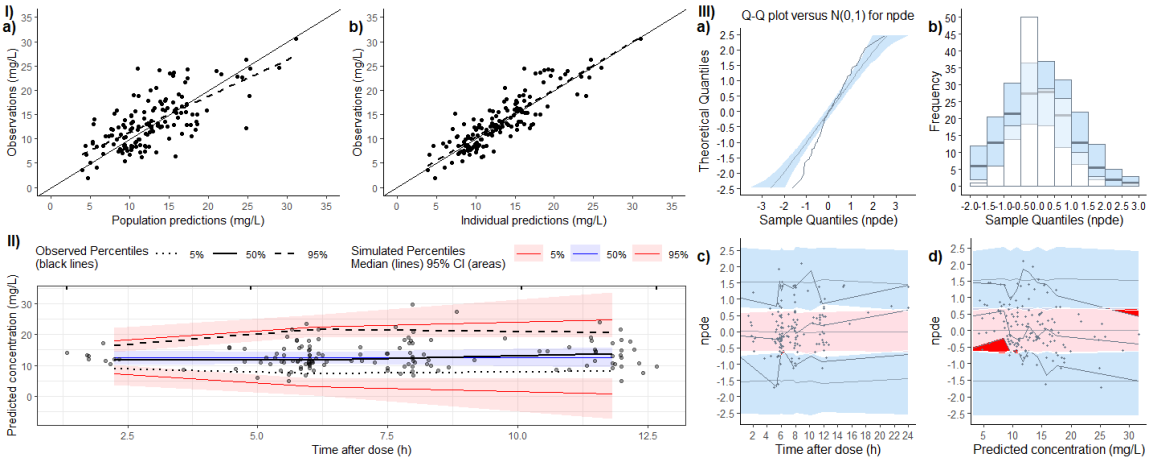


Figure 1. – (I) Goodness-of-fit plots: observations versus **(a)** population and **(b)** individual predictions - identity function is represented as a solid line and trend as a dashed line. **(II)** pcVPC - values beyond 13 hours after dose (n = 7) were outside the regular administration protocol and therefore truncated. **(III)** NPDE **- (a)** Q-Q plot of NPDE, **(b)** Histogram of NPDE, **(c)** NPDE versus time after dose, **(d)** NPDE versus predicted concentration. All plots include simulated percentiles presented as colored areas (blue for 2.5th and 97.5th, pink for the median). The corresponding percentiles of the observed data are shown as black lines. Red shaded areas indicate deviations of the observed percentiles from the simulated percentiles

2.4.4. Monte Carlo Simulations

Monte Carlo simulations were performed using the **Grimsley and Thomson**[33] model which demonstrated the best overall predictive performance. First, the achievement of therapeutic targets was assessed globally before each subgroup of the nomogram was examined individually. Throughout the latter evaluation, it became apparent that the optimal interval between doses was 8 hours, regardless of PMA and PNA. **Table 3** compares the probability of target attainment with the current nomogram to that of the novel initial dosing regimen, which advocates a loading dose of 15 mg/kg followed by maintenance doses of 11 mg/kg every 8 hours for patients treated in the CHUSJ neonatal intensive care unit. The application of this regimen resulted in similar median values, namely Bayesian AUC_{24h} of 456.1 mg x h/L and trough of 12.3 mg/L, although they were more consistent among all 6 subgroups. In addition, both methods used to estimate the AUC_{24h} were found to be comparable; the equation of **Pai et *al.***[27] provided slightly lower values, as expected. A more aggressive maintenance dose of 12 mg/kg increases the risk of toxicity. A comparison of maintenance doses of 11 and 12 mg/kg using the 2 methods of AUC_{24h} estimation can be found in **Supplemental Digital Content - Table S5**.

Table 3. – Current Versus Novel Initial Dosing Nomogram Based on **Grimsley and Thomson**[33] Model

Current Initial Dosing Nomogram (L = 15 mg/kg, M = 10 mg/kg)*	Trough = 10-20	Trough >20	Median (IQR) Trough (mg/L)	AUC_{24h} = 400-600	AUC_{24h} >600	Median (IQR) AUC_{24h} (mg x h/L)
PMA $<$ 30, PNA $\leq$ 14 (q12h)†	20.1	0.0	5.5 (1.2-9.1)	6.7	0.0	277.0 (238.4-327.6)
PMA $<$ 30, PNA $>$ 14 (q8h)†	48.1	6.9	11.3 (7.3-15.3)	48.9	3.1	405.5 (349.1-477.9)
30 $\leq$ PMA $\leq$ 36, PNA $\leq$ 14 (q8h)†	45.9	11.1	11.3 (7.5-15.5)	49.3	9.7	420.0 (359.9-494.4)
30 $\leq$ PMA $\leq$ 36, PNA $>$ 14 (q6h)†	51.3	30.1	15.7 (11.0-21.2)	46.5	40.8	563.0 (465.0-682.5)
PMA $\geq$ 37, PNA $\leq$ 7 (q8h)†	53.5	2.3	10.2 (7.7-14.5)	48.8	9.3	408.4 (378.5-500.2)
PMA $\geq$ 37, PNA $>$ 7 (q6h)†	52.4	27.2	15.8 (11.2-20.8)	50.0	35.6	546.9 (447.5-656.8)
Total (n = 1309)‡	44.8	17.6	12.5 (7.5-18.0)	40.9	22.3	456.3 (346.0-580.2)

Table 3. – (Cont.)

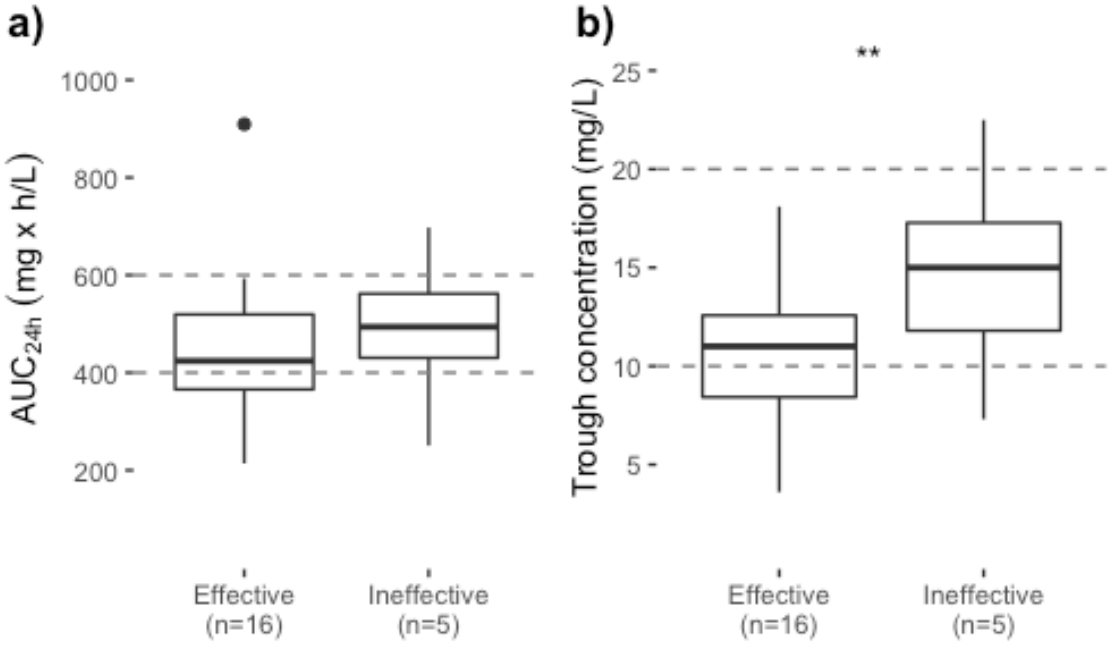
Novel Initial Dosing Nomogram (L = 15 mg/kg, M = 11 mg/kg)*	Trough = 10-20	Trough > 20	Median (IQR) Trough (mg/L)	AUC_{24h} = 400-600	AUC_{24h} > 600	Median (IQR) AUC_{24h} (mg x h/L)
PMA $<$ 30, PNA $\leq$ 14 (q8h)†	48.1	10.5	11.0 (7.5-16.0)	53.2	13.5	452.7 (383.7-543.3)
PMA $<$ 30, PNA $>$ 14 (q8h)†	52.2	10.4	12.3 (8.4-16.4)	60.4	8.2	445.0 (379.2-524.0)
30 $\leq$ PMA $\leq$ 36, PNA $\leq$ 14 (q8h)†	54.2	12.6	12.6 (8.6-16.7)	56.5	16.4	458.8 (388.8-541.7)
30 $\leq$ PMA $\leq$ 36, PNA $>$ 14 (q8h)†	52.0	11.5	12.2 (7.8-17.1)	53.5	17.6	466.0 (386.4-563.7)
PMA $\geq$ 37, PNA $\leq$ (q8h)†	57.8	8.9	12.2 (8.6-16.1)	60.0	17.8	445.8 (401.8-540.9)
PMA $\geq$ 37, PNA $>$ 7 (q8h)†	51.9	14.3	12.9 (8.6-17.2)	52.9	16.7	455.6 (372.5-548.8)
Total (n = 1389)‡	51.8	12.1	12.3 (8.2-16.9)	54.6	15.6	456.1 (383.7-544.1)

Values are reported as a percentage (%) unless specified otherwise; *L = Loading dose; M = Maintenance dose; †PMA is expressed in weeks and PNA in days (administration interval); ‡Simulated patients were removed whenever trough > peak concentration.

2.4.5. Effectiveness and toxicity outcomes

The AUC_{24h} and trough concentration values are shown in **Figure 2** with respect to their effectiveness and toxicity outcomes**.** Unsurprisingly, neonates experiencing AKI generally had higher vancomycin exposure; differences in AUC_{24h} and trough concentrations were both statistically significant. Only 5 newborns (7.9%) were likely to develop AKI because of the elevation of their SCr levels over the course of therapy. Vancomycin concentrations sampled near the time of AKI detection were notably high (range of 12.9-24.5 mg/L), with a single measurement below 20 mg/L. A summary of these patients is available in **Supplemental Digital Content - Table S6**. In contrast, two-thirds of the effectiveness outcomes could not be ascertained, leaving only 21 patients, among whom the majority (76.2%) received effective vancomycin treatment.

1) Effectiveness



2) Toxicity

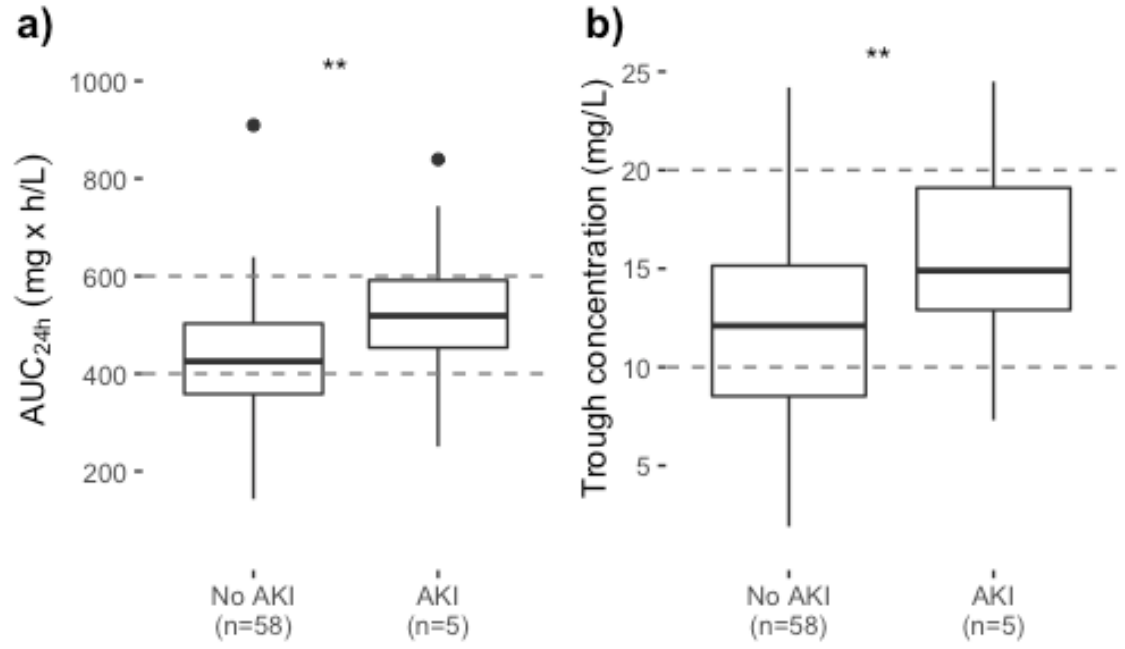


Figure 2. – Boxplots of effectiveness **(1)** and toxicity **(2)** outcomes relative to **(a)** AUC_{24h} or **(b)** trough concentration - **P < 0.05; **P < 0.01* - Dashed lines represent lower and upper limits of therapeutic target

2.5. Discussion

PopPK models are purposely designed to fit the PK profile of a specific population, meaning that their use is more often than not limited to the hospital in which they were developed.[68] However, their transferability can be investigated through external evaluation with the application of datasets from different centers. This could likely be the first step leading to the clinical implementation of an AUC-guided Bayesian approach for vancomycin TDM, especially given the abundance of the literature.[3,69] Indeed, 28 neonatal PopPK models, mainly defined by 3 recurring covariates (weight, SCr, and PMA), were evaluated externally.

The acceptability thresholds applied to the predictive performance metrics were relatively consistent among external evaluation studies of vancomycin PopPK models. Most of them used MDPE $\leq \pm 20\%$, MDAPE $\leq 30\%$, $F_{20} \geq 35\%$ and $F_{30} \geq 50\%$ as criteria for satisfactory performance.[70,71] Regardless, we opted for a slightly stricter cutoff with MDPE $\leq \pm 15\%$,[25] a decision motivated by the (1) large number of models available for evaluation already identified[3,11,12] and (2) intended clinical use of adequate models, which aims to advise physicians caring for vulnerable neonatal patients. Interestingly, one more model would have been accepted had we chosen the most common thresholds,[38] although this was unlikely to outperform any of the 5 models that moved forward to simulation-based diagnostics.[28,29,32,33,43]

Grimsley and Thomson[33] was the most reliable model for predicting blood vancomycin concentrations in neonates of the CHUSJ. A previous study suggested that the SCr assay could affect predictive performance[68]; this model also applies the Jaffe method. Moreover, the characteristics of its neonatal population were most similar to those of the CHUSJ, which undoubtedly played a favorable role in its acceptance. It has a relatively simple, although uncommon, structure with a weight-to-SCr ratio expressed as a predictor of CL. The equations for CL and V_d in this model[33] are defined as follows:

$$\boldsymbol{CL\ (L/h) = 3.56 \times \frac{Weight\ (kg)}{Serum\ creatinine\ (\mu mol/L)}}$$

$$\boldsymbol{V_d\ (L) = 0.669 \times Weight\ (kg)}$$

However, it did not include PMA as a covariate in comparison with most PopPK models.[15,17,20,29-32,34,36,40,42-47]

The retrospective study design led to inherent complications, particularly during data collection. We implemented missing values using the LOCF method because it seemed to be the most intuitive.[72] This decision may have affected the predictive performance of specific models. For instance, the best-performing PopPK model in the CHUSJ population had a weight-to-SCr ratio that estimated vancomycin CL.[33] Unfortunately, these covariates were not necessarily recorded daily, although they were continually required to evaluate the models properly. The fact that SCr levels were assessed solely at the physician's request could explain some of the missing values. In reality, they are usually available within 1 or 2 days, and the differences between the last observation and the next observation are always checked to confirm biological and physiological plausibilities. However, fluctuations in SCr levels may be less predictable and may be more critical than weight fluctuations. In addition, it is challenging to draw clear conclusions regarding the effectiveness of vancomycin treatment.

Therefore, the effectiveness outcomes will not be discussed extensively because of the limited sample size. As for toxicity, similarly low rates of AKI have already been reported in the neonatal literature.[73] In addition to higher trough concentrations, the likelihood of AKI was further enhanced by concurrent administration of nephrotoxins.[74,75] Three CHUSJ patients received either piperacillin-tazobactam (66.6%) or furosemide (33.3%), whereas the patient with the lowest vancomycin concentration was administered both plus sulfamethoxazole-trimethoprim. Notably, AKI was the main factor cited for guideline revision and was a precursor to the transition of vancomycin TDM from trough concentration to AUC_{24h}. Fortunately, PopPK-generated Bayesian estimates have already been determined to be reliable even if only trough concentrations are measured,[76,77]

which is ideal, bearing in mind the previously established clinical practice.[7] Also, AUC_{24h} estimated by Bayesian methods and equation[27] provided similar values in Monte Carlo simulations, suggesting that limited sampling might be possible in neonates.

The novel initial dosage regimen resulted in AUC_{24h} and trough concentration values similar to those reported in **Figure 2** for patients receiving effective and safe vancomycin treatment. It ideally aligns with the latest recommendations as well, aiming to target an AUC_{24h} closer to 400 than 600 mg x h/L.[8] Our regimen achieved therapeutic target a little over 50% of the time, better than most results obtained in the literature.[78] Furthermore, a standardized dosage regimen essentially simplifies the current nomogram. All subgroups responded comparably, with percentages of target attainment ranging from 52.9% to 60.4%. Although the majority of modern dosage nomograms adhere to this structure, this is not the first time a standardized regimen has been advocated for neonates. Indeed, **de Hoog et *al.***[59] suggested a similar administration scheme in 2000; the lower dose of 10 mg/kg every 8 hours was consistent with the lower therapeutic target (trough of 5–15 mg/L) at that time. More recently, **Mulubwa et *al.***[37] proposed a 12 mg/kg every 8 hours regimen, which was found to be riskier than the 11 mg/kg for a slightly higher target attainment in our simulations.

The initial dosage regimen was based on a target AUC_{24h} of 400-600 mg x h/L to improve treatment outcomes for severe MRSA infections, even if it was primarily derived from data in adults, meaning its applicability to neonates warrants further studies.[8,79] In fact, vancomycin was intended to treat MRSA for only 2 (3.2%) patients in the external dataset, both of whom had a MIC of 2 mg/L. Such values are likely attributable to the method of MIC determination, as the E-test was used instead of broth microdilution.[8,80] Also, infections caused by coagulase-negative staphylococci (CoNS), like *Staphylococcus epidermidis* (36.5%), were significantly more prevalent in CHUSJ neonatal intensive care unit as attested in **Supplemental Digital Content - Table S7**, which is in accordance with most observations reported in the literature.[81-83] A lower AUC_{24h}/MIC target may well

apply for CoNS because their MIC tends to be higher than that of MRSA.[24,84] Besides, the advantages of AUC_{24h} over trough concentration for vancomycin TDM might be questioned in neonatal patients. Indeed, a recent retrospective study found that trough concentrations showed better predictive accuracy than AUC_{24h}, the latter offering little insight into treatment outcomes past the first dose assessment.[85] Others endorsed similar conclusions, adding that attainment of a trough target between 10 and 15 mg/L within the first 24 hours of treatment was a crucial component promoting therapeutic success.[86] Until more evidence is available regarding the therapeutic exposure or concentration of vancomycin in neonatal populations, the novel initial dosage regimen should be used with caution and judgment. Nevertheless, we provide a standard method that can be replicated using more suitable targets in the future.

Some limitations are discussed above, namely the (1) retrospective nature of this study: removal of certain PopPK models, impact on data quality, limited sample size on effectiveness outcomes, or (2) uncertainty regarding the ideal therapeutic target of vancomycin in neonatology: lack of pediatric studies, higher prevalence of CoNS infections versus MRSA, and benefits of AUC_{24h} over trough concentration. In addition, the impact of maternal SCr levels in younger newborns should be evaluated to ensure that the **Grimsley and Thomson**[33] model remains sufficiently predictable, considering its CL equation. Finally, **De Cock et *al.***[19] contributed 2 models: the vancomycin model using the amikacin covariate model was assessed as **Cristea et *al.***[18] from a subsequent study for distinction purposes, whereas the independent reference model of vancomycin remained **De Cock et *al.*** [19] These populations overlapped with **Allegaert et *al.*** [17] We acknowledge that they all mostly originated from the same neonatal population but still evaluated them as distinct models as they presented some differences; their predictive performance was comparable, although insufficient. Likewise for **Leroux et *al.***, [47] but one had to be excluded because cystatin C levels were not available in the CHUSJ clinical records. Therefore, only the SCr model was assessed as **Leroux et *al.***[47]

2.6. Conclusion

We successfully evaluated a vancomycin PopPK model and used it to advocate a simpler initial dosing regimen for CHUSJ neonates. Clinical implementation of an AUC-guided Bayesian approach is expected to reduce the time needed to reach a therapeutic target, mitigate the risks of experiencing nephrotoxicity, and limit the number of blood samples required to monitor vancomycin exposure versus PK equations involving a minimum of 2 concentrations.[8] Nonetheless, there are still conflicting data to support the benefits of this paradigm shift in newborns. Thus, future studies should address the differences in the prognostic power of the AUC_{24h} and trough concentrations to propose a suitable therapeutic target for this special population to ensure effective and safe treatment.

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2.8. Supplemental Digital Content

Table 1. – Concurrent nephrotoxins of interest

Categories	Drugs/Classes (example when applicable)
Antimicrobials	Antiviral agents (valacyclovir), Aminoglycosides (tobramycin), Amphotericin B, Colistin, Sulfamethoxazole-Trimethoprim and Piperacillin-Tazobactam
Chemotherapies	Platinum-based drugs (cisplatin), Ifosfamide, Mitomycin, Gemcitabine, Methotrexate, Interleukin-12 in high doses and Antiangiogenic agents (bevacizumab)
Immunosuppressants	Cyclosporine, Tacrolimus and Sirolimus/everolimus
Analgesics	**NSAIDs** (naproxen) and Selective COX-2 inhibitors (celecoxib)
Others	**ACEIs** (enalapril), **ARBs** (valsartan), Diuretics (furosemide) and IV bisphosphonates (zoledronic acid)

NSAIDs = Nonsteroidal anti-inflammatory drugs - **ACEIs** = Angiotensin converting enzyme inhibitors - **ARBs** = Angiotensin II receptor blockers

Table 2. – Current initial dosing nomogram in neonatology at CHUSJ

Postmenstrual age (PMA)	Postnatal age (PNA)	Administration interval
$<$ 30 weeks	$\leq$ 14 days	12 hours
	$>$ 14 days	8 hours
30 to 36 weeks	$\leq$ 14 days	8 hours
	$>$ 14 days	6 hours
$\geq$ 37 weeks	$\leq$ 7 days	8 hours
	$>$ 7 days	6 hours

Table 3. – Summary description of assessed neonatal PopPK models of vancomycin

Original publication	Model description					PK parameters	
	Number of compartments	Study design	Software	Estimation methods	Sampling	CL (L/h/kg)	V_d (L/kg)
Allegaert et *al.*[17]	1	Retrospective	NONMEM	FOCE	Peak and trough	0.023	0.56
Alsutan et *al.*[42]	1	Retrospective	Monolix	SAEM	Peak and trough	0.097	0.87
Capparelli et *al.*[28]	2	NA	NONMEM	FOCE	Peak, trough, random	0.066	0.79
Chen et *al.*[29]	1	Retrospective	NONMEM	FOCE-I	Peak and trough	0.103	0.58
Chung and Seto[43]	1	Retrospective	NONMEM	FOCE-I	Peak, trough, random	0.088	0.93
Cristea et *al.*[18,19]	2	NA	NONMEM	FOCE-I	Peak, trough, random	0.053	0.91
Dao et *al.*[30]	1	Retrospective	NONMEM	FOCE-I	Peak, trough, random	0.273	0.63
De Cock et *al.*[19]	2	NA	NONMEM	FOCE-I	Peak, trough, random	0.038	0.62
Frymoyer et *al.*[31]	1	Retrospective	NONMEM	FOCE-I	Peak, trough, random	0.095	0.60
Germovsek et *al.*[32]	1	Prospective	NONMEM	FOCE-I	Peak, trough, random	0.081	0.56
Grimsley and Thomson[33]	1	Prospective	NONMEM	FO/POSTHOC	Peak and trough	0.073	0.67
Hui et *al.*[44]	2	Retrospective	NONMEM	FOCE-I	NA	0.082	0.45
Jarugula et *al.*[45]	1	Retrospective	Pumas	FOCE	NA	0.068	0.85
Jung et *al.*[46]	1	Retrospective	NONMEM	FOCE-I	Peak and trough	0.049	0.73
Kimura et *al.*[34]	1	NA	NONMEM	FO/POSTHOC	Peak and trough	0.076	0.66

Table S3. – (Cont.)

Leroux et *al.*[47]	1	NA	NONMEM	FOCE-I	Continuous infusion	0.068	0.29
Li et *al.*[16]	1	NA	NONMEM	FOCE-I	Peak and trough	0.147	0.72
Li et *al.*[35]	1	Retrospective	NONMEM	FOCE-I	Peak and trough	0.107	0.91
Lo et *al.*[20]	1	Retrospective	NONMEM	FOCE-I	NA	0.043	0.52
Marqués-Miñana et *al.*[15]	1	NA	NONMEM	FO/POSTHOC	Peak and trough	0.066	0.57
Mehrotra et *al.*[36]	1	Retrospective	NONMEM	FOCE	Peak and trough	0.072	0.68
Mulubwa et *al.*[37]	1	NA	Monolix	SAEM	Trough	0.069	0.60
Oudin et *al.*[38]	1	Prospective	NONMEM	FOCE	Continuous infusion	1.173[a]	0.86
Sasano et *al.*[48]	1	NA	NONMEM	FOCE-I	Trough	0.063	0.93
Seay et *al.*[14]	2	Retrospective	NONMEM	FO/POSTHOC	Peak and trough	0.059	0.44
Sheng et *al.*[39]	1	Retrospective	NONMEM	FO/POSTHOC	Peak and trough	0.143	1.38
Tseng et *al.*[40]	1	Retrospective	NONMEM	FOCE-I	Peak, trough, random	0.052	0.50
Zhao et *al.*[41]	1	Prospective	NONMEM	FOCE-I	Continuous infusion	0.040	0.56

FO(CE) = First-Order (Conditional Estimation) - SAEM = Stochastic Approximation Expectation Maximisation - I = Interaction - [a] CL/µmol/L

Table 4. – Characteristics of CHUSJ external population compared to those of inadequate models (A-F)

Characteristics (Units)	**Type of value**	**CHUSJ**	**Allegaert et *al.*[17]**	**Alsultan et *al.*[42]**	**Dao et *al.*[30]**	**De Cock et *al.*[18,19]**	**Frymoyer et *al.*[31]**
Number of patients (M/F)	Numbers	63 (37/26)	249 (NA)	162 (73/52)[a,b]	405 (231/174)[a]	273 (NA)	249 (128/121)[a]
Gestational age (weeks)	Mean ± SD	29.4 ± 5.6	NA	28.0 ± 2.9	NA	NA	NA
	Median (IQR) or [range]	27 [22-41]	29 [23-34]	[22-35]	29.0 (26.7-34.9) [24.0-42.1]	29 [23-34]	34 (27-39) [22-42]**
Postnatal age (days)	Mean ± SD	27.2 ± 25.5	NA	10.7 ± 7.5**	NA	NA	NA
	Median (IQR) or [range]	18.7 [2.9-137.8]	11 [1-27]**	[1-30]	12.3 (5-14) [0-146]**	14 [1-28]**	19 (10-42) [0-173]
Postmenstrual age (weeks)	Mean ± SD	33.2 ± 6.5	NA	29.8 ± 3.15**	NA	NA	NA
	Median (IQR) or [range]	31.9 [25.0-50.6]	31 [24-37]*	[22-39]	32.0 (28.3-36.5) [24.6-61.0]	30 [24-38]*	39 (32-42) [24-54]**
Weight (kg)	Mean ± SD	2.0 ± 1.2	1.249 ± 0.466**	1.0 ± 0.29**	NA	NA	NA
	Median (IQR) or [range]	1.5 [0.7-4.7]	NA	[0.46-1.7]	1.100 (0.800-2.170) [0.462-5.660]**	1.170 [0.415-2.630]**	2.9 (1.6-3.7) [0.5-6.3]**

Table S4. – (A-F) (Cont.)

Birth weight (kg)	Mean ± SD	1.5 ± 1.0	1.221 ± 0.473	0.95 ± 0.27**	NA	NA	NA
	Median (IQR) or [range]	0.9 [0.5-4.2]	NA	[0.46-1.5]	1.050 (0.790-2.170) [0.462-4.330]	1.140 [0.385-2.550]	2.0 (0.9-3.1) [0.4-4.4]**
Serum creatinine (µmol/L)	Mean ± SD	49.2 ± 15.2	NA	NA	NA	NA	NA
	Median (IQR) or [range]	45.3 [29.6-92.3]	NA	NA	54 (31-68) [5-276]*	NA	NA
Serum creatinine (mg/dL)	Mean ± SD	0.6 ± 0.2	NA	0.65 ± 0.22**	NA	NA	NA
	Median (IQR) or [range]	0.5 [0.3-1.0]	NA	[0.2-1.5]	NA	NA	0.4 (0.3-0.6) [0.1-2.7]**
Number of blood samples	Number	144	648	214	1831	689	1702

* $p < 0.05$ - ** $p < 0.001$- [a] Values derived from available information found in the original publication – [b] Including missing values as reported in the original publication

Table 4. – Characteristics of CHUSJ external population compared to those of inadequate models (H-L)

Characteristics (Units)	**Type of value**	**CHUSJ**	**Hui et *al.*[44]**	**Jarugula et *al.*[45]**	**Jung et *al.*[46]**	**Kimura et *al.*[34]**	**Leroux et *al.*[47]**
Number of patients (M/F)	Numbers	63 (37/26)	207 (112/95)	934 (547/387)[a]	93 (57/36)	19 (9/10)	66 (29/37)
Gestational age (weeks)	Mean ± SD	29.4 ± 5.6	NA	NA	31.9 ± 4.7**	NA	NA
	Median (IQR) or [range]	27 [22-41]	30.1 (6.9) [24.1-41.3]	NA	[22.9-40.3]	[24.1-41.3]	32 [23-41]**
Postnatal age (days)	Mean ± SD	27.2 ± 25.5	NA	57.89**	65.1 ± 86.8**	NA	NA
	Median (IQR) or [range]	18.7 [2.9-137.8]	17 (14) [7-114]	43.6 (18.64-86.18) [0-184]**	[0.7-562.8][a]	[3-71]	13 [1-106]**
Postmenstrual age (weeks)	Mean ± SD	33.2 ± 6.5	NA	42.41**	41.2 ± 14.2**	NA	NA
	Median (IQR) or [range]	31.9 [25.0-50.6]	33.7 (7.3) [25.7-53.3]	41.99 (34.85-48.58) [20.89-66.68]**	[25.6-110.0]	[25.1-48.4]	34 [26-46]
Weight (kg)	Mean ± SD	2.0 ± 1.2	NA	3.57**	3.2 ± 2.6**	NA	NA
	Median (IQR) or [range]	1.5 [0.7-4.7]	1.68 (1.13) [0.47-7.36]	3.58 (1.97-4.91) [0.37-11.88]**	[0.4-14.9]	[0.710-5.200]	1.925 [0.530-3.840]

Table S4. – (H-L) (Cont.)

Birth weight (kg)	Mean ± SD	1.5 ± 1.0	NA	NA	NA	NA	NA
	Median (IQR) or [range]	0.9 [0.5-4.2]	1.32 (0.89) [0.44-4.14]	NA	NA	NA	1.590 [0.512-3.950]
Serum creatinine (µmol/L)	Mean ± SD	49.2 ± 15.2	NA	NA	NA	NA	NA
	Median (IQR) or [range]	45.3 [29.6-92.3]	42 (34) [15-252]*	NA	NA	NA	41 [12-153]*
Serum creatinine (mg/dL)	Mean ± SD	0.6 ± 0.2	NA	0.46**	0.4 ± 0.3**	NA	NA
	Median (IQR) or [range]	0.5 [0.3-1.0]	NA	0.33 (0.25-0.51) [0.1-4.54]**	[0.1-3.37]	[0.2-0.9]	NA
Number of blood samples	Number	144	689	2471	3902	88	108

* $p < 0.05$ - ** $p < 0.001$ - [a] Values derived from available information found in the original publication

Table 4. – Characteristics of CHUSJ external population compared to those of inadequate models (L-M)

Characteristics (Units)	**Type of value**	**CHUSJ**	**Li et *al.*[16]**	**Li et *al.*[35]**	**Lo et *al.*[20]**	**Marqués-Miñana et *al.*[15]**	**Mehrotra et *al.*[36]**
Number of patients (M/F)	Numbers	63 (37/26)	94 (58/36)	80 (54/26)	116 (66/50)[a]	70 (33/37)	134 (72/62)
Gestational age (weeks)	Mean ± SD	29.4 ± 5.6	37.18 ± 3.71**	34.70 ± 4.31**	NA	32.2 ± 5.0**	32.7 ± 5.7**
	Median (IQR) or [range]	27 [22-41]	39.0 [25.7-41.4]**	34.0 [25.7-41.1]**	NA	[24.0-42.0]	[23-41]
Postnatal age (days)	Mean ± SD	27.2 ± 25.5	67.14 ± 80.85**	32.3 ± 24.1	NA	16.9 ± 10.9*	26.8 ± 24.3
	Median (IQR) or [range]	18.7 [2.9-137.8]	88.5 [1-345]**	24 [4-126]	NA	[4.0-63.0]	[1-121]
Postmenstrual age (weeks)	Mean ± SD	33.2 ± 6.5	NA	39.40 ± 3.60**	NA	34.6 ± 5.3	36.5 ± 5.2**
	Median (IQR) or [range]	31.9 [25.0-50.6]	NA	40.0 [29.0-47.1]**	NA	[25.1-48.1]	[24.6-44.0]
Weight (kg)	Mean ± SD	2.0 ± 1.2	4.686 ± 2.570**	2.87 ± 0.89**	NA	1.7 ± 0.8	2.5 ± 1.1**
	Median (IQR) or [range]	1.5 [0.7-4.7]	4.0 [1.4-18.0]**	2.74 [1.40-5.60]**	NA	[0.7-3.7]	[0.6-5.3]

Table S4. – (L-M) (Cont.)

Birth weight (kg)	Mean ± SD	1.5 ± 1.0	2.9780 ± 0.81549**	NA	NA	NA	NA
	Median (IQR) or [range]	0.9 [0.5-4.2]	3.200 [0.850-4.400]**	NA	NA	NA	NA
Serum creatinine (µmol/L)	Mean ± SD	49.2 ± 15.2	19.91 ± 7.45**	23.2 ± 10.4**	76 ± 2**	NA	NA
	Median (IQR) or [range]	45.3 [29.6-92.3]	18.25 [5.50-50.00]**	28.30 [5.85-61.60]**	[31-143][a]	NA	NA
Serum creatinine (mg/dL)	Mean ± SD	0.6 ± 0.2	NA	NA	NA	NA	0.60 ± 0.38
	Median (IQR) or [range]	0.5 [0.3-1.0]	NA	NA	NA	NA	[0.2-2.5]
Number of blood samples	Number	144	205	165	835	NA	267

* $p < 0.05$ - ** $p < 0.001$ - [a] Values derived from available information found in the original publication

Table 4. – Characteristics of CHUSJ external population compared to those of inadequate models (M-S)

Characteristics (Units)	**Type of value**	**CHUSJ**	**Mulubwa et *al.*[37]**	**Oudin et *al.*[38]**	**Sasano et *al.*[48]**	**Seay et *al.*[14]**
Number of patients (M/F)	Numbers	63 (37/26)	19 (8/11)	68 (NA)	19 (13/6)	192 (81/111)[a]*
Gestational age (weeks)	Mean ± SD	29.4 ± 5.6	NA	29.5 ± 27	26.4 ± 2.5**	29.6 ± 5.2
	Median (IQR) or [range]	27 [22-41]	31 [23-34]	27 (26-30) [23-41]*	26.0 [22.6-30.3][a]**	[22-42]
Postnatal age (days)	Mean ± SD	27.2 ± 25.5	NA	21.6 ± 23.0	30.4 ± 17.2	14.5 ± 11.4**
	Median (IQR) or [range]	18.7 [2.9-137.8]	14 [3-58]**	14 (10-27) [4-169]**	28 [0-75]	[1-73]
Postmenstrual age (weeks)	Mean ± SD	33.2 ± 6.5	NA	32.7 ± 5.3	30.8 ± 3.7*	NA
	Median (IQR) or [range]	31.9 [25.0-50.6]	33.0 [30.0-34.7]	31 (29-35) [27-47]*	30.4 [23.9-39.0][a]*	NA
Weight (kg)	Mean ± SD	2.0 ± 1.2	NA	1.50 ± 0.97*	0.9019 ± 0.2703**	1.48 ± 1.05*
	Median (IQR) or [range]	1.5 [0.7-4.7]	1.480 [0.925-2.620]	1.10 (0.90-1.62) [0.58-4.60]**	0.887 [0.448-1.457]**	[0.39-4.35]

Table S4. – (M-S) (Cont.)

Birth weight (kg)	Mean ± SD	1.5 ± 1.0	NA	NA	0.6611 ± 0.1438**	NA
	Median (IQR) or [range]	0.9 [0.5-4.2]	1.27 [0.63-2.69]	NA	0.632 [0.420-0.978]**	NA
Serum creatinine (µmol/L)	Mean ± SD	49.2 ± 15.2	NA	NA	NA	NA
	Median (IQR) or [range]	45.3 [29.6-92.3]	51 [26-74]	NA	NA	NA
Serum creatinine (mg/dL)	Mean ± SD	0.6 ± 0.2	NA	NA	0.45 ± 0.30**	NA
	Median (IQR) or [range]	0.5 [0.3-1.0]	NA	NA	0.35 [0.07-2.40]**	NA
Number of blood samples	Number	144	45	151	62	520

* $p < 0.05$ - ** $p < 0.001$ - [a] Values derived from available information found in the original publication

Table 4. – Characteristics of CHUSJ external population compared to those of inadequate models (S-Z)

Characteristics (Units)	Type of value	CHUSJ	Sheng et *al.*[39]	Tseng et *al.*[40]	Zhao et *al.*[41]
Number of patients (M/F)	Numbers	63 (37/26)	61 (34/27)	76 (44/32)[a]	116 (59/57)
Gestational age (weeks)	Mean ± SD	29.4 ± 5.6	NA	NA	NA
	Median (IQR) or [range]	27 [22-41]	NA	26.2 (25.0-28.8) [23.9-40.3]*	NA
Postnatal age (days)	Mean ± SD	27.2 ± 25.5	NA	NA	26 ±25
	Median (IQR) or [range]	18.7 [2.9-137.8]	29.2 [1.095-354.05][a]	17.4 (11.4-40.6) [4.0-223.7]	17 [1-120]
Postmenstrual age (weeks)	Mean ± SD	33.2 ± 6.5	NA	NA	33.8 ± 5.3
	Median (IQR) or [range]	31.9 [25.0-50.6]	37.86 [26.00-41.43]**	30.1 (27.9-36.2) [25.1-57.5]*	32.7 [24.4-49.4]
Weight (kg)	Mean ± SD	2.0 ± 1.2	NA	NA	1.700 ± 0.964
	Median (IQR) or [range]	1.5 [0.7-4.7]	3.15 [0.95-16.0]**	1.043 (0.811-1.919) [0.320-6.590]**	1.416 [0.460-5.680]*
Birth weight (kg)	Mean ± SD	1.5 ± 1.0	NA	NA	1.331 ± 0.839
	Median (IQR) or [range]	0.9 [0.5-4.2]	NA	0.828 (0.699-1.076) [0.320-3.655]**	1.010 [0.510-3.930]

Table S4. – (S-Z) (Cont.)

Serum creatinine (µmol/L)	Mean ± SD	49.2 ± 15.2	NA	NA	48 ± 33
	Median (IQR) or [range]	45.3 [29.6-92.3]	32.3 [10.4-109]**	43 (36-59) [7.5-130.0]*	42 [5-228]*
Serum creatinine (mg/dL)	Mean ± SD	0.6 ± 0.2	NA	NA	NA
	Median (IQR) or [range]	0.5 [0.3-1.0]	NA	NA	NA
Number of blood samples	Number	144	72	429	207

* $p < 0.05$ - ** $p < 0.001$ - [a] Values derived from available information found in the original publication

Table 5. – Maintenance doses of 11 versus 12 mg/kg with different AUC24h estimation methods

Novel initial dosing nomogram (L = 15 mg/kg, M = 11 mg/kg)[a]	Bayesian[d] = 400-600	Bayesian[d] > 600	Median (IQR) AUC_{24h} Bayesian[d] (mg x h/L)	Equation[e] = 400-600	Equation[e] > 600	Median (IQR) AUC_{24h} equation[e] (mg x h/L)
PMA $<$ 30, PNA $\leq$ 14 (q8h)[b]	53.2	13.5	452.7 (383.7-543.3)	50.6	11.8	435.1 (350.2-528.1)
PMA $<$ 30, PNA $>$ 14 (q8h)[b]	60.4	8.2	445.0 (379.2-524.0)	47.8	15.7	448.0 (353.4-526.7)
30 $\leq$ PMA $\leq$ 36, PNA $\leq$ 14 (q8h)[b]	56.5	16.4	458.8 (388.8-541.7)	49.1	17.8	453.8 (367.8-549.0)
30 $\leq$ PMA $\leq$ 36, PNA $>$ 14 (q8h)[b]	53.5	17.6	466.0 (386.4-563.7)	53.3	14.7	459.2 (371.9-550.0)
PMA $\geq$ 37, PNA $\leq$ 7 (q8h)[b]	60.0	17.8	445.8 (401.8-540.9)	62.2	8.9	439.0 (387.7-521.5)
PMA $\geq$ 37, PNA $>$ 7 (q8h)[b]	52.9	16.7	455.6 (372.5-548.8)	49.7	14.8	455.0 (353.8-539.3)
Total (n = 1389)[c]	54.6	15.6	456.1 (383.7-544.1)	51.0	14.6	452.5 (362.3-542.2)

Table S5. – (Cont.)

Higher initial dosing nomogram (L = 15 mg/kg, M = 12 mg/kg)[a]	Bayesian[d] = 400-600	Bayesian[d] > 600	Median (IQR) AUC_{24h} Bayesian[d] (mg x h/L)	Equation[e] = 400-600	Equation[e] > 600	Median (IQR) AUC_{24h} equation[e] (mg x h/L)
PMA $<$ 30, PNA $\leq$ 14 (q8h)[b]	58.8	22.3	492.4 (414.8-592.1)	51.3	19.3	474.1 (382.6-571.3)
PMA $<$ 30, PNA $>$ 14 (q8h)[b]	61.8	16.2	486.2 (411.8-568.6)	54.4	16.2	486.5 (384.7-565.7)
30 $\leq$ PMA $\leq$ 36, PNA $\leq$ 14 (q8h)[b]	56.7	23.3	499.1 (416.9-587.0)	53.0	23.3	489.2 (402.9-591.5)
30 $\leq$ PMA $\leq$ 36, PNA $>$ 14 (q8h)[b]	53.5	27.4	507.8 (420.0-613.8)	52.2	24.0	498.2 (409.3-596.7)
PMA $\geq$ 37, PNA $\leq$ 7 (q8h)[b]	66.7	22.2	482.7 (440.9-583.9)	66.7	17.8	474.0 (429.7-562.4)
PMA $\geq$ 37, PNA $>$ 7 (q8h)[b]	50.5	25.5	497.1 (404.0-601.4)	49.7	21.4	494.1 (389.9-583.9)
Total (n = 1405)[c]	55.3	24.1	497.4 (414.8-596.2)	52.2	21.4	489.2 (393.8-585.4)

Values are reported as a percentage (%) unless specified otherwise; [a] L = Loading dose; M = Maintenance dose; [b] PMA is expressed in weeks and PNA in days (administration interval); [c] Simulated patients were removed whenever trough > peak concentration; [d] Bayesian estimation based on **Grimsley and Thomson[33]** model; [e] Equation underpredicting AUC_{24h} as formulated **by Pai et *al.*[27]**

Table 6. – Summary description of patients with AKI

Patient	PMA (weeks)	Weight (kg)	Dose (mg) [dose interval]	Vancomycin concentration (mg/L)	Concurrent nephrotoxins
AKI-1	25	0.70	6.5 [q12h]	20.5	Piperacillin-tazobactam
AKI-2	27	0.90	8 [q12h]	23.4	-
AKI-3	39	3.30	35 [q6h]	24.5	Piperacillin-tazobactam
AKI-4	51	4.60	43 [q6h]	12.9	Piperacillin-tazobactam, furosemide and sulfamethoxazole-trimethoprim
AKI-5	29	1.56	16 [q12h]	20.0	Furosemide

Table 7. – Infectious pathogens identified and their MIC values when applicable

Bacteria	**Number of patients**	**Vancomycin MIC**
Staphylococcus aureus	3	-
Methicillin-resistant *Staphylococcus aureus* (MRSA)	2	2
Coagulase-negative staphylococci (CoNS)	11	-
Staphylococcus capitis	2	-
Staphylococcus epidermidis	23	-
Staphylococcus hominis	2	-
Staphylococcus warneri	6	-
Acinetobacter calcoaceticus-baumannii	1	-
Corynebacterium sp.	1	0.25
Enterobacter cloacae	1	-
Enterococcus faecalis	3	-
Escherichia coli	3	-
Haemophilus parainfluenzae	1	-
Klebsiella oxytoca	2	-
Klebsiella pneumoniae	1	-
Lactobacillus sp.	1	> 256
Lactobacillus rhamnosus	1	256
Proteus mirabilis	1	-
Pseudomonas aeruginosa	1	-
Streptococcus gr. mitis	2	0.5

Chapitre 3 - External evaluation of neonatal vancomycin population pharmacokinetic models: Moving from first-order equations to Bayesian-guided therapeutic monitoring

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Ce deuxième article a été publié le 15 novembre 2024 dans le journal Pharmacotherapy (https://doi.org/10.1002/phar.4623). Il repose aussi sur l'évaluation externe de modèles PopPK, mais dans la population néonatale du CMES plutôt que celle du CHUSJ. Pour ce papier, ma contribution s'étend de l'amendement du protocole en vue du transfert du projet en multicentrique jusqu'à l'écriture du manuscrit, en passant par la mise en forme de la base de données externe, les analyses statistiques et PK tout comme les simulations de Monte-Carlo. En ce qui concerne les multiples coauteurs, Marie-Élaine Métras, Isabelle Viel-Thériault et Amélie Marsot ont conçu l'étude, collaborant avec Julie Autmizguine qui n'a pu réviser cet article, tout en assurant la supervision du projet. Camille Gaudreault a collecté les données des patients du CMES rétrospectivement sous la direction de Marie-

Hélène Dubé, Marie-Christine Boulanger et Karine Cloutier, et j'ai ensuite adapté sa base de données pour l'évaluation avec NONMEM. Mehdi El Hassani m'a guidé afin de réaliser les simulations de Monte-Carlo par moi-même. Comme pour le premier article, Aysenur Yaliniz a effectué une première revue de littérature en janvier 2022, que j'ai mise à jour pour une dernière fois en septembre 2023. Veuillez noter que du matériel supplémentaire a été ajouté selon l'ordre de présentation après les références.

3.1. Abstract

Introduction

Guidelines for vancomycin therapeutic monitoring recommend using a Bayesian approach with a population pharmacokinetic model to estimate the 24 h area under the concentration-time curve over first-order equations. Thus, we performed an external evaluation of population pharmacokinetic models of vancomycin in neonates and compared Bayesian results with those observed in clinical practice via pharmacokinetic equations to improve therapeutic monitoring by proposing optimized initial dosing nomograms and assessing the feasibility of reduced blood sampling strategies using the most predictive models.

Methods

Models were identified from the literature and evaluated via an external neonatal population. A priori predictive performance was first assessed by prediction-based diagnostics, then by simulation-based diagnostics and a posteriori analyses only if deemed satisfactory; model-informed vancomycin exposure was also compared with reference first-order pharmacokinetic equations. The best-performing models were ultimately subjected to Monte Carlo simulations to develop new initial dosing nomograms offering the highest probability of achieving therapeutic target.

Results

A total of 28 population pharmacokinetic models were evaluated in the external dataset, which includes 72 neonates and 380 vancomycin concentrations. Eleven models had adequate predictive performance with bias $\leq \pm 15\%$ and imprecision $\leq 30\%$, while the Bayesian approach yielded over 75% agreement with reference exposure values in most cases. Nonetheless, **Capparelli et *al.*** and **Mehrotra et *al.*** models performed the best overall, showing the lowest imprecisions of 16.8% and 16.9%, respectively; both models

recommended higher dosage regimens than the theoretical nomogram currently applied to favor therapeutic target attainment.

Discussion

We externally evaluated numerous neonatal population pharmacokinetic models of vancomycin and used the most predictive ones to advocate new initial dosing nomograms. Clinical implementation of the Bayesian approach could reduce the time needed to reach therapeutic target and limit the number of blood samples in newborns compared with traditional pharmacokinetic equations.

Keywords

Antibiotics, vancomycin, neonatology, therapeutic drug monitoring, population pharmacokinetic models and external evaluation

3.2. Introduction

The toxicity profile of vancomycin has raised ongoing concerns since its addition to the antibiotic armamentarium in 1958.[1] Still, growing antibiotic resistance has brought it to the forefront as a valuable treatment against resistant gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA).[1] In 2009, the first consensus guidelines published by a committee including the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists paved the way for vancomycin therapeutic drug monitoring (TDM). Herein, steady-state trough concentrations were suggested as the most practical method to promote optimal vancomycin treatments.[2] A minimal trough concentration of 10 mg/L was recommended to favor effectiveness and lessen the risk of developing antibiotic resistance, but up to 15-20 mg/L was advocated for adult and pediatric patients infected by MRSA.[2,3] Although widely adopted, trough concentrations have emerged as a suboptimal surrogate for the 24 h area under the concentration-time curve (AUC_{24h}) over

minimum inhibitory concentration (assuming a MIC of 1 mg/L) because of large interindividual variability which remained unexplained, leading to poor correlation.[4] Therefore, two clinically viable alternatives were introduced by the authors to calculate AUC_{24h}, namely the Bayesian- or equation-based approaches.[4]

In 2020, a revision of the aforementioned consensus guidelines was published, with the input of the Pediatric Infectious Diseases Society, to lower vancomycin-related nephrotoxicity.[5] Herein, implementation of an AUC-guided Bayesian approach based on population pharmacokinetic (PopPK) models was preferably suggested to reach a therapeutic AUC_{24h} of 400 to 600 mg*h/L with potentially less samples than first-order pharmacokinetic (PK) equations requiring at least two blood levels, typically a trough and a peak.[5] These models enable the integration of clinically relevant covariates to better describe a population's PK profile a priori as well as offer patient-tailored estimation a posteriori, with the PopPK model representing the Bayesian prior and additonal patient-specific information provided serving as the Bayesian conditional posterior to further improve accuracy.[5] Nonetheless, PopPK models must be carefully assessed to ensure reliable predictions,[6] with thorough methods such as external evaluation often conducted to advise on their transferability.[7]

The latest guidelines recommendations are currently implemented at the Centre mère-enfant Soleil du CHU de Québec-Université Laval (CMES) using first-order PK equations, but we hypothesized that a predictive PopPK model could improve the TDM practice via optimized initial doses, faster dose adjustment if necessary, and reduced blood sampling strategies in neonatology, without impairing the AUC_{24h} value.[5] We evaluated the predictive performance of published PopPK models, a priori and a posteriori, with our external dataset complete, including peak and trough (P+T) concentrations, or truncated, limited to trough (T) levels only, and then compared each model-derived Bayesian AUC_{24h} values with the equation-based reference for correspondence. Finally, Monte Carlo

simulations were conducted using the best-performing models to suggest optimized initial dosing nomograms of vancomycin.

3.3. Methods

3.3.1. Literature review and model selection

A literature review on neonatal vancomycin PopPK models was actualized through September 2023 using the PubMed search strategy initially proposed by **Marsot et *al.***[8] Vancomycin models developed using a PopPK approach, in neonatal to young infants populations, and published in English were included. Unavailability of covariates in our external database, an incomplete description, or a modeling strategy other than the nonlinear mixed-effects method led to model exclusion.

3.3.2. Patients

This retrospective, single-center, observational study was conducted at the CMES according to the Declaration of Helsinki. The multicentric research protocol was previously approved (MP-21-2021-3329) by the Centre Hospitalier Universitaire Sainte-Justine's ethics committees and certified via an institutional feasibility review (MEO-21-2023-6385). Then, admissible patients were recruited from the pharmacy's electronic database if they satisfied the following inclusion criteria: neonates (including preterm and term newborns or young infants) treated with intravenous vancomycin in the neonatal intensive care unit for at least 48 h between April, 2018 and March, 2022. Some patients had multiple treatments in this period, each of them was considered separately. The absence of observed vancomycin concentrations or other significant covariates necessary for model evaluation was the only exclusion criterion.

3.3.3. Data collection

After patient recruitment, the following relevant information was extracted from their clinical records: patient characteristics (gestational (GA), postnatal (PNA), or postmenstrual (PMA = GA + PNA) ages, sex, weight at birth or the time of treatment, and serum creatinine (SCr) levels), along with every vancomycin administrations or concentrations. Coadministration of dopamine,[9] amoxicillin/clavulanate and spironolactone,[10] ceftriaxone,[11] amikacin, or non-selective cyclooxygenase (NCOX) inhibitors[12-14] were also recovered to perform the external evaluation on some models. Two more models[12,15] included a small for gestational age (SGA) covariate, for which newborns were classified relative to their birth weight, and sex using the Fenton growth chart.[16] Newborns were considered premature if born prior to 37 weeks of gestation.[17]

3.3.4. Vancomycin and bioanalytical methods

Vancomycin was administered over a 60 min intravenous infusion. The neonatal dosage regimen currently employed at CMES recommends a 15 mg/kg dose for meningitis or a 10 mg/kg dose for bacteremia, with dose intervals of 6, 8, 12 or 18 h based on PMA and PNA (**Supporting Information-Table S1**). Vancomycin samples were collected on the third dose, just before administration (i.e., trough) and 30 min post-infusion (i.e., peak), with resulting blood concentrations measured by particle-enhanced turbidimetric inhibition immunoassay on the Dimension Vista® (Siemens Healthcare Diagnostics). SCr levels were analyzed under request by the enzymatic creatinine method on the Dimension Vista® (Siemens Healthcare Diagnostics). The Lower Limit Of Quantification (LLOQ) for blood levels of vancomycin and SCr were 0.8 mg/L and 12.4 µmol/L, respectively.

3.3.5. External evaluation

Models of interest were transcribed for evaluation into NONMEM software (Version 7.5; ICON Development Solutions) using MAXEVAL=0 in the $EST record, meaning original parameter values (THETA, ETA, SIGMA) were directly applied. Each model was tested

individually, as NONMEM predicted vancomycin concentrations everytime one was recorded in the external CMES dataset. Then, the predictive performance of PopPK models was assessed with prediction-based diagnostics on the P+T dataset. After, prediction-based diagnostics and Bayesian forecasting on the T dataset, along with simulation-based diagnostics on the P+T dataset were performed only for suitable models.

3.3.5.1. Prediction-based diagnostics

The relative prediction error (PE%) was calculated for each population predictions (C_{pred}) and their corresponding observed (C_{obs}) vancomycin concentrations using the following equation:

$$\boldsymbol{PE}(\%) = \frac{\left(\boldsymbol{C_{pred}} - \boldsymbol{C_{obs}}\right)}{\boldsymbol{C_{obs}}} \times \mathbf{100}\%$$

The median value (MDPE) and median absolute value (MDAPE) of PE% were then considered to inform the bias and imprecision of PopPK models, respectively. The PE% distribution was further assessed looking at the percentage of values included between $\pm$20% (F_{20}) or $\pm$30% (F_{30}). Models required at least a MDPE $\leq \pm$15%, MDAPE $\leq$30%, values of F_{20} >35%, and F_{30} >50% to be considered acceptable a priori,[18] and reassessed on the T dataset. Observed concentrations were plotted against both the population and individual predictions. Additionally, we calculated the correspondence rate of AUC_{24h} results obtained with the Bayesian approach, as a ratio of total daily dose (mg) over individual-predicted clearance (L/h), versus the reference equation-based approach applied at CMES, described by Equation 4 in **Pai et *al.***,[4] arranged in three classes: subtherapeutic (<400 mg*h/L), therapeutic (400-600 mg*h/L), or supratherapeutic (>600 mg*h/L). Correspondence was achieved when both AUC_{24h} belonged to the same class, whereas underestimation reflected a Bayesian value in a lower class (likewise with overestimation in a higher class) than the CMES reference.

3.3.5.2. Simulation-based diagnostics

Visual Predictive Check (VPC) and Normalized Prediction Distribution Errors (NPDE) were plotted for suitable models, using R (Version 4.1.1; https://www.r-project.org/) with the VPC and NPDE packages, respectively. Both simulation-based diagnostics were performed following 1000 simulations of the P+T dataset. In the VPC plot, observed concentrations should fit within their respective percentiles of simulated values. As for the NPDE, it should follow a normal distribution with a mean of 0 and a variance of 1.[19]

3.3.5.3. Bayesian forecasting

The relative individual prediction error (IPE%) was also calculated for each model, however the individual predictions (C_{ipred}) were used rather than C_{pred}.

$$\boldsymbol{IPE}(\%) = \frac{\left(\boldsymbol{C_{ipred}} - \boldsymbol{C_{obs}}\right)}{\boldsymbol{C_{obs}}} \times \mathbf{100}\%$$

For predictive models a priori, Bayesian Conditional Posterior (BCP) were obtained on patients who had at least three pairs of concentrations (i.e., trough and peak) within the same treatment, as the C_{ipred} were adjusted in relation to previous C_{obs}. In short, the first C_{ipred} (BCP-1) was merely affected by the interindividual variability component in contrast with C_{pred}, while the second C_{ipred} (BCP-2) was corrected after adding information on the first C_{obs}, and the third C_{ipred} (BCP-3) considered the two previous C_{obs}.

3.3.6. Monte Carlo simulations

Monte Carlo simulations were performed using the best-performing PopPK models. From the current initial dosing nomogram, various combinations of maintenance doses from 10 to 15 mg/kg in 1 mg/kg increments, at intervals of 6, 8, 12 or 18 h, with or without a 15 mg/kg loading dose, were tested on 1500 simulated patients. The proportion of simulated patients in each dosing subgroup together with their characteristics was based on our external dataset.[20] Observed concentrations below the LLOQ of 0.8 mg/L were imputed at 0.4 mg/L. The AUC_{24h} was calculated using the Bayesian and equation-based

approaches, simulating both trough and peak concentrations on the third dose to mirror clinical practice at the CMES. The initial dosage regimen providing the highest percentage of therapeutic, with low supratherapeutic (especially >800 mg*h/L), AUC_{24h} values was selected.

3.3.7. Statistical analysis

CMES neonatal population characteristics were described via means ± standard deviation (SD) and medians (interquartile range (IQR)) or [range]; two-sided tests were performed at a significance level of 5% to compare the results to those of all PopPK models. Values were compared with Student's *T*-test if expressed by means or Mann-Whitney *U*-test if medians. Categorical variables were analyzed using the χ^2 test. All statistical analyses were conducted on R (Version 4.1.1; https://www.r-project.org/).

3.4. Results

3.4.1. Review of published PopPK models

Twenty-eight neonatal PopPK models of vancomycin were retained for evaluation.[9-15,21-41] A description of each model is available in **Supporting Information-Table S2**. Most were developed using a one-compartment structure (82.1%) along with similar covariates, namely weight (at the time of treatment or birth, 100%), age (PMA or PNA, 75.0%), and SCr (67.9%) on clearance as well as weight (96.4%) on volume of distribution.

3.4.2. External neonatal population

CMES initial external population included 78 patients, however, six were excluded due to the absence of SCr levels, leaving 72 patients (93 treatment episodes) in whom 380 (181 pairs of trough and peak) in the P+T or 197 trough vancomycin concentrations in the T dataset were quantified. The median (IQR) reference AUC_{24h} and trough concentration

were of 440.4 (359.4-512.2) mg*h/L and 9.9 (7.8-12.5) mg/L, respectively. If only the initial dose was considered, however, these values dropped to 409.3 (329.7-491.1) mg*h/L and 8.6 (6.5-11.6) mg/L, respectively. Four neonates received vancomycin treatments for meningitis (4.3%), nonetheless, the median (IQR) initial dose of 14.9 (10.0-15.0) mg/kg was actually administered. The characteristics of CMES external population are summarized in **Table 1**. Newborns of CMES showed some statistical differences with those of all PopPK models (**Table 1** and **Supporting Information-Table S3**).

Table 1. – Characteristics of CMES external neonatal population compared to those of the most predictive models

Characteristics (Units)	**Type of value**	**Capparelli et *al.*[22]**	**Mehrotra et *al.*[35]**	**CMES**
Number of patients (M/F)	Count	374 (172/202)[a]*	134 (72/62)	72 (43/29)
Gestational age (weeks)	Mean ± SD	33.5 ± 6.0*	32.7 ± 5.7*	30.4 ± 5.9
	Median (IQR) or [range]	33.5 (28-40)*	[23-41]	28 [23-40]
Postnatal age (days)	Mean ± SD	70 ± 100*	26.8 ± 24.3	28.6 ± 24.2
	Median (IQR) or [range]	27 (15-74)	[1-121]	21.4 [4.3-125.0]
Postmenstrual age (weeks)	Mean ± SD	NA	36.5 ± 5.2*	34.5 ± 5.9
	Median (IQR) or [range]	NA	[24.6-44.0]	34.0 [24.3-49.0]
Weight (kg)	Mean ± SD	2.82 ± 2.33*	2.5 ± 1.1*	2.1 ± 1.3
	Median (IQR) or [range]	2.00 (1.04-3.60)	[0.6-5.3]	1.9 [0.5-6.6]

Table 1. – (Cont.)

Birth weight (kg)	Mean ± SD	NA	NA	1.7 ± 1.1
	Median (IQR) or [range]	NA	NA	1.1 [0.4-4.8]
Serum creatinine (µmol/L)	Mean ± SD	NA	NA	37.5 ± 13.4
	Median (IQR) or [range]	NA	NA	36.8 [17.0-79.0]
Serum creatinine (mg/dL)	Mean ± SD	0.7 ± 0.5*	0.60 ± 0.38*	0.4 ± 0.2
	Median (IQR) or [range]	0.6 (0.4-0.9)*	[0.2-2.5]	0.4 [0.2-0.9]
Number of blood samples	Count	1103	267	380

*$p < 0.05$ - CMES: External neonatal population - IQR: Interquartile Range - M/F: Male/Female - NA: Not Available - SD: Standard Deviation - [a] Values derived from available information found in the original publication

3.4.3. External evaluation

A priori predictive performance was related to bias, imprecision, F_{20} and F_{30} at the population level, with values reported in **Figure 1** or **Supporting Information-Table S4** for all PopPK models. Eleven models were able to predict vancomycin concentrations accurately enough to be considered predictive in the P+T dataset[13,21-23,27,30-32,34,35,37]; their biases and imprecisions ranged from -12.4% to 14.8% and 16.8%-24.6%, respectively. Usually, these models predictive performance deteriorated if solely trough concentrations remained in the T dataset, rendering half of them unacceptable. The correspondence rates were always over 70.7% among the suitable PopPK models, even in the T dataset, but never exceeded 86.7%. All these results were analyzed in parallel with the goodness-of-fit and simulation-based diagnostics plots to determine the best models. Finally, **Capparelli et *al.***[22] and **Mehrotra et *al.***,[35] a two- and one-compartment model, respectively, were both selected. **Figure 2** illustrates their goodness-of-fit and boxplots comparing the model-predicted Bayesian with CMES equation-based reference AUC_{24h}, whereas the equivalent for the nine other adequate models may be found in **Supporting Information-Figure S1**. Simulation-based diagnostics plots, VPC and NPDE, are available for the 11 predictive models in **Supporting Information-Figure S2**.

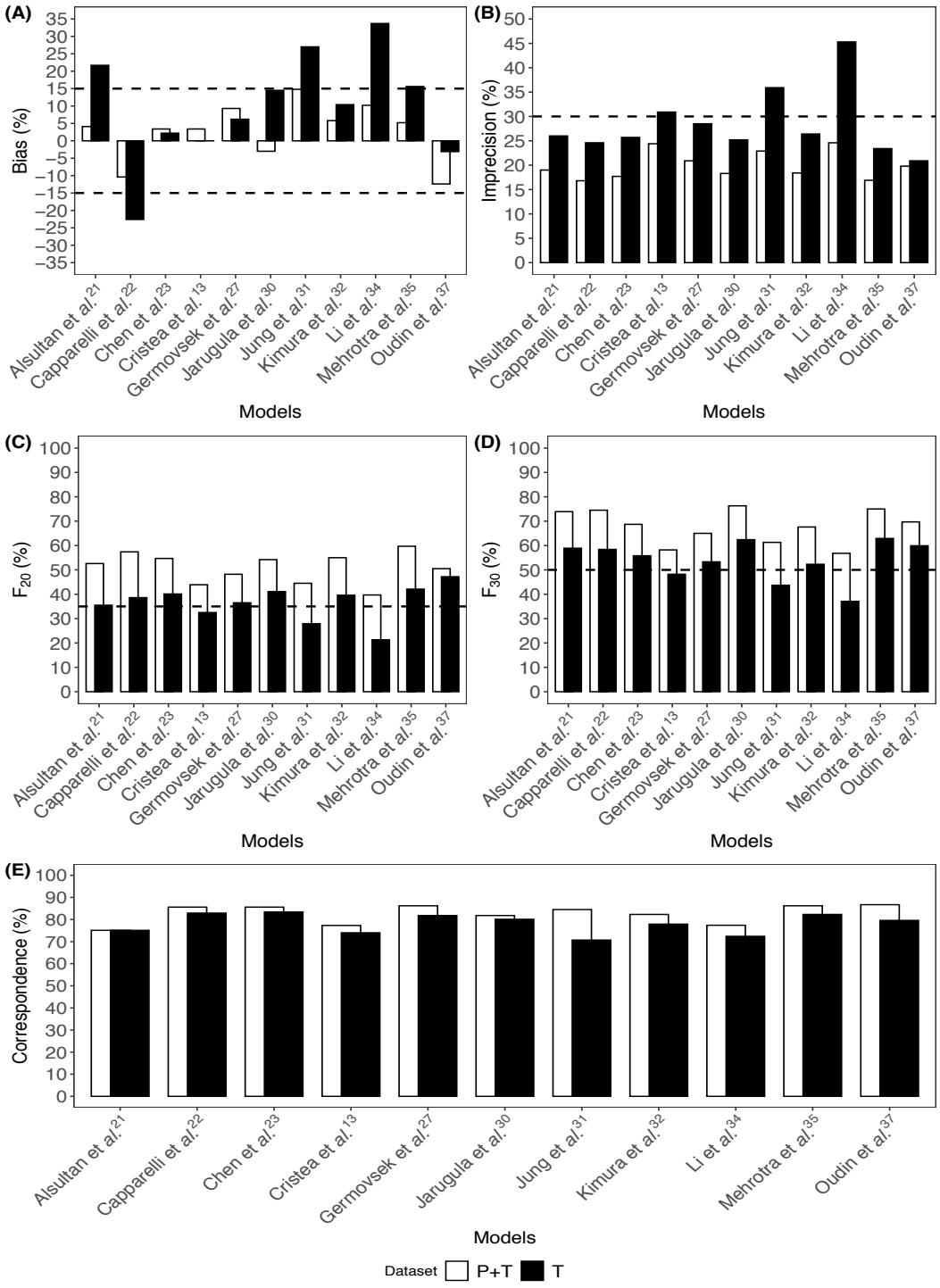
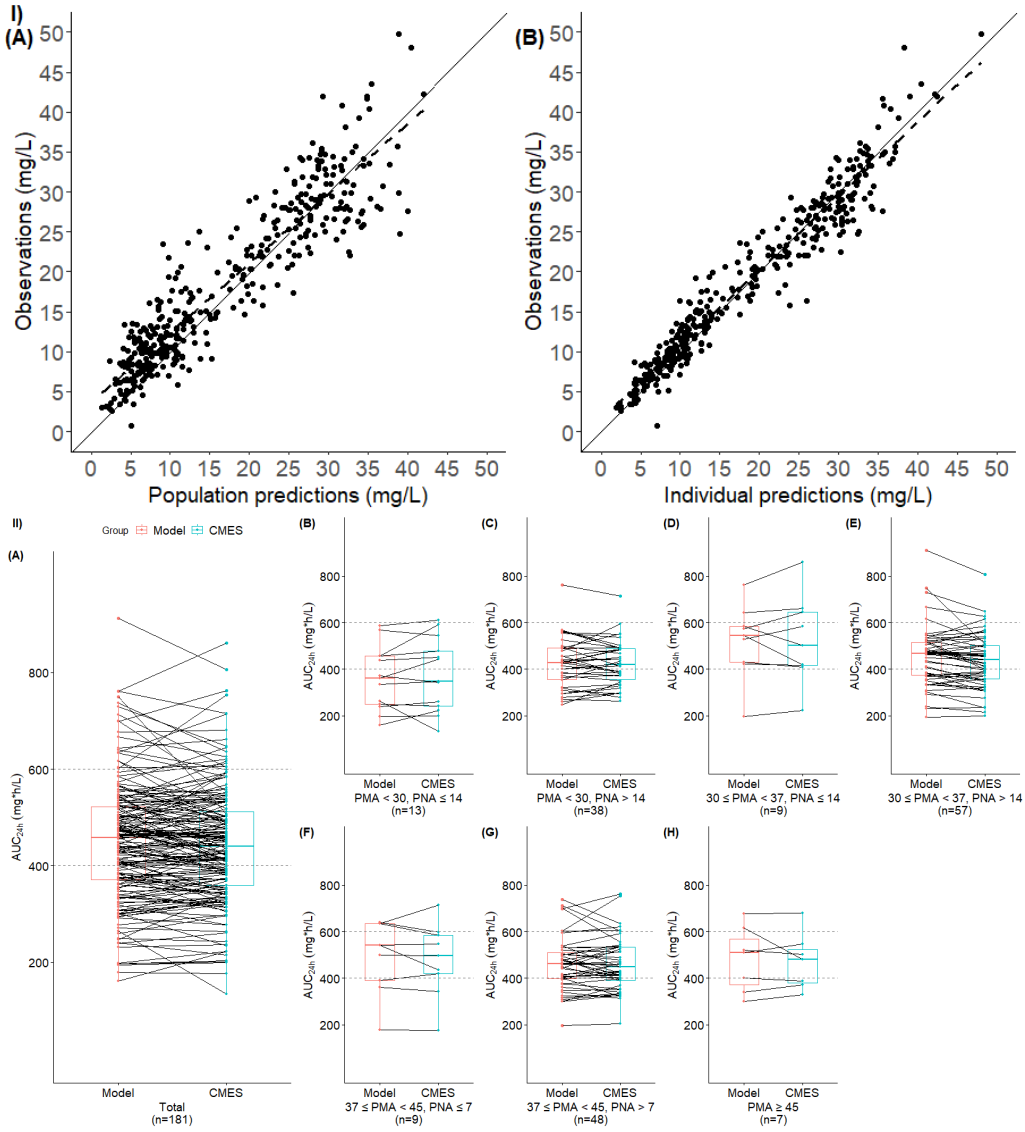


Figure 1. – A priori predictive performance of suitable models **(A)** Bias, **(B)** Imprecision, **(C)** F_{20}, **(D)** F_{30} and **(E)** Correspondence - Values in white and black are obtained on complete (P+T) and truncated (T) dataset, respectively - Acceptability thresholds are represented by dashed lines - F_{20}/F_{30}: Percentage of values between $\pm$20/30%

1) Capparelli et *al.* (22)



2) Mehrotra et *al.* (35)

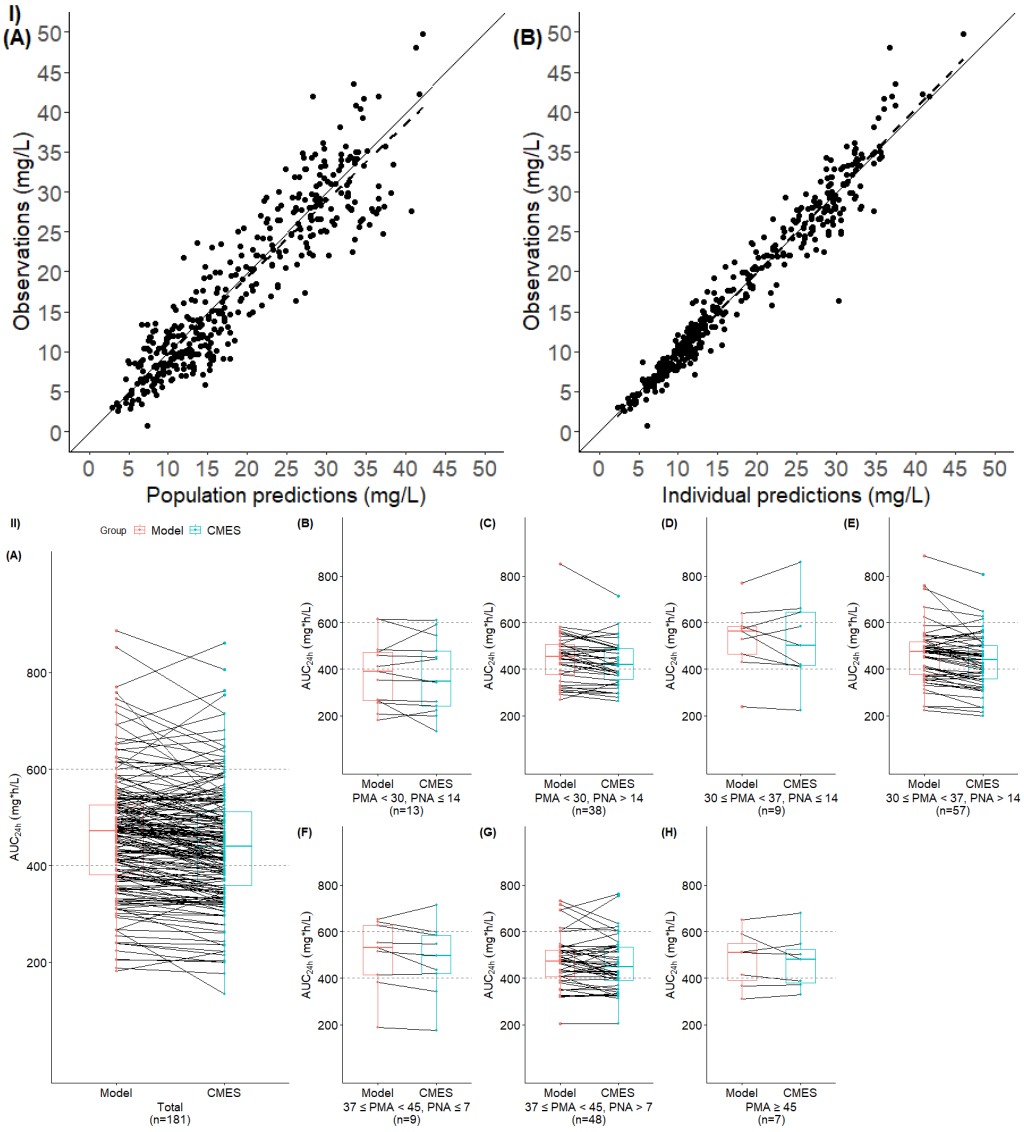


Figure 2. – I) Goodness-of-fit plots using the complete (P+T) dataset - Observations versus **(A)** Population or **(B)** Individual predictions - Identity function is represented as a solid line, Trend as a dashed line. **II)** Boxplots of Bayesian (Model) versus reference equation-based AUC_{24h} (CMES) - **(A)** Total - **(B)** PMA $<$ 30, PNA $\leq$ 14 - **(C)** PMA $<$ 30, PNA $>$ 14 - **(D)** 30 $\leq$ PMA $<$ 37, PNA $\leq$ 14 - **(E)** 30 $\leq$ PMA $<$ 37, PNA $>$ 14 - **(F)** 37 $\leq$ PMA $<$ 45, PNA $\leq$ 7 - **(G)** 37 $\leq$ PMA $<$ 45, PNA $>$ 7 - **(H)** PMA $\geq$ 45, where postmenstrual age (PMA) is expressed in weeks and postnatal age (PNA) in days - AUC_{24h}: 24 h area under the concentration-time curve, where therapeutic target is delimited by dashed lines

3.4.4. Bayesian forecasting

A posteriori predictive performance was measured by bias and imprecision at the individual level, with 26 treatment episodes (28.0%) being available for BCP. **Figure 3** and **Supporting Information-Table S5** indicate individual results were improved over their population counterpart; biases and imprecisions ranging from -12.5% to 1.3% and 5.4%-15.3%, respectively, in the same 11 adequate PopPK models in the P+T dataset. Furthermore, the negative impact observed on predictive performance in the T dataset seemed less detrimental than it was at the population level. Interestingly, nearly every BCP-1 and BCP-2 was underpredicted (i.e., negative bias), whereas the trend switched on BCP-3 with most bias values being positive. **Capparelli et *al.***[22] improved slightly with imprecisions lowering from 10.6% (BCP-1) to 9.1% (BCP-3). On the contrary, **Mehrotra et *al.***[35] appeared to get worse as imprecisions climbed from 6.9% (BCP-1) to 10.4% (BCP-3).

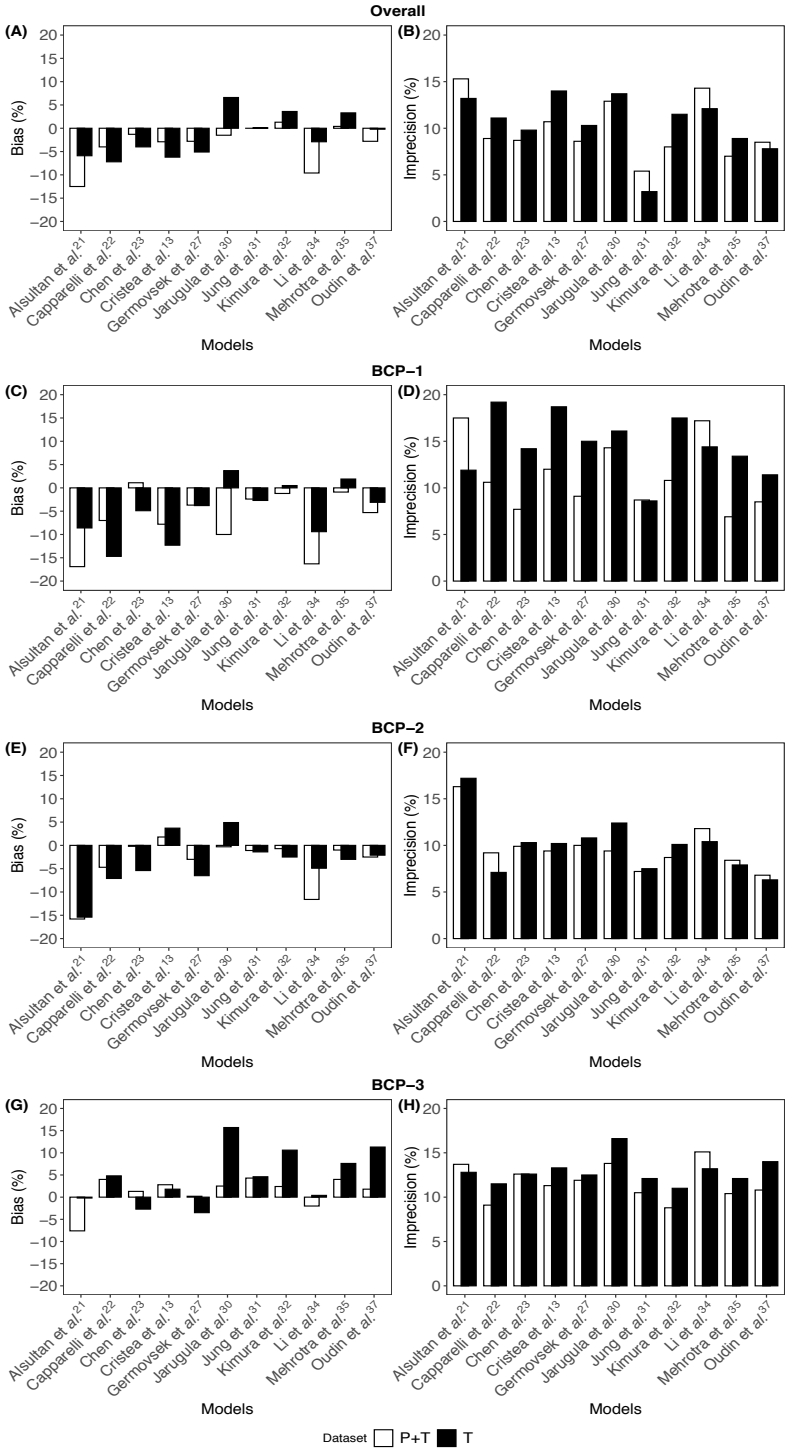


Figure 3. – A posteriori predictive performance of suitable models Overall: **(A)** Bias, **(B)** Imprecision, BCP-1: **(C)** Bias, **(D)** Imprecision, BCP-2: **(E)** Bias, **(F)** Imprecision and BCP-3: **(G)** Bias, **(H)** Imprecision - Values in white and black are obtained on complete (P+T) and truncated (T) dataset, respectively - BCP: Bayesian Conditional Posterior

3.4.5. Initial dosing nomogram

Monte Carlo simulations were conducted using **Capparelli et *al.***[22] and **Mehrotra et *al.***[35] models. The simulated neonatal population was purposely designed to resemble our external patients; median (IQR) values of the main covariates found in the best models[22,35] are likened in **Supporting Information-Table S6**. CMES current initial dosing nomogram was insufficient to reach the therapeutic AUC_{24h} target and the two models suggested higher initial doses of vancomycin, ranging from 24 mg/kg/day to 48 mg/kg/day. **Table 2** and **Table 3** compares the probability of target attainment with the current versus the new initial dosing nomograms, either using the **Capparelli et *al.***[22] or **Mehrotra et *al.***[35] models. Generally, the **Capparelli et *al.***[22] model required greater doses than **Mehrotra et *al.***,[35] except for the older (PMA $\geq$ 45 weeks) group where an initial dose of 12 mg/kg every 6 h was proposed in both cases. The administration intervals remained mostly unchanged, yet the younger (PMA $<$ 30 weeks, PNA $\leq$ 14 days) group would benefit from 13 mg/kg with **Capparelli et *al.***,[22] or 12 mg/kg **Mehrotra et *al.***[35] every 12 h, rather than 10 mg/kg every 18 h, to improve therapeutic target attainment. Simulation results were typically higher than those observed at CMES for identical initial dosing regimens (**Supporting Information-Table S7**), whereas Bayesian and equation-based approaches resulted in comparable AUC_{24h} values (**Supporting Information-Table S8**).

Table 2. – Percentage of target attainment with CMES versus new initial dosing nomogram using **Capparelli et *al.*** [22]

Current initial dosing nomogram CMES[a]	Trough = 10-20	Trough >20	Median (IQR) trough (mg/L)	B-AUC_{24h}[b] = 400-600	B-AUC_{24h}[b] >600	Median (IQR) B-AUC_{24h}[b] (mg*h/L)
PMA $<$ 30, PNA $\leq$ 14 (10 mg/kg q18h)[c]	5.5	0.0	4.0 (0.9-6.6)	1.4	0.0	229.1 (187.5-275.4)
PMA $<$ 30, PNA $>$ 14 (10 mg/kg q12h)[c]	17.1	0.3	6.0 (3.1-8.8)	19.8	1.5	325.8 (264.6-393.9)
30 $\leq$ PMA $<$ 37, PNA $\leq$ 14 (10 mg/kg q12h)[c]	11.1	0.0	4.7 (1.8-7.5)	4.9	0.0	274.8 (229.9-317.4)
30 $\leq$ PMA $<$ 37, PNA $>$ 14 (10 mg/kg q8h)[c]	21.3	0.0	6.2 (3.1-9.4)	28.2	3.7	338.4 (278.3-420.0)
37 $\leq$ PMA $<$ 45, PNA $\leq$ 7 (10 mg/kg q12h)[c]	15.5	0.0	4.9 (2.1-8.5)	18.2	0.0	287.8 (230.5-363.0)
37 $\leq$ PMA $<$ 45, PNA $>$ 7 (10 mg/kg q8h)[c]	18.8	0.6	6.1 (3.1-9.0)	23.5	3.3	324.5 (261.1-407.8)
PMA $\geq$ 45 (10 mg/kg q6h)[c]	20.8	0.0	7.1 (4.3-9.2)	35.4	4.2	361.9 (328.8-469.0)
Total (n = 1491)[d]	17.2	0.2	5.6 (2.7-8.8)	20.9	2.3	314.1 (251.0-393.8)

Table 2. – Capparelli et *al.*[22] (Cont.)

New initial dosing nomogram proposed[22]	Trough = 10-20	Trough >20	Median (IQR) trough (mg/L)	B-AUC_{24h}[b] = 400-600	B-AUC_{24h}[b] >600	Median (IQR) B-AUC_{24h}[b] (mg*h/L)
PMA $<$ 30, PNA $\leq$ 14 (13 mg/kg q12h)[c]	34.5	0.7	8.2 (4.4-11.4)	47.6	15.2	436.3 (353.5-534.3)
PMA $<$ 30, PNA $>$ 14 (13 mg/kg q12h)[c]	30.1	0.6	7.8 (4.4-11.2)	45.1	11.2	424.9 (338.1-512.8)
30 $\leq$ PMA $<$ 37, PNA $\leq$ 14 (11 mg/kg q8h)[c]	34.6	0.0	8.3 (5.1-11.3)	55.6	13.6	444.5 (363.2-536.8)
30 $\leq$ PMA $<$ 37, PNA $>$ 14 (13 mg/kg q8h)[c]	33.2	1.4	8.1 (4.4-11.8)	44.0	17.7	442.6 (355.9-551.8)
37 $\leq$ PMA $<$ 45, PNA $\leq$ 7 (14 mg/kg q12h)[c]	32.7	0.9	7.2 (3.6-11.7)	40.7	11.5	406.0 (316.0-521.2)
37 $\leq$ PMA $<$ 45, PNA $>$ 7 (13 mg/kg q8h)[c]	31.5	2.4	7.7 (4.1-11.1)	41.8	14.8	425.5 (333.0-529.9)
PMA $\geq$ 45 (12 mg/kg q6h)[c]	31.3	2.1	8.6 (5.3-11.1)	43.8	20.8	432.2 (389.8-564.0)
Total (n = 1497)[d]	32.2	1.3	7.9 (4.3-11.4)	44.5	14.8	432.2 (344.1-532.7)

Values are reported as percentages (%) unless specified otherwise - CMES: External hospital of interest - IQR: Interquartile Range - [a] Theoretical CMES nomogram assuming bacteremia - [b] B-AUC_{24h}: Bayesian 24 h area under the concentration-time curve (AUC_{24h}) from **Capparelli et *al.*[22]** - [c] Postmenstrual age (PMA) is expressed in weeks, postnatal age (PNA) in days (dosage regimen) - [d] Simulated patients were removed whenever trough > peak concentration

Table 3. – Percentage of target attainment with CMES versus new initial dosing nomogram using **Mehrotra et *al.***[35]

Current initial dosing nomogram CMES[a]	Trough = 10-20	Trough >20	Median (IQR) trough (mg/L)	B-AUC_{24h}[b] = 400-600	B-AUC_{24h}[b] >600	Median (IQR) B-AUC_{24h}[b] (mg*h/L)
PMA $<$ 30, PNA $\leq$ 14 (10 mg/kg q18h)[c]	7.6	0.0	5.6 (3.4-7.6)	8.3	0.7	271.3 (236.5-328.7)
PMA $<$ 30, PNA $>$ 14 (10 mg/kg q12h)[c]	34.8	0.3	8.6 (6.2-11.1)	39.8	6.5	391.6 (329.1-463.5)
30 $\leq$ PMA $<$ 37, PNA $\leq$ 14 (10 mg/kg q12h)[c]	29.6	0.0	8.5 (5.8-10.3)	37.0	4.9	381.1 (306.0-447.6)
30 $\leq$ PMA $<$ 37, PNA $>$ 14 (10 mg/kg q8h)[c]	38.8	1.4	9.1 (6.7-11.9)	40.6	14.3	414.5 (342.3-521.2)
37 $\leq$ PMA $<$ 45, PNA $\leq$ 7 (10 mg/kg q12h)[c]	17.7	0.0	6.4 (4.3-9.4)	26.5	0.9	318.1 (255.6-405.5)
37 $\leq$ PMA $<$ 45, PNA $>$ 7 (10 mg/kg q8h)[c]	32.0	0.6	8.5 (5.7-10.6)	33.2	7.7	373.4 (294.9-449.2)
PMA $\geq$ 45 (10 mg/kg q6h)[c]	32.7	0.0	7.9 (6.1-11.2)	38.8	8.2	398.5 (293.4-464.4)
Total (n = 1497)[d]	31.1	0.6	8.2 (5.7-10.8)	34.3	8.0	374.9 (302.8-459.7)

Table 3. – Mehrotra et *al.*[35] (Cont.)

New initial dosing nomogram proposed[35]	Trough = 10-20	Trough >20	Median (IQR) trough (mg/L)	B-AUC_{24h}[b] = 400-600	B-AUC_{24h}[b] >600	Median (IQR) B-AUC_{24h}[b] (mg*h/L)
PMA $<$ 30, PNA $\leq$ 14 (12 mg/kg q12h)[c]	54.5	3.5	10.8 (8.1-13.4)	55.2	23.8	482.8 (407.9-592.7)
PMA $<$ 30, PNA $>$ 14 (12 mg/kg q12h)[c]	51.6	2.1	10.3 (7.8-13.3)	56.0	17.7	470.0 (396.1-558.2)
30 $\leq$ PMA $<$ 37, PNA $\leq$ 14 (12 mg/kg q12h)[c]	51.9	1.2	10.2 (7.1-12.4)	56.8	9.9	454.1 (368.4-543.7)
30 $\leq$ PMA $<$ 37, PNA $>$ 14 (11 mg/kg q8h)[c]	46.2	3.0	9.9 (7.5-13.1)	44.8	20.8	455.7 (375.5-574.3)
37 $\leq$ PMA $<$ 45, PNA $\leq$ 7 (10 mg/kg q8h)[c]	46.9	2.7	9.9 (7.7-13.6)	46.0	20.4	468.4 (377.4-581.7)
37 $\leq$ PMA $<$ 45, PNA $>$ 7 (12 mg/kg q8h)[c]	48.1	2.4	10.0 (7.0-12.5)	47.8	15.7	451.0 (354.9-541.1)
PMA $\geq$ 45 (12 mg/kg q6h)[c]	38.8	4.1	9.5 (7.5-13.4)	46.9	16.3	472.9 (355.5-557.6)
Total (n = 1495)[d]	48.8	2.6	10.2 (7.5-13.1)	49.8	18.5	460.0 (377.4-562.6)

Values are reported as percentages (%) unless specified otherwise - CMES: External hospital of interest - IQR: Interquartile Range- [a] Theoretical CMES nomogram assuming bacteremia - [b] B-AUC_{24h}: Bayesian 24 h area under the concentration-time curve (AUC_{24h}) from **Mehrotra et *al.*[35]** - [c] Postmenstrual age (PMA) is expressed in weeks, postnatal age (PNA) in days (dosage regimen) - [d] Simulated patients were removed whenever trough > peak concentration

3.5. Discussion

In this study, we successfully identified two predictive PopPK models and simulated new optimized initial vancomycin dosing nomograms for CMES newborns to reach therapeutic target more effectively and possibly reduce blood sampling. Although it is not the first study externally evaluating vancomycin PopPK models in neonates,[18,24,42,43] our study stands out because we assessed the most models (i.e., 28 models) and had 380 vancomycin concentrations, including 182 peaks, allowing us to assess limited sampling strategies using real-life data in neonates for the first time, to the best of our knowledge.[44,45] The use of first-order PK equations was introduced preemptively by some CMES clinicians back in 2016, a few years before the latest guidelines were published.[5] Unfortunately, it requires at least two blood samples to calculate AUC_{24h}, which represents a significant drawback, notably in newborns where frequent sampling increases the risks of iatrogenic anemia, among other risk factors.[46] PopPK models may provide a solution to this problem, either by limiting blood collection to a single trough, which our results demonstrated as feasible for some models despite an inevitable loss of predictive performance, or guiding physicians to select ideal initial doses to reach the therapeutic target more effectively, reducing the need for subsequent TDM adjustments, hopefully improving clinical outcomes and reducing toxicity. Considering the sizeable amount of neonatal vancomycin PopPK models already developed and their recurrent covariates, we believe external evaluation should be prioritized.[8]

Although there is no formal consensus regarding the suitable predictive performance of PopPK models in external evaluations,[47] our criteria were identical to another recent study in neonatal vancomycin models.[18] Eleven models were predictive in the P+T dataset of CMES, but it is worth noting that the similar numbers of troughs (197) and peaks (182) available from the external dataset helped in this regard. Indeed, it is easier to obtain low PE% values with peaks versus troughs since the denominator (i.e., C_{obs}) is typically larger. Accordingly, only five models retained an acceptable predictive performance in the T

dataset; our best model's negative and positive biases were amplified to an unacceptable extent, with **Capparelli et *al.*** [22] going from -10.4% to -22.6%, and **Mehrotra et *al.*** [35] from 5.2% to 15.6%, respectively. This observation is illustrated in **Supporting Information-Figure S3**, where goodness-of-fit plots are traced for the two models using the T dataset.

This loss of predictive performance was anticipated for **Capparelli et *al.*** [22] since the removal of peak concentrations impairs the distribution phase knowledge,[48] which is particularly relevant in a two-compartment model. **Mehrotra et *al.***,[35] a one-compartment model, fell just outside the MDPE $\leq \pm 15\%$ requirements. Their PK equations, both including weight, age, and SCr, are further described in **Supporting Information-Figure S4**. Regardless of their inability to perform satisfactorily in the T dataset, **Capparelli et *al.*** [22] and **Mehrotra et *al.*** [35] were the best models owing to similar imprecisions of 16.8% and 16.9%, F_{20} of 57.4% and 59.7%, F_{30} of 74.5% and 75.0%, along with correspondence rates of 85.6% and 86.2%, respectively, despite a few statistically significant differences with our external CMES population. This may be attributable to the number of patients and vancomycin concentrations (**Table 1**), especially for **Capparelli et *al.*** [22] which is richly sampled. Nevertheless, other alternatives, such as the **Chen et *al.*** [23] or **Oudin et *al.*** [37] models, may be preferred if the reduction of blood sampling is the main concern since they performed better than the **Capparelli et *al.*** [22] and **Mehrotra et *al.*** [35] models in the T dataset (**Figure 1**).

Good levels of correspondence were usually observed, with a majority (67.9%) of PopPK models presenting over 75% agreement with the CMES reference. Classes were divided using theoretical thresholds[5] and closeness of AUC_{24h} values to the limits appeared as the biggest factor for disagreement. Interestingly, a greater negative correlation was observed between the correspondence rates and individual, rather than population, results. Indeed, **Supporting Information-Figure S5**, including the predictive performance results of all 28 models, shows that the individual imprecision (R^2 = 0.826) was almost twice as likely to explain correspondence rates better than the population one (R^2 =

0.441), in which lower imprecision values provides higher correspondence rates. These observations are consistent with the fact that individual-predicted clearances are used as a denominator to calculate Bayesian AUC_{24h}.

At the individual level, BCP resuted in three different scenarios illustrated in **Figure 3**: a progressive decrease, progressive increase, or fluctuations in imprecision values. These trends could not be linked to the models' structure or covariates, but they still presented adequate levels of bias and imprecision notwithstanding a few exceptions.[21,34] The **Capparelli et *al.***[22] model should be preferred to **Mehrotra et *al.***[35] for a posteriori dosage adjustment due to its progressive decrease in imprecision. Globally, the propensity of the **Capparelli et *al.***[22] model to underpredict, or the **Mehrotra et *al.***[35] model to overpredict vancomycin concentrations was maintained a posteriori, even if both models tended to overpredict AUC_{24h} against CMES reference; these trends were replicated in our Monte Carlo simulations (**Supporting Information-Table S7**).

The new dosing nomograms frequently proposed an initial dose of 13 mg/kg for **Capparelli et *al.***[22] and 12 mg/kg for **Mehrotra et *al.***[35] A 15 mg/kg loading dose was not retained as it had hardly any benefits on target achievement while increasing risks of toxicity for any given dose. The most significant changes applied to young preterm (PMA $<$ 30 weeks, PNA $\leq$ 14 days) neonates, where a higher initial dose and shorter administration intervals should promote better therapeutic target attainment; it is consistent with results observed at CMES in **Figure 2**. These initial doses are likely on the safer side considering models typically overpredicted AUC_{24h}. Despite nonnegligible levels of AUC_{24h} >600 mg*h/L, either 14.8%[22] or 18.5%,[35] only a small fraction was exceeding 800 mg*h/L, 2.5%[22] or 2.9%,[35] in the **Capparelli et *al.***[22] and **Mehrotra et *al.***[35] models, respectively. Of note, guidelines suggested AUC_{24h} up to 800 mg*h/L in pediatric patients since nephrotoxicity appears less problematic than in adults.[5] Interestingly, **Supporting Information-Table S7** shows a less significant difference between model-predicted AUC_{24h} and CMES reference for newborns with PNA $\leq$ 14 days, with PNA $\leq$ 7 days even

generating lower AUC_{24h} values. This could be due to the fluctuations of SCr and its poor reliability to describe kidney function in the early stages of life,[49,50] which constitutes a limit of our study because the best models[22,35] both include this covariate (**Supporting Information-Figure S4**).

Other limitations of our study are the retrospective design, impacting the quantity (unavailable covariates) and possibly the quality of our data, together with the method applied to generate simulated patients.[20] Indeed, the mean $\pm$ SD values of all subgroups were used to simulate virtual patients characteristics, meaning larger variations in the CMES dataset could have impaired the validity of simulations. This is evidenced **Supporting Information-Table S6**, in which one outlier at PMA = 36 weeks in the third age subgroup ($30 \leq$ PMA < 37, PNA ≤ 14) had a weight of 5.1 kg, resulting in a median weight of 2.6 kg for simulated patients versus 1.5 kg for CMES neonates.

3.6. Conclusion

We successfully evaluated 28 neonatal vancomycin PopPK models and selected the two most predictive ones[22,35] to propose optimized initial dosing nomograms for CMES neonates. It is expected that these nomograms, derived from the two most predictive models, should achieve therapeutic target faster, particularly as steady-state is not required if TDM adjustments are required, and limit the need for subsequent TDM adjustments. Therefore, we believe our objective to improve CMES TDM practice using PopPK may come to fruition since we were able to propose new optimized initial vancomycin dosing nomograms readily available for clinical implementation and demonstrated the feasibility of limited sampling strategies.

3.7. References

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3.8. Supporting Information

Table 1. – CMES current neonatal initial dosing nomogram

Postmenstrual age (PMA)	Postnatal age (PNA)	Administration interval
≤ 29 weeks	≤ 14 days	18 hours
	> 14 days	12 hours
30 to 36 weeks	≤ 14 days	12 hours
	> 14 days	8 hours
37 to 44 weeks	≤ 7 days	12 hours
	> 7 days	8 hours
≥ 45 weeks	-	6 hours

Table 2. – Overview of assessed neonatal PopPK models of vancomycin

Original publication	Model description					PK parameters	
	Number of compartments	Study design	Software	Estimation methods	Sampling	Clearance (L/h/kg)	Volume of distribution (L/kg)
Allegaert et *al.* (12)	1	Retrospective	NONMEM	FOCE	Peak and trough	0.023	0.56
Alsultan et *al.* (21)	1	Retrospective	Monolix	SAEM	Peak and trough	0.097	0.87
Capparelli et *al.* (22)	2	-	NONMEM	FOCE	Peak, trough, random	0.066	0.79
Chen et *al.* (23)	1	Retrospective	NONMEM	FOCE-I	Peak and trough	0.103	0.58
Chung and Seto (24)	1	Retrospective	NONMEM	FOCE-I	Peak, trough, random	0.088	0.93
Cristea et *al.* (13,14)	2	-	NONMEM	FOCE-I	Peak, trough, random	0.053	0.91
Dao et *al.* (25)	1	Retrospective	NONMEM	FOCE-I	Peak, trough, random	0.273	0.63
De Cock et *al.* (14)	2	-	NONMEM	FOCE-I	Peak, trough, random	0.038	0.62
Frymoyer et *al.* (26)	1	Retrospective	NONMEM	FOCE-I	Peak, trough, random	0.095	0.60
Germovsek et *al.* (27)	1	Prospective	NONMEM	FOCE-I	Peak, trough, random	0.081	0.56
Grimsley and Thomson (28)	1	Prospective	NONMEM	FO/POSTHOC	Peak and trough	0.073	0.67
Hui et *al.* (29)	2	Retrospective	NONMEM	FOCE-I	-	0.082	0.45
Jarugula et *al.* (30)	1	Retrospective	Pumas	FOCE	-	0.068	0.85
Jung et *al.* (31)	1	Retrospective	NONMEM	FOCE-I	Peak and trough	0.049	0.73
Kimura et *al.* (32)	1	-	NONMEM	FO/POSTHOC	Peak and trough	0.076	0.66

Table S2. – (Cont.)

Leroux et *al.* (33)	1	-	NONMEM	FOCE-I	Continuous infusion	0.068	0.29
Li et *al.* (11)	1	-	NONMEM	FOCE-I	Peak and trough	0.147	0.72
Li et *al.* (34)	1	Retrospective	NONMEM	FOCE-I	Peak and trough	0.107	0.91
Lo et *al.* (15)	1	Retrospective	NONMEM	FOCE-I	-	0.043	0.52
Marqués-Miñana et *al.* (10)	1	-	NONMEM	FO/POSTHOC	Peak and trough	0.066	0.57
Mehrotra et *al.* (35)	1	Retrospective	NONMEM	FOCE	Peak and trough	0.072	0.68
Mulubwa et *al.* (36)	1	-	Monolix	SAEM	Trough	0.069	0.60
Oudin et *al.* (37)	1	Prospective	NONMEM	FOCE	Continuous infusion	1.173[a]	0.86
Sasano et *al.* (38)	1	-	NONMEM	FOCE-I	Trough	0.063	0.93
Seay et *al.* (9)	2	Retrospective	NONMEM	FO/POSTHOC	Peak and trough	0.059	0.44
Sheng et *al.* (39)	1	Retrospective	NONMEM	FO/POSTHOC	Peak and trough	0.143	1.38
Tseng et *al.* (40)	1	Retrospective	NONMEM	FOCE-I	Peak, trough, random	0.052	0.50
Zhao et *al.* (41)	1	Prospective	NONMEM	FOCE-I	Continuous infusion	0.040	0.56

FO(CE): First-Order (Conditional Estimation) - SAEM: Stochastic Approximation Expectation Maximisation - I: Interaction - [a] CL/µmol/L

Table 3. – 1) Characteristics of CMES neonatal population compared to adequate models (A-G)

Characteristics (Units)	**Type of value**	**CMES**	**Alsultan et *al.* (21)**	**Chen et *al.* (23)**	**De Cock et *al.* (13,14)[a]**	**Germovsek et *al.* (27)**
Number of patients (M/F)	Count	72 (43/29)	162 (73/52)[b,c]	213 (NA)	273 (NA)	54 (NA)
Gestational age (weeks)	Mean ± SD	30.4 ± 5.9	28.0 ± 2.9*	NA	NA	NA
	Median (IQR) or [range]	28 [23-40]	[22-35]	36.9 [25-42]*	29 [23-34]	29.0 [23.7-41.9]
Postnatal age (days)	Mean ± SD	28.6 ± 24.2	10.7 ± 7.5*	NA	NA	NA
	Median (IQR) or [range]	21.4 [4.3-125.0]	[1-30]	26 [6-59]	14 [1-28]*	30 [1-156]
Postmenstrual age (weeks)	Mean ± SD	34.5 ± 5.9	29.8 ± 3.15*	NA	NA	NA
	Median (IQR) or [range]	34.0 [24.3-49.0]	[22-39]	39.8 [28-47.9]*	30 [24-38]*	NA
Weight (kg)	Mean ± SD	2.1 ± 1.3	1.0 ± 0.29*	NA	NA	NA
	Median (IQR) or [range]	1.9 [0.5-6.6]	[0.46-1.7]	2.73 [0.88-5.10]*	1.170 [0.415-2.630]*	NA

Table S3. – 1) (A-G) (Cont.)

Birth weight (kg)	Mean ± SD	1.7 ± 1.1	0.95 ± 0.27*	NA	NA	NA
	Median (IQR) or [range]	1.1 [0.4-4.8]	[0.46-1.5]	2.53 [0.70-4.70]*	1.140 [0.385-2.550]*	NA
Serum creatinine (µmol/L)	Mean ± SD	37.5 ± 13.4	NA	NA	NA	NA
	Median (IQR) or [range]	36.8 [17.0-79.0]	NA	NA	NA	31 [18-98]*
Serum creatinine (mg/dL)	Mean ± SD	0.4 ± 0.2	0.65 ± 0.22*	NA	NA	NA
	Median (IQR) or [range]	0.4 [0.2-0.9]	[0.2-1.5]	0.28 [0.11-0.72]*	NA	NA
Number of blood samples	Count	380	214	330	689	183[b]

* $p < 0.05$ - CMES: External neonatal population - M/F: Male/Female - SD: Standard Deviation - IQR: Interquartile Range - NA: Not Available – [a] **Cristea et *al.*** (13), model derived using the amikacin covariate model, and **De Cock et *al.*** (14), independent reference model, are both issued from the same neonatal population - [b] Values derived from available information found in the original publication – [c] Including missing values as reported in the original publication

Table 3. – 1) Characteristics of CMES neonatal population compared to adequate models (J-L)

Characteristics (Units)	**Type of value**	**CMES**	**Jarugula et *al.* (30)**	**Jung et *al.* (31)**	**Kimura et *al.* (32)**	**Li et *al.* (34)**
Number of patients (M/F)	Count	72 (43/29)	934 (547/387)[b]	93 (57/36)	19 (9/10)	80 (54/26)
Gestational age (weeks)	Mean ± SD	30.4 ± 5.9	NA	31.9 ± 4.7*	NA	34.70 ± 4.31*
	Median (IQR) or [range]	28 [23-40]	NA	[22.9-40.3]	[24.1-41.3]	34.0 [25.7-41.1]*
Postnatal age (days)	Mean ± SD	28.6 ± 24.2	57.89*	65.1 ± 86.8*	NA	32.3 ± 24.1
	Median (IQR) or [range]	21.4 [4.3-125.0]	43.6 (18.64-86.18) [0-184]*	[0.7-562.8][b]	[3-71]	24 [4-126]
Postmenstrual age (weeks)	Mean ± SD	34.5 ± 5.9	42.41*	41.2 ± 14.2*	NA	39.40 ± 3.60*
	Median (IQR) or [range]	34.0 [24.3-49.0]	41.99 (34.85-48.58) [20.89-66.68]*	[25.6-110.0]	[25.1-48.4]	40.0 [29.0-47.1]*
Weight (kg)	Mean ± SD	2.1 ± 1.3	3.57*	3.2 ± 2.6*	NA	2.87 ± 0.89*
	Median (IQR) or [range]	1.9 [0.5-6.6]	3.58 (1.97-4.91) [0.37-11.88]*	[0.4-14.9]	[0.710-5.200]	2.74 [1.40-5.60]*

Table S3. – 1) (J-L) (Cont.)

Birth weight (kg)	Mean ± SD	1.7 ± 1.1	NA	NA	NA	NA
	Median (IQR) or [range]	1.1 [0.4-4.8]	NA	NA	NA	NA
Serum creatinine (µmol/L)	Mean ± SD	37.5 ± 13.4	NA	NA	NA	23.2 ± 10.4*
	Median (IQR) or [range]	36.8 [17.0-79.0]	NA	NA	NA	28.30 [5.85-61.60]*
Serum creatinine (mg/dL)	Mean ± SD	0.4 ± 0.2	0.46	0.4 ± 0.3	NA	NA
	Median (IQR) or [range]	0.4 [0.2-0.9]	0.33 (0.25-0.51) [0.1-4.54]*	[0.1-3.37]	[0.2-0.9]	NA
Number of blood samples	Count	380	2471	3902	88	165

* $p < 0.05$ - CMES: External neonatal population - M/F: Male/Female - SD: Standard Deviation - IQR: Interquartile Range - NA: Not Available - [b] Values derived from available information found in the original publication

Table 3. – 1) Characteristics of CMES neonatal population compared to adequate models (O)

Characteristics (Units)	**Type of value**	**CMES**	**Oudin et *al.* (37)**
Number of patients (M/F)	Count	72 (43/29)	68 (NA)
Gestational age (weeks)	Mean ± SD	30.4 ± 5.9	29.5 ± 27
	Median (IQR) or [range]	28 [23-40]	27 (26-30) [23-41]*
Postnatal age (days)	Mean ± SD	28.6 ± 24.2	21.6 ± 23.0*
	Median (IQR) or [range]	21.4 [4.3-125.0]	14 (10-27) [4-169]*
Postmenstrual age (weeks)	Mean ± SD	34.5 ± 5.9	32.7 ± 5.3*
	Median (IQR) or [range]	34.0 [24.3-49.0]	31 (29-35) [27-47]*
Weight (kg)	Mean ± SD	2.1 ± 1.3	1.50 ± 0.97*
	Median (IQR) or [range]	1.9 [0.5-6.6]	1.10 (0.90-1.62) [0.58-4.60]*

Table S3. – 1) (O) (Cont.)

Birth weight (kg)	Mean ± SD	1.7 ± 1.1	NA
	Median (IQR) or [range]	1.1 [0.4-4.8]	NA
Serum creatinine (µmol/L)	Mean ± SD	37.5 ± 13.4	NA
	Median (IQR) or [range]	36.8 [17.0-79.0]	NA
Serum creatinine (mg/dL)	Mean ± SD	0.4 ± 0.2	NA
	Median (IQR) or [range]	0.4 [0.2-0.9]	NA
Number of blood samples	Count	380	151

* $p < 0.05$ - CMES: External neonatal population - M/F: Male/Female - SD: Standard Deviation - IQR: Interquartile Range - NA: Not Available

Table 3. – 2) Characteristics of CMES neonatal population compared to inadequate models (A-F)

Characteristics (Units)	**Type of value**	**CMES**	**Allegaert et *al.* (12)**	**Chung and Seto (24)**	**Dao et *al.* (25)**	**Frymoyer et *al.* (26)**
Number of patients (M/F)	Count	72 (43/29)	249 (NA)	442 (259/183)[a]	405 (231/174)[a]	249 (128/121)[a]
Gestational age (weeks)	Mean ± SD	30.4 ± 5.9	NA	NA	NA	NA
	Median (IQR) or [range]	28 [23-40]	29 [23-34]	28.43 (25.29-34.86)*	29.0 (26.7-34.9) [24.0-42.1]	34 (27-39) [22-42]*
Postnatal age (days)	Mean ± SD	28.6 ± 24.2	NA	NA	NA	NA
	Median (IQR) or [range]	21.4 [4.3-125.0]	11 [1-27]*	21.00 (9.00-41.49)	12.3 (5-14) [0-146]*	19 (10-42) [0-173]*
Postmenstrual age (weeks)	Mean ± SD	34.5 ± 5.9	NA	NA	NA	NA
	Median (IQR) or [range]	34.0 [24.3-49.0]	31 [24-37]*	34.35 (30.17-38.54)	32.0 (28.3-36.5) [24.6-61.0]*	39 (32-42) [24-54]*
Weight (kg)	Mean ± SD	2.1 ± 1.3	1.249 ± 0.466*	NA	NA	NA
	Median (IQR) or [range]	1.9 [0.5-6.6]	NA	1.73 (1.02-2.50)*	1.100 (0.800-2.170) [0.462-5.660]*	2.9 (1.6-3.7) [0.5-6.3]*

Table S3. – 2) (A-F) (Cont.)

Birth weight (kg)	Mean ± SD	1.7 ± 1.1	1.221 ± 0.473*	NA	NA	NA
	Median (IQR) or [range]	1.1 [0.4-4.8]	NA	1.04 (0.73-2.15)*	1.050 (0.790-2.170) [0.462-4.330]*	2.0 (0.9-3.1) [0.4-4.4]*
Serum creatinine (µmol/L)	Mean ± SD	37.5 ± 13.4	NA	NA	NA	NA
	Median (IQR) or [range]	36.8 [17.0-79.0]	NA	29.00 (21.00-43.00)*	54 (31-68) [5-276]*	NA
Serum creatinine (mg/dL)	Mean ± SD	0.4 ± 0.2	NA	NA	NA	NA
	Median (IQR) or [range]	0.4 [0.2-0.9]	NA	NA	NA	0.4 (0.3-0.6) [0.1-2.7]
Number of blood samples	Count	380	648	666	1831	1702

* $p < 0.05$ - CMES: External neonatal population - M/F: Male/Female - SD: Standard Deviation - IQR: Interquartile Range - NA: Not Available - [a] Values derived from available information found in the original publication

Table 3. – 2) Characteristics of CMES neonatal population compared to inadequate models (G-L)

Characteristics (Units)	**Type of value**	**CMES**	**Grimsley and Thomson (28)**	**Hui et *al.* (29)**	**Leroux et *al.* (33)**	**Li et *al.* (11)**
Number of patients (M/F)	Count	72 (43/29)	59 (38/21)[a]	207 (112/95)	66 (29/37)	94 (58/36)
Gestational age (weeks)	Mean ± SD	30.4 ± 5.9	NA	NA	NA	37.18 ± 3.71*
	Median (IQR) or [range]	28 [23-40]	29 [25-41]	30.1 (6.9) [24.1-41.3]	32 [23-41]*	39.0 [25.7-41.4]*
Postnatal age (days)	Mean ± SD	28.6 ± 24.2	NA	NA	NA	67.14 ± 80.85*
	Median (IQR) or [range]	21.4 [4.3-125.0]	19 [2-76]*	17 (14) [7-114]*	13 [1-106]*	88.5 [1-345]*
Postmenstrual age (weeks)	Mean ± SD	34.5 ± 5.9	NA	NA	NA	NA
	Median (IQR) or [range]	34.0 [24.3-49.0]	32 [26-45]*	33.7 (7.3) [25.7-53.3]	34 [26-46]	NA
Weight (kg)	Mean ± SD	2.1 ± 1.3	NA	NA	NA	4.686 ± 2.570*
	Median (IQR) or [range]	1.9 [0.5-6.6]	1.52 [0.57-4.23]*	1.68 (1.13) [0.47-7.36]*	1.925 [0.530-3.840]	4.0 [1.4-18.0]*

Table S3. – 2) (G-L) (Cont.)

Birth weight (kg)	Mean ± SD	1.7 ± 1.1	NA	NA	NA	2.9780 ± 0.81549*
	Median (IQR) or [range]	1.1 [0.4-4.8]	NA	1.32 (0.89) [0.44-4.14]	1.590 [0.512-3.950]	3.200 [0.850-4.400]*
Serum creatinine (µmol/L)	Mean ± SD	37.5 ± 13.4	NA	NA	NA	19.91 ± 7.45*
	Median (IQR) or [range]	36.8 [17.0-79.0]	49 [18-172]*	42 (34) [15-252]*	41 [12-153]*	18.25 [5.50-50.00]*
Serum creatinine (mg/dL)	Mean ± SD	0.4 ± 0.2	NA	NA	NA	NA
	Median (IQR) or [range]	0.4 [0.2-0.9]	NA	NA	NA	NA
Number of blood samples	Count	380	347	689	108	205

* $p < 0.05$ - CMES: External neonatal population - M/F: Male/Female - SD: Standard Deviation - IQR: Interquartile Range - NA: Not Available - [a] Values derived from available information found in the original publication

Table 3. – 2) Characteristics of CMES neonatal population compared to inadequate models (L-S)

Characteristics (Units)	**Type of value**	**CMES**	**Lo et *al.* (15)**	**Marqués-Miñana et *al.* (10)**	**Mulubwa et *al.* (36)**	**Sasano et *al.* (38)**
Number of patients (M/F)	Count	72 (43/29)	116 (66/50)[a]	70 (33/37)	19 (8/11)	19 (13/6)
Gestational age (weeks)	Mean ± SD	30.4 ± 5.9	NA	32.2 ± 5.0*	NA	26.4 ± 2.5*
	Median (IQR) or [range]	28 [23-40]	NA	[24.0-42.0]	31 [23-34]	26.0 [22.6-30.3][a]*
Postnatal age (days)	Mean ± SD	28.6 ± 24.2	NA	16.9 ± 10.9*	NA	30.4 ± 17.2
	Median (IQR) or [range]	21.4 [4.3-125.0]	NA	[4.0-63.0]	14 [3-58]*	28 [0-75]
Postmenstrual age (weeks)	Mean ± SD	34.5 ± 5.9	NA	34.6 ± 5.3	NA	30.8 ± 3.7*
	Median (IQR) or [range]	34.0 [24.3-49.0]	NA	[25.1-48.1]	33.0 [30.0-34.7]	30.4 [23.9-39.0][a]*
Weight (kg)	Mean ± SD	2.1 ± 1.3	NA	1.7 ± 0.8*	NA	0.9019 ± 0.2703*
	Median (IQR) or [range]	1.9 [0.5-6.6]	NA	[0.7-3.7]	1.480 [0.925-2.620]*	0.887 [0.448-1.457]*

Table S3. – 2) (L-S) (Cont.)

Birth weight (kg)	Mean ± SD	1.7 ± 1.1	NA	NA	NA	0.6611 ± 0.1438*
	Median (IQR) or [range]	1.1 [0.4-4.8]	NA	NA	1.27 [0.63-2.69]*	0.632 [0.420-0.978]*
Serum creatinine (µmol/L)	Mean ± SD	37.5 ± 13.4	76 ± 2*	NA	NA	NA
	Median (IQR) or [range]	36.8 [17.0-79.0]	[31-143][a]	NA	51 [26-74]*	NA
Serum creatinine (mg/dL)	Mean ± SD	0.4 ± 0.2	NA	NA	NA	0.45 ± 0.30
	Median (IQR) or [range]	0.4 [0.2-0.9]	NA	NA	NA	0.35 [0.07-2.40]*
Number of blood samples	Count	380	835	NA	45	62

* $p < 0.05$ - CMES: External neonatal population - M/F: Male/Female - SD: Standard Deviation - IQR: Interquartile Range - NA: Not Available - [a] Values derived from available information found in the original publication

Table 3. – 2) Characteristics of CMES neonatal population compared to inadequate models (S-Z)

Characteristics (Units)	**Type of value**	**CMES**	**Seay et *al.* (8)**	**Sheng et *al.* (39)**	**Tseng et *al.* (40)**	**Zhao et *al.* (41)**
Number of patients (M/F)	Count	72 (43/29)	192 (81/111)[a]*	61 (34/27)	76 (44/32)[a]	116 (59/57)
Gestational age (weeks)	Mean ± SD	30.4 ± 5.9	29.6 ± 5.2	NA	NA	NA
	Median (IQR) or [range]	28 [23-40]	[22-42]	NA	26.2 (25.0-28.8) [23.9-40.3]*	NA
Postnatal age (days)	Mean ± SD	28.6 ± 24.2	14.5 ± 11.4*	NA	NA	26 ±25
	Median (IQR) or [range]	21.4 [4.3-125.0]	[1-73]	29.2 [1.095-354.05][a]	17.4 (11.4-40.6) [4.0-223.7]*	17 [1-120]*
Postmenstrual age (weeks)	Mean ± SD	34.5 ± 5.9	NA	NA	NA	33.8 ± 5.3
	Median (IQR) or [range]	34.0 [24.3-49.0]	NA	37.86 [26.00-41.43]*	30.1 (27.9-36.2) [25.1-57.5]*	32.7 [24.4-49.4]*
Weight (kg)	Mean ± SD	2.1 ± 1.3	1.48 ± 1.05*	NA	NA	1.700 ± 0.964*
	Median (IQR) or [range]	1.9 [0.5-6.6]	[0.39-4.35]	3.15 [0.95-16.0]*	1.043 (0.811-1.919) [0.320-6.590]*	1.416 [0.460-5.680]*

Table S3. – 2) (S-Z) (Cont.)

Birth weight (kg)	Mean ± SD	1.7 ± 1.1	NA	NA	NA	1.331 ± 0.839*
	Median (IQR) or [range]	1.1 [0.4-4.8]	NA	NA	0.828 (0.699-1.076) [0.320-3.655]*	1.010 [0.510-3.930]*
Serum creatinine (µmol/L)	Mean ± SD	37.5 ± 13.4	NA	NA	NA	48 ± 33*
	Median (IQR) or [range]	36.8 [17.0-79.0]	NA	32.3 [10.4-109]*	43 (36-59) [7.5-130.0]*	42 [5-228]*
Serum creatinine (mg/dL)	Mean ± SD	0.4 ± 0.2	NA	NA	NA	NA
	Median (IQR) or [range]	0.4 [0.2-0.9]	NA	NA	NA	NA
Number of blood samples	Count	380	520	72	429	207

* $p < 0.05$ - CMES: External neonatal population - M/F: Male/Female - SD: Standard Deviation - IQR: Interquartile Range - NA: Not Available - [a] Values derived from available information found in the original publication

Table 4. – 1) A priori predictive performance of adequate neonatal vancomycin PopPK models

Original publication	Dataset	Population level				AUC_{24h} estimation		
		Bias (%)	Imprecision (%)	F_{20} (%)	F_{30} (%)	Correspondence (%)	Under (%)	Over (%)
Alsultan et *al.* (21)	P+T	4.1	19.0	52.6	73.9	75.1	21.0	3.9
	T	21.7	26.0	35.5	58.9	75.1	19.9	5.0
Capparelli et *al.* (22)	P+T	-10.4	16.8	57.4	74.5	85.6	4.4	9.9
	T	-22.6	24.6	38.6	58.4	82.9	4.4	12.7
Chen et *al.* (23)	P+T	3.4	17.7	54.7	68.7	85.6	4.4	9.9
	T	2.2	25.7	40.1	55.8	83.4	5.0	11.6
Cristea et *al.* (13)	P+T	3.4	24.4	43.9	58.2	77.3	6.1	16.6
	T	0.0	30.9	32.5	48.2	74.0	5.5	20.4
Germovsek et *al.* (27)	P+T	9.3	20.9	48.2	65.0	86.2	6.1	7.7
	T	6.2	28.5	36.5	53.3	81.8	4.4	13.8
Jarugula et *al.* (30)	P+T	-3.0	18.3	54.2	76.3	81.8	5.5	12.7
	T	14.5	25.2	41.1	62.4	80.1	7.7	12.2

Table S4. – 1) (Cont.)

Jung et *al.* (31)	P+T	14.8	22.9	44.5	61.3	84.5	4.4	11.0
	T	27.0	35.9	27.9	43.7	70.7	6.1	23.2
Kimura et *al.* (32)	P+T	5.8	18.4	55.0	67.6	82.3	1.7	16.0
	T	10.4	26.4	39.6	52.3	77.9	3.3	18.8
Li et *al.* (34)	P+T	10.2	24.6	39.7	56.8	77.4	16.0	6.6
	T	33.7	45.3	21.3	37.1	72.4	20.4	7.2
Mehrotra et *al.* (35)	P+T	5.2	16.9	59.7	75.0	86.2	1.7	12.2
	T	15.6	23.4	42.1	62.9	82.3	5.5	12.2
Oudin et *al.* (37)	P+T	-12.4	19.8	50.5	69.7	86.7	3.3	9.9
	T	-3.1	20.9	47.2	59.9	79.6	10.5	9.9

P+T: Complete dataset - T: Truncated dataset - AUC_{24h}: 24-hour area under the concentration-time curve - F_{20}/F_{30}: Percentage of values between $\pm$20/30% - Under: Underestimation - Over: Overestimation

Table 4. – 2) A priori predictive performance of inadequate neonatal vancomycin PopPK models

Original publication	Population level				AUC_{24h} estimation		
	Bias (%)	Imprecision (%)	F_{20} (%)	F_{30} (%)	Correspondence (%)	Under (%)	Over (%)
Allegaert et *al.* (12)	-35.7	36.3	28.2	43.9	85.6	3.9	10.5
Chung and Seto (24)	-25.2	26.5	33.7	60.0	81.2	13.3	5.5
Dao et *al.* (25)	105.0	105.0	1.6	3.9	22.7	0.0	77.3
De Cock et *al.* (14)	36.1	39.0	25.3	37.6	74.0	2.8	23.2
Frymoyer et *al.* (26)	-24.6	26.3	34.7	57.9	81.2	13.8	5.0
Grimsley and Thomson (28)	-24.7	25.7	35.0	61.3	81.8	12.7	5.5
Hui et *al.* (29)	25.9	28.0	34.5	53.4	80.7	2.2	17.1
Leroux et *al.* (33)	23.0	52.8	15.5	24.7	19.3	0.0	80.7
Li et *al.* (11)	-20.1	23.6	41.6	61.6	75.7	21.5	2.8

Table S4. – 2) (Cont.)

Lo et *al.* (15)	56.5	58.2	16.8	24.5	75.7	3.3	21.0
Marqués-Miñana et *al.* (10)	22.7	27.6	37.6	52.1	84.0	5.0	11.0
Mulubwa et *al.* (36)	15.5	31.0	31.6	48.7	37.6	16.6	45.9
Sasano et *al.* (38)	129.1	129.1	2.4	3.7	70.7	1.7	27.6
Seay et *al.* (9)	65.5	65.5	13.2	21.3	66.3	6.1	27.6
Sheng et *al.* (39)	-51.6	52.5	10.5	20.3	48.1	0.0	51.9
Tseng et *al.* (40)	176.5	176.5	1.3	2.9	23.8	0.0	76.2
Zhao et *al.* (41)	57.0	57.0	11.6	24.2	61.9	1.1	37.0

All results are issued from the complete (P+T) dataset only - AUC_{24h}: 24-hour area under the concentration-time curve - F_{20}/F_{30}: Percentage of values between $\pm$20/30% - Under: Underestimation - Over: Overestimation

Table 5. – 1) A posteriori predictive performance of adequate neonatal vancomycin PopPK models

Original publication	Dataset	Individual level		BCP-1		BCP-2		BCP-3	
		Bias (%)	Imprecision (%)	Bias (%)	Imprecision (%)	Bias (%)	Imprecision (%)	Bias (%)	Imprecision (%)
Alsultan et *al.* (21)	P+T	-12.5	15.3	-16.9	17.5	-15.8	16.3	-7.6	13.7
	T	-5.9	13.2	-8.6	11.9	-15.4	17.2	-0.2	12.8
Capparelli et *al.* (22)	P+T	-4.0	8.9	-7.0	10.6	-4.7	9.2	4.0	9.1
	T	-7.2	11.1	-14.7	19.2	-7.1	7.1	4.8	11.5
Chen et *al.* (23)	P+T	-1.3	8.7	1.1	7.7	-0.2	9.9	1.3	12.6
	T	-4.0	9.8	-4.9	14.2	-5.4	10.3	-2.7	12.6
Cristea et *al.* (13)	P+T	-2.9	10.7	-7.8	12.0	1.8	9.4	2.8	11.3
	T	-6.2	14.0	-12.3	18.7	3.7	10.2	1.8	13.3
Germovsek et *al.* (27)	P+T	-2.8	8.6	-3.7	9.1	-3.0	10.0	0.2	11.9
	T	-5.1	10.3	-3.8	15.0	-6.5	10.8	-3.5	12.5
Jarugula et *al.* (30)	P+T	-1.5	12.9	-10.0	14.3	-0.3	9.4	2.5	13.8
	T	6.6	13.7	3.7	16.1	4.9	12.4	15.7	16.6

Table S5. – 1) (Cont.)

Jung et *al.* (31)	P+T	0.0	5.4	-2.4	8.7	-1.1	7.2	4.3	10.5
	T	0.1	3.2	-2.7	8.6	-1.4	7.5	4.6	12.1
Kimura et *al.* (32)	P+T	1.3	8.0	-1.2	10.8	-0.7	8.7	2.4	8.8
	T	3.6	11.5	0.5	17.5	-2.5	10.1	10.6	11.0
Li et *al.* (34)	P+T	-9.6	14.3	-16.3	17.2	-11.6	11.8	-2.0	15.1
	T	-2.9	12.1	-9.4	14.4	-4.9	10.4	0.4	13.2
Mehrotra et *al.* (35)	P+T	0.4	7.0	-0.9	6.9	-1.0	8.4	4.0	10.4
	T	3.3	8.9	1.9	13.4	-3.0	7.9	7.6	12.1
Oudin et *al.* (37)	P+T	-2.8	8.5	-5.3	8.5	-2.5	6.8	1.8	10.8
	T	-0.2	7.8	-3.1	11.4	-2.1	6.3	11.3	14.0

P+T: Complete dataset - T: Truncated dataset - BCP: Bayesian Conditional Posterior

Table 5. – 2) A posteriori predictive performance of inadequate neonatal vancomycin PopPK models

Original publication	**Individual level**	
	Bias (%)	**Imprecision (%)**
Allegaert et *al.* (12)	0.0	5.0
Chung and Seto (24)	-8.2	12.3
Dao et *al.* (25)	42.5	42.5
De Cock et *al.* (14)	10.0	18.3
Frymoyer et *al.* (26)	-9.4	14.6
Grimsley and Thomson (28)	-7.6	11.3
Hui et *al.* (29)	7.6	11.8
Leroux et *al.* (33)	26.6	30.7
Li et *al.* (11)	-16.7	17.3

Table S5. – 2) (Cont.)

Lo et *al.* (15)	8.8	12.3
Marqués-Miñana et *al.* (10)	-0.2	6.8
Mulubwa et *al.* (36)	9.3	25.9
Sasano et *al.* (38)	10.2	17.7
Seay et *al.* (9)	6.2	11.7
Sheng et *al.* (39)	-17.2	34.7
Tseng et *al.* (40)	26.0	28.7
Zhao et *al.* (41)	14.5	15.2

All results are issued from the complete (P+T) dataset only

Table 6. – Characteristics of CMES external population compared with those of simulated patients

Characteristics (Units)		Number of treatments (%)	Gestational age (weeks)	Postnatal age (days)	Postmenstrual age (weeks)	Weight (kg)	Serum creatinine (mg/dL)
CMES external population	**PMA $<$ 30, PNA $\leq$ 14**	9 (9.7)	25.5 (24.0-27.0)	11.3 (8.8-13.5)	27.3 (25.8-28.0)	0.8 (0.8-1.0)	0.6 (0.5-0.6)
	PMA $<$ 30, PNA $>$ 14	21 (22.6)	25.0 (24.0-26.0)	20.7 (16.4-21.8)	28.0 (27.0-29.0)	0.9 (0.8-1.1)	0.5 (0.4-0.6)
	30 $\leq$ PMA $<$ 37, PNA $\leq$ 14	5 (5.4)	30.0 (29.0-30.0)	8.7 (8.0-13.6)	31.0 (30.4-31.5)	1.5 (1.2-1.7)	0.4 (0.4-0.6)
	30 $\leq$ PMA $<$ 37, PNA $>$ 14	27 (29.0)	26.5 (25.0-28.0)	38.8 (28.7-48.2)	32.1 (30.9-34.0)	1.4 (1.2-1.7)	0.4 (0.3-0.4)
	37 $\leq$ PMA $<$ 45, PNA $\leq$ 7	7 (7.5)	40.0 (38.5-40.0)	5.8 (4.7-6.2)	40.7 (39.0-41.0)	3.2 (3.0-3.4)	0.5 (0.4-0.6)
	37 $\leq$ PMA $<$ 45, PNA $>$ 7	21 (22.6)	36.5 (34.8-38.3)	15.5 (10.3-38.2)	39.6 (38.0-41.1)	3.0 (2.6-3.5)	0.3 (0.2-0.4)
	PMA $\geq$ 45	3 (3.2)	37.0 (36.3-37.5)	73.9 (67.6-79.1)	47.1 (46.5-47.7)	4.2 (4.0-5.0)	0.2 (0.2-0.3)
	Total	93 (100)	27.0 (25.0-35.0)	20.7 (13.2-37.8)	32.2 (29.0-38.2)	1.4 (1.0-2.7)	0.4 (0.3-0.5)

Table S6. – (Cont.)

Simulated neonatal patients	**PMA $<$ 30, PNA $\leq$ 14**	145 (9.7)	24.9 (24.0-25.9)	10.7 (8.6-12.6)	26.5 (25.5-27.3)	0.9 (0.8-1.0)	0.6 (0.5-0.7)
	PMA $<$ 30, PNA $>$ 14	339 (22.6)	24.7 (24.0-25.5)	20.1 (15.9-24.1)	27.8 (26.9-28.6)	1.0 (0.9-1.1)	0.5 (0.5-0.6)
	30 $\leq$ PMA $<$ 37, PNA $\leq$ 14	81 (5.4)	30.3 (29.5-31.0)	11.8 (10.4-12.8)	31.9 (31.1-32.7)	2.6 (2.0-3.3)	0.5 (0.4-0.6)
	30 $\leq$ PMA $<$ 37, PNA $>$ 14	435 (29.0)	27.5 (26.1-29.1)	36.7 (23.5-47.7)	32.8 (31.3-34.4)	1.8 (1.4-2.3)	0.4 (0.3-0.5)
	37 $\leq$ PMA $<$ 45, PNA $\leq$ 7	113 (7.5)	38.5 (37.7-39.2)	5.7 (5.1-6.2)	39.3 (38.6-40.1)	3.4 (3.2-3.6)	0.5 (0.4-0.6)
	37 $\leq$ PMA $<$ 45, PNA $>$ 7	338 (22.5)	33.4 (30.5-36.7)	48.8 (24.8-64.2)	39.8 (38.4-41.3)	3.4 (2.8-3.8)	0.4 (0.3-0.5)
	PMA $\geq$ 45	49 (3.3)	36.6 (34.3-37.9)	84.8 (68.8-98.2)	47.4 (46.2-49.4)	4.0 (3.5-4.4)	0.3 (0.3-0.4)
	Total	1500 (100)	27.9 (25.3-32.3)	22.4 (13.4-44.2)	32.6 (28.5-38.6)	1.8 (1.1-3.4)	0.4 (0.4-0.6)

Values are reported as Median (Interquartile Range) unless specified otherwise - Postmenstrual age (PMA) is expressed in weeks, postnatal age (PNA) in days

Table 7. – 1) Comparison of actual CMES reference versus **Capparelli et *al.*** (22) equivalent doses

Actual initial dosing nomogram CMES[a]	Trough = 10-20	Trough > 20	Median (IQR) trough (mg/L)	R-AUC_{24h}[b] = 400-600	R-AUC_{24h}[b] > 600	Median (IQR) R-AUC_{24h}[b] (mg*h/L)
PMA $<$ 30, PNA $\leq$ 14 (15 mg/kg q18h)[d]	25.0	0.0	5.7 (4.4-9.4)	41.7	0.0	333.4 (256.0-460.0)
PMA $<$ 30, PNA $>$ 14 (15 mg/kg q12h)[d]	33.3	0.0	9.2 (7.8-11.6)	42.9	4.8	391.1 (346.0-489.2)
30 $\leq$ PMA $<$ 37, PNA $\leq$ 14 (15 mg/kg q12h)[d]	42.9	0.0	8.5 (7.4-10.1)	57.1	14.3	416.8 (400.9-460.9)
30 $\leq$ PMA $<$ 37, PNA $>$ 14 (15 mg/kg q8h)[d]	26.1	4.3	8.3 (7.1-10.1)	34.8	8.7	394.5 (319.4-455.1)
37 $\leq$ PMA $<$ 45, PNA $\leq$ 7 (15 mg/kg q12h)[d]	57.1	0.0	12.6 (8.8-15.0)	71.4	14.3	545.8 (427.2-592.0)
37 $\leq$ PMA $<$ 45, PNA $>$ 7 (15 mg/kg q8h)[d]	50.0	0.0	9.2 (6.6-13.6)	35.0	20.0	441.4 (335.1-540.1)
PMA $\geq$ 45 (14 mg/kg q8h)[d]	33.3	0.0	8.5 (7.5-9.7)	33.3	0.0	373.2 (351.5-427.6)
Total (n = 93)	36.6	1.1	8.6 (6.5-11.6)	41.9	9.7	409.3 (329.7-491.1)

Table S7. – 1) Capparelli et *al.* (22) (Cont.)

Equivalent initial dosing nomogram (22)	Trough = 10-20	Trough > 20	Median (IQR) trough (mg/L)	E-AUC_{24h}[c] = 400-600	E-AUC_{24h}[c] > 600	Median (IQR) E-AUC_{24h}[c] (mg*h/L)
PMA $<$ 30, PNA $\leq$ 14 (15 mg/kg q18h)[d]	17.9	0.0	5.5 (2.3-9.1)	34.5	4.8	364.2 (265.3-449.4)
PMA $<$ 30, PNA $>$ 14 (15 mg/kg q12h)[d]	40.1	2.9	9.0 (5.3-12.7)	45.7	23.9	475.5 (375.4-595.0)
30 $\leq$ PMA $<$ 37, PNA $\leq$ 14 (15 mg/kg q12h)[d]	27.2	0.0	7.1 (4.1-10.3)	53.1	9.9	433.9 (352.6-543.4)
30 $\leq$ PMA $<$ 37, PNA $>$ 14 (15 mg/kg q8h)[d]	40.2	3.9	9.1 (5.4-13.4)	47.4	26.4	500.0 (397.2-606.8)
37 $\leq$ PMA $<$ 45, PNA $\leq$ 7 (15 mg/kg q12h)[d]	33.6	0.9	7.6 (3.9-12.2)	41.6	16.8	444.5 (340.0-557.7)
37 $\leq$ PMA $<$ 45, PNA $>$ 7 (15 mg/kg q8h)[d]	38.0	5.0	9.1 (4.9-12.5)	47.2	24.3	504.6 (375.0-596.9)
PMA $\geq$ 45 (14 mg/kg q8h)[d]	20.4	0.0	6.7 (3.9-9.3)	44.9	16.3	420.5 (350.5-497.0)
Total (n = 1499)[e]	35.7	3.0	8.4 (4.6-12.2)	45.5	21.3	469.7 (362.6-580.4)

Values are reported as percentages (%) unless specified otherwise - CMES: External hospital of interest - IQR: Interquartile Range - [a] Actual initial doses frequently administered in CMES external dataset - [b] R-AUC_{24h}: CMES reference 24-hour area under the concentration-time curve (AUC_{24h}) using **Pai et *al.*** (4) Eq.(4) - [c] E-AUC_{24h}: Equation-based AUC_{24h} using **Pai et *al.*** (4) Eq.(4) after simulations with **Capparelli et *al.*** (22) - [d] Postmenstrual age (PMA) is expressed in weeks, postnatal age (PNA) in days (dosage regimen) - [e] Simulated patients were removed whenever trough > peak concentration

Table 7. – 2) Comparison of actual CMES reference versus **Mehrotra et *al.*** (35) equivalent doses

Actual initial dosing nomogram CMES[a]	Trough = 10-20	Trough > 20	Median (IQR) trough (mg/L)	R-AUC_{24h}[b] = 400-600	R-AUC_{24h}[b] > 600	Median (IQR) R-AUC_{24h}[b] (mg*h/L)
PMA $<$ 30, PNA $\leq$ 14 (15 mg/kg q18h)[d]	25.0	0.0	5.7 (4.4-9.4)	41.7	0.0	333.4 (256.0-460.0)
PMA $<$ 30, PNA $>$ 14 (15 mg/kg q12h)[d]	33.3	0.0	9.2 (7.8-11.6)	42.9	4.8	391.1 (346.0-489.2)
30 $\leq$ PMA $<$ 37, PNA $\leq$ 14 (15 mg/kg q12h)[d]	42.9	0.0	8.5 (7.4-10.1)	57.1	14.3	416.8 (400.9-460.9)
30 $\leq$ PMA $<$ 37, PNA $>$ 14 (15 mg/kg q8h)[d]	26.1	4.3	8.3 (7.1-10.1)	34.8	8.7	394.5 (319.4-455.1)
37 $\leq$ PMA $<$ 45, PNA $\leq$ 7 (15 mg/kg q12h)[d]	57.1	0.0	12.6 (8.8-15.0)	71.4	14.3	545.8 (427.2-592.0)
37 $\leq$ PMA $<$ 45, PNA $>$ 7 (15 mg/kg q8h)[d]	50.0	0.0	9.2 (6.6-13.6)	35.0	20.0	441.4 (335.1-540.1)
PMA $\geq$ 45 (14 mg/kg q8h)[d]	33.3	0.0	8.5 (7.5-9.7)	33.3	0.0	373.2 (351.5-427.6)
Total (n = 93)	36.6	1.1	8.6 (6.5-11.6)	41.9	9.7	409.3 (329.7-491.1)

Table S7. – 2) Mehrotra et *al.* (35) (Cont.)

Equivalent initial dosing nomogram (35)	Trough = 10-20	Trough > 20	Median (IQR) trough (mg/L)	E-AUC_{24h}[c] = 400-600	E-AUC_{24h}[c] > 600	Median (IQR) E-AUC_{24h}[c] (mg*h/L)
PMA $<$ 30, PNA $\leq$ 14 (15 mg/kg q18h)[d]	33.1	2.1	8.4 (5.3-10.9)	41.4	9.7	401.7 (326.0-492.8)
PMA $<$ 30, PNA $>$ 14 (15 mg/kg q12h)[d]	65.2	9.1	12.7 (9.8-16.6)	49.3	36.6	548.4 (460.6-663.3)
30 $\leq$ PMA $<$ 37, PNA $\leq$ 14 (15 mg/kg q12h)[d]	63.0	6.2	12.8 (9.1-15.5)	46.9	37.0	542.9 (465.4-644.1)
30 $\leq$ PMA $<$ 37, PNA $>$ 14 (15 mg/kg q8h)[d]	61.9	15.5	13.6 (10.3-17.8)	43.0	47.1	587.1 (472.7-706.7)
37 $\leq$ PMA $<$ 45, PNA $\leq$ 7 (15 mg/kg q12h)[d]	41.6	5.3	9.6 (6.6-13.9)	49.6	18.6	473.4 (359.5-574.4)
37 $\leq$ PMA $<$ 45, PNA $>$ 7 (15 mg/kg q8h)[d]	55.2	10.4	12.5 (8.7-15.5)	48.1	38.3	558.7 (446.7-643.6)
PMA $\geq$ 45 (14 mg/kg q8h)[d]	32.7	0.0	7.3 (5.4-11.3)	51.0	8.2	440.1 (348.4-510.2)
Total (n = 1497)[e]	55.9	9.8	12.2 (8.5-15.8)	46.4	35.1	536.6 (432.1-648.7)

Values are reported as percentages (%) unless specified otherwise - CMES: External hospital of interest - IQR: Interquartile Range - [a] Actual initial doses frequently administered in CMES external dataset - [b] R-AUC_{24h}: CMES reference 24-hour area under the concentration-time curve (AUC_{24h}) using **Pai et *al.*** (4) Eq.(4) - [c] E-AUC_{24h}: Equation-based AUC_{24h} using **Pai et *al.*** (4) Eq.(4) after simulations with **Mehrotra et *al.*** (35) - [d] Postmenstrual age (PMA) is expressed in weeks, postnatal age (PNA) in days (dosage regimen) - [e] Simulated patients were removed whenever trough > peak concentration

Table 8. – Comparison of AUC_{24h} calculation methods using both best-performing models (22,35)

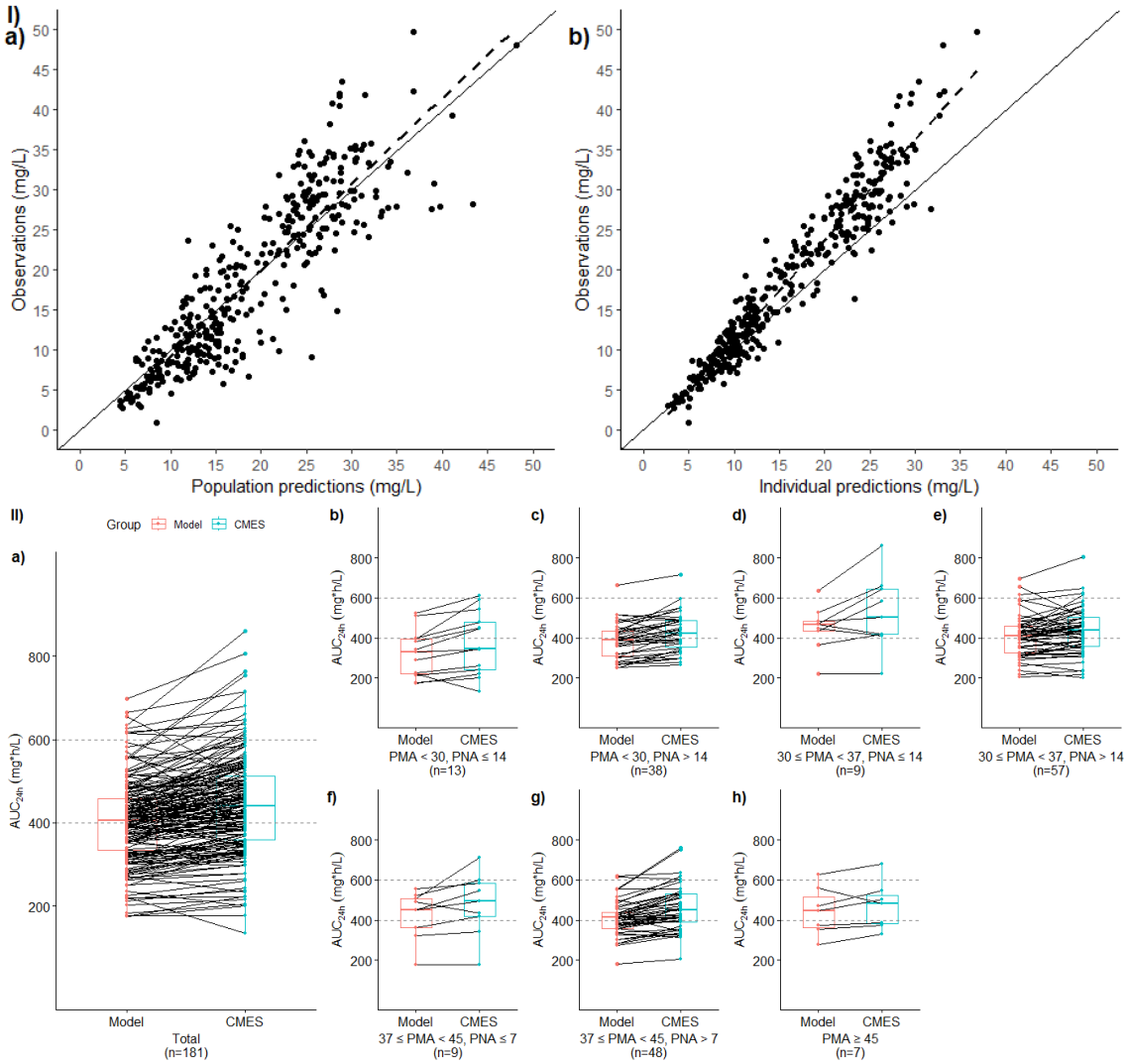
New initial dosing nomogram proposed (22)	E-AUC_{24h}[a] = 400-600	E-AUC_{24h}[a] > 600	Median (IQR) E-AUC_{24h}[a] (mg*h/L)	B-AUC_{24h}[b] = 400-600	B-AUC_{24h}[b] > 600	Median (IQR) B-AUC_{24h}[b] (mg*h/L)
PMA $<$ 30, PNA $\leq$ 14 (13 mg/kg q12h)[c]	46.2	12.4	418.1 (311.9-509.3)	47.6	15.2	436.3 (353.5-534.3)
PMA $<$ 30, PNA $>$ 14 (13 mg/kg q12h)[c]	43.7	9.4	411.4 (320.3-517.2)	45.1	11.2	424.9 (338.1-512.8)
30 $\leq$ PMA $<$ 37, PNA $\leq$ 14 (11 mg/kg q8h)[c]	51.9	8.6	424.7 (360.0-514.4)	55.6	13.6	444.5 (363.2-536.8)
30 $\leq$ PMA $<$ 37, PNA $>$ 14 (13 mg/kg q8h)[c]	44.5	14.1	433.9 (342.0-526.4)	44.0	17.7	442.6 (355.9-551.8)
37 $\leq$ PMA $<$ 45, PNA $\leq$ 7 (14 mg/kg q12h)[c]	42.5	12.4	413.6 (312.1-519.2)	40.7	11.5	406.0 (316.0-521.2)
37 $\leq$ PMA $<$ 45, PNA $>$ 7 (13 mg/kg q8h)[c]	46.6	13.9	440.6 (326.7-520.1)	41.8	14.8	425.5 (333.0-529.9)
PMA $\geq$ 45 (12 mg/kg q6h)[c]	52.1	18.8	453.1 (387.4-565.6)	43.8	20.8	432.2 (389.8-564.0)
Total (n = 1497)[d]	45.4	12.6	425.8 (329.5-522.6)	44.5	14.8	432.2 (344.1-532.7)

Table S8. – (Cont.)

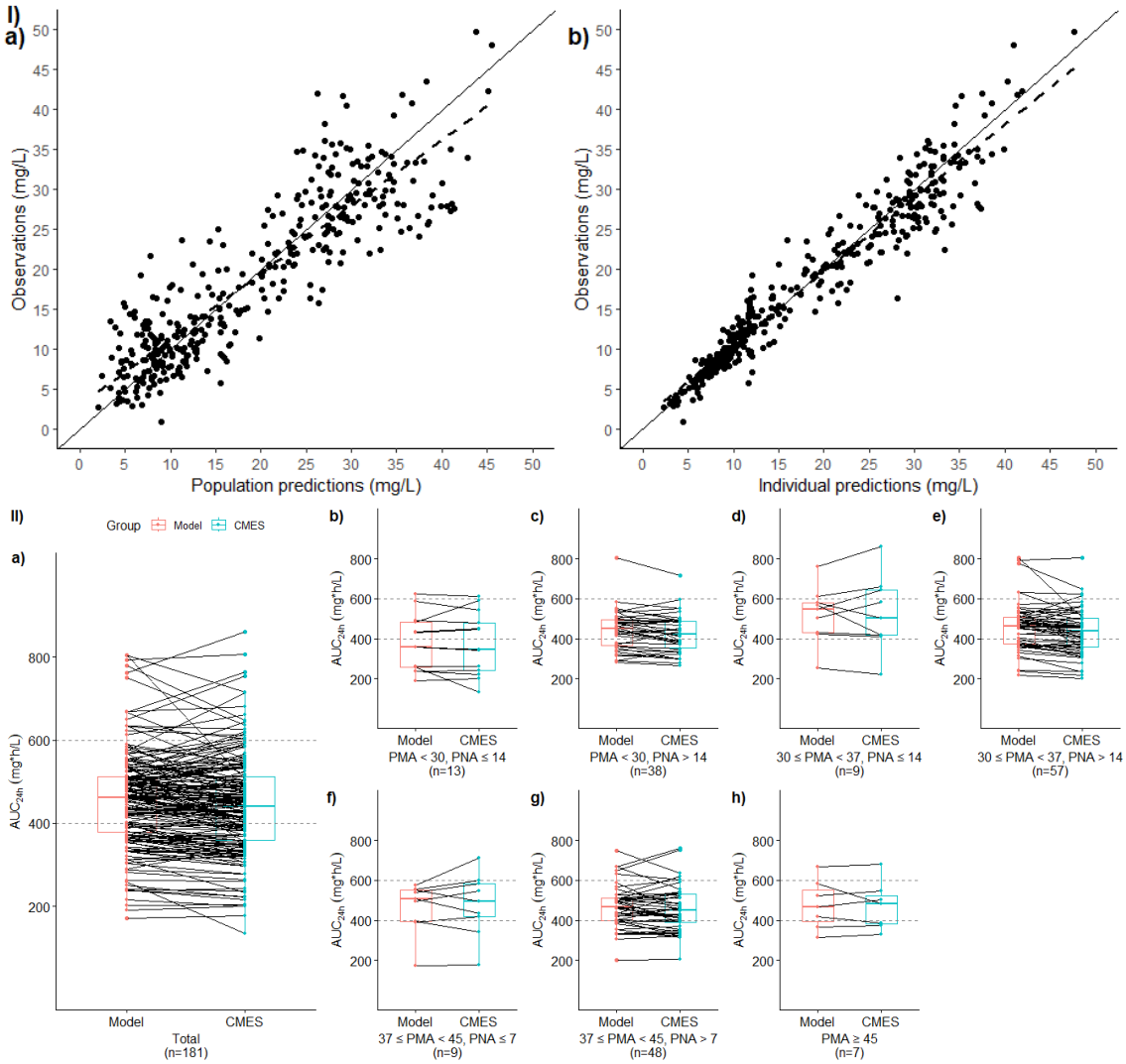
New initial dosing nomogram proposed (35)	E-AUC_{24h}[a] = 400-600	E-AUC_{24h}[a] > 600	Median (IQR) E-AUC_{24h}[a] (mg*h/L)	B-AUC_{24h}[b] = 400-600	B-AUC_{24h}[b] > 600	Median (IQR) B-AUC_{24h}[b] (mg*h/L)
PMA $<$ 30, PNA $\leq$ 14 (12 mg/kg q12h)[c]	51.0	14.7	446.9 (359.7-537.0)	55.2	23.8	482.8 (407.9-592.7)
PMA $<$ 30, PNA $>$ 14 (12 mg/kg q12h)[c]	52.2	10.9	438.6 (367.9-531.4)	56.0	17.7	470.0 (396.1-558.2)
30 $\leq$ PMA $<$ 37, PNA $\leq$ 14 (12 mg/kg q12h)[c]	60.5	6.2	432.2 (371.0-512.3)	56.8	9.9	454.1 (368.4-543.7)
30 $\leq$ PMA $<$ 37, PNA $>$ 14 (11 mg/kg q8h)[c]	49.0	11.1	431.6 (349.9-519.3)	44.8	20.8	455.7 (375.5-574.3)
37 $\leq$ PMA $<$ 45, PNA $\leq$ 7 (10 mg/kg q8h)[c]	52.2	9.7	437.4 (337.3-517.5)	46.0	20.4	468.4 (377.4-581.7)
37 $\leq$ PMA $<$ 45, PNA $>$ 7 (12 mg/kg q8h)[c]	51.6	11.3	446.4 (353.3-516.8)	47.8	15.7	451.0 (354.9-541.1)
PMA $\geq$ 45 (12 mg/kg q6h)[c]	57.1	16.3	479.5 (388.0-559.6)	46.9	16.3	472.9 (355.5-557.6)
Total (n = 1495)[d]	51.6	11.2	439.0 (355.6-522.8)	49.8	18.5	460.0 (377.4-562.6)

Values are reported as percentages (%) unless specified otherwise - IQR: Interquartile Range - [a] E-AUC_{24h}: Equation-based 24-hour area under the concentration-time curve (AUC_{24h}) using **Pai et *al.*** (4) Eq.(4) after simulations with **Capparelli et *al.*** (22) above or **Mehrotra et *al.*** (35) below - [b] B-AUC_{24h}: Bayesian AUC_{24h} from **Capparelli et *al.*** (22) above or **Mehrotra et *al.*** (35) below - [c] Postmenstrual age (PMA) is expressed in weeks, postnatal age (PNA) in days (dosage regimen) - [d] Simulated patients were removed whenever trough > peak concentration

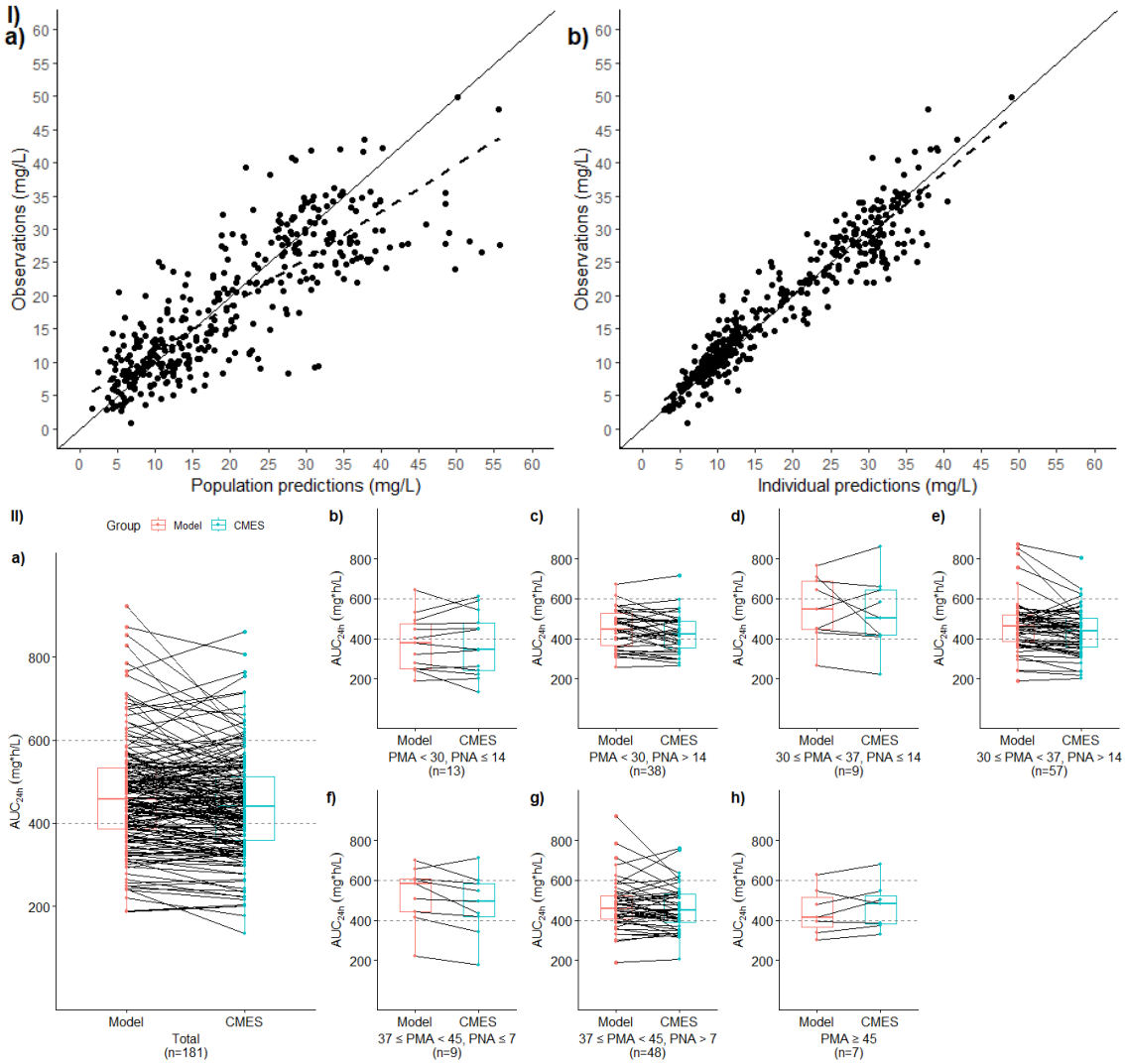
1) Alsultan et *al.* (21)



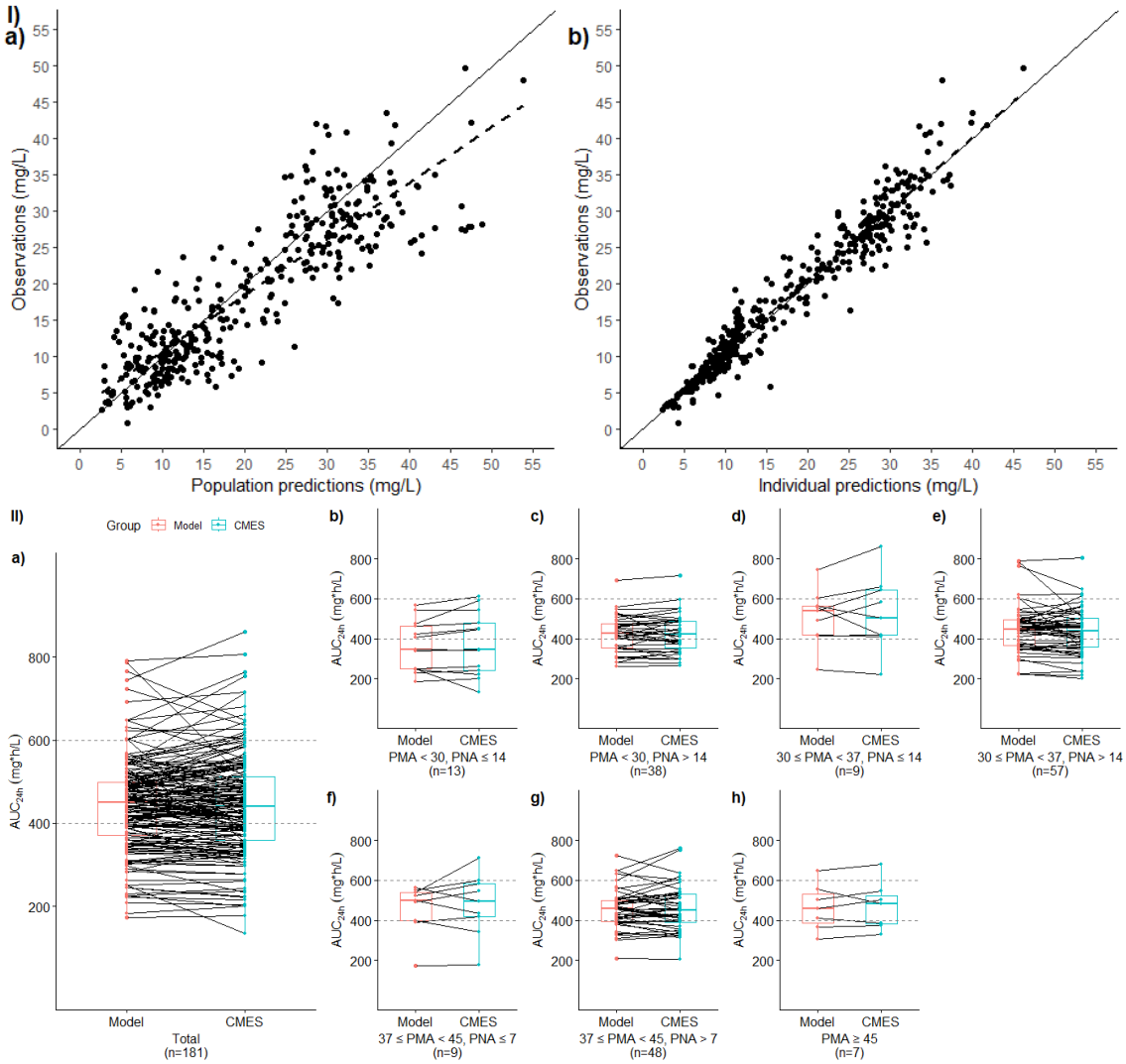
2) Chen et *al.* (23)



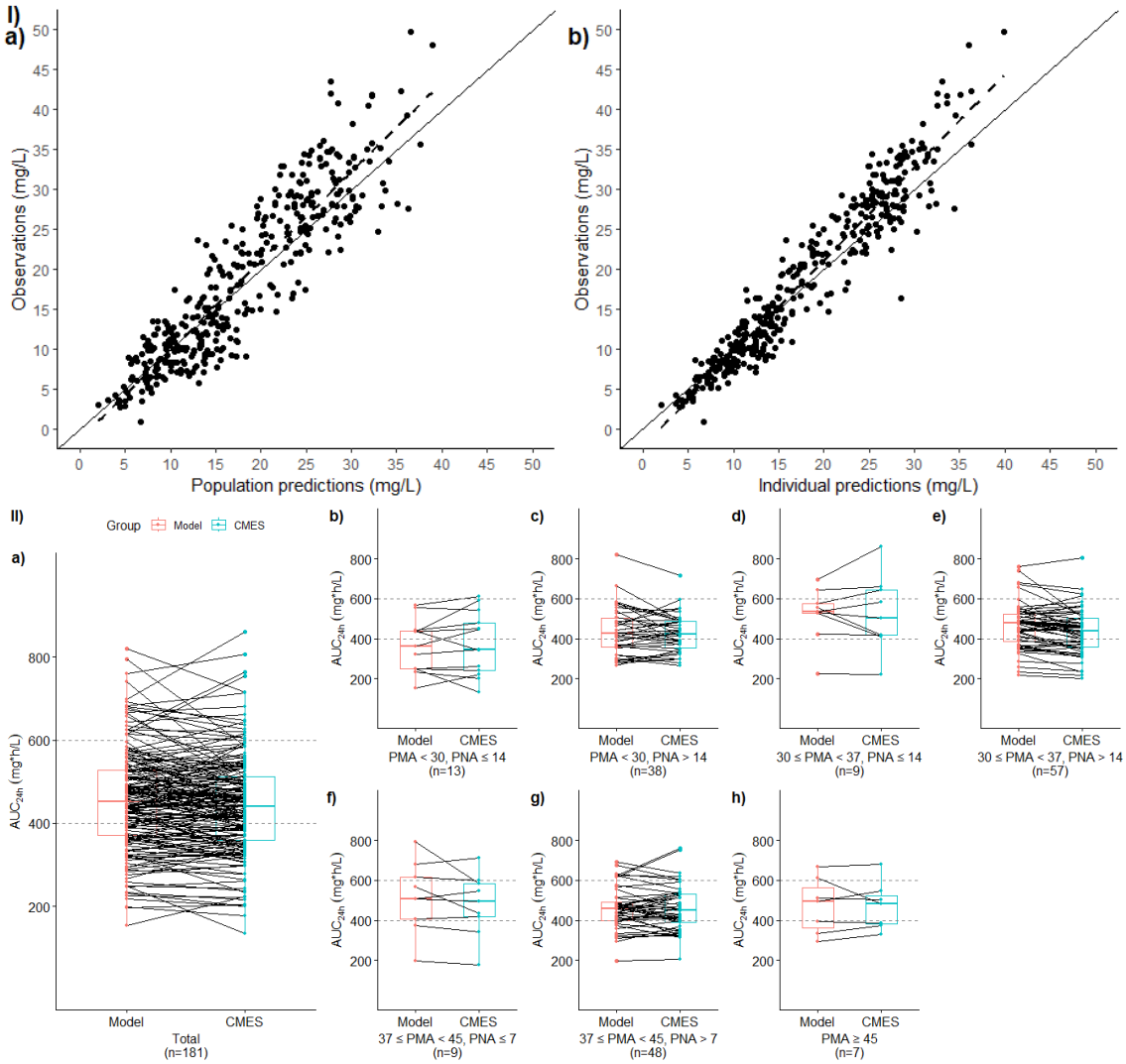
3) Cristea et *al.* (13)



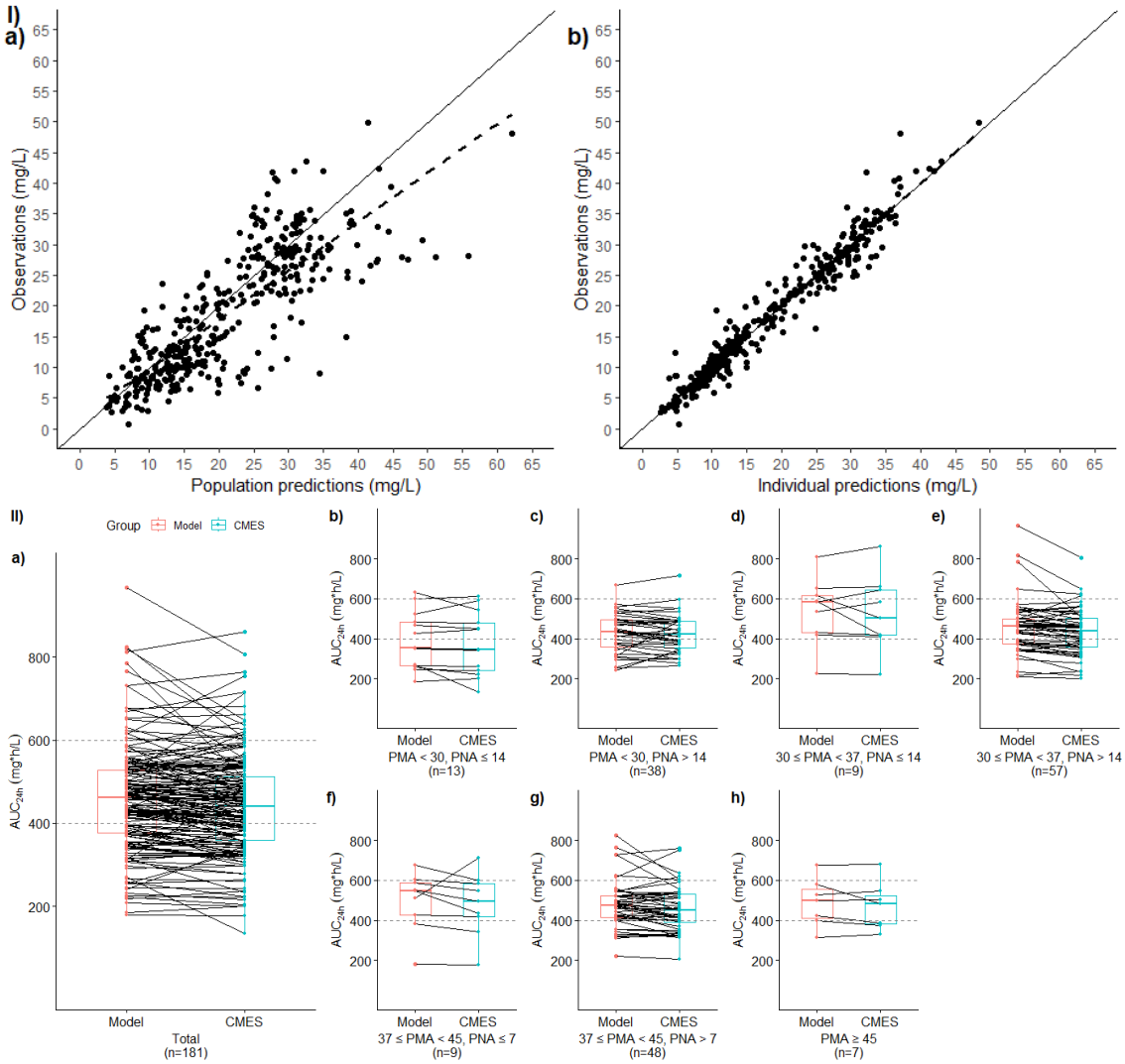
4) Germovsek et *al.* (27)



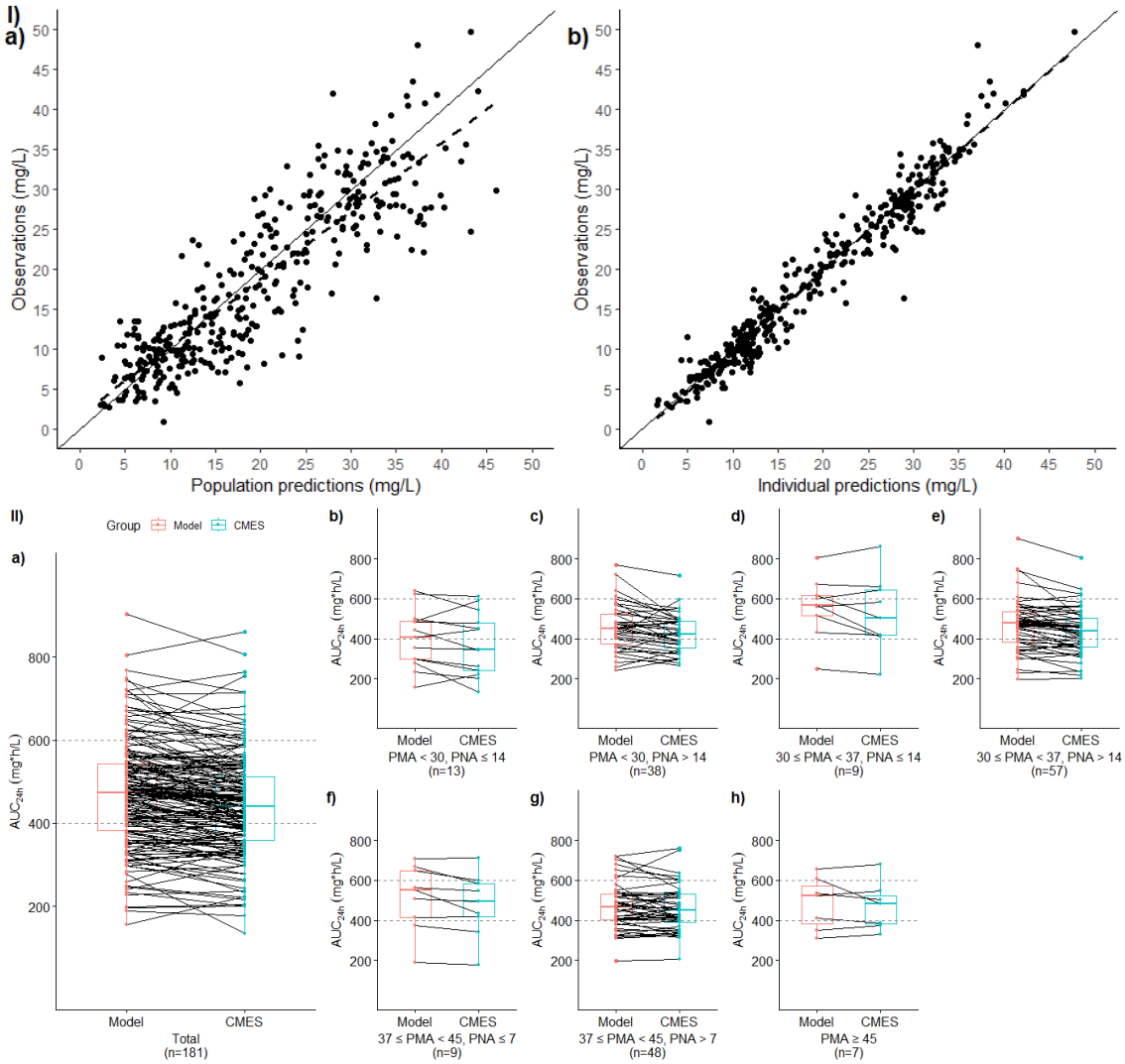
5) Jarugula et *al.* (30)



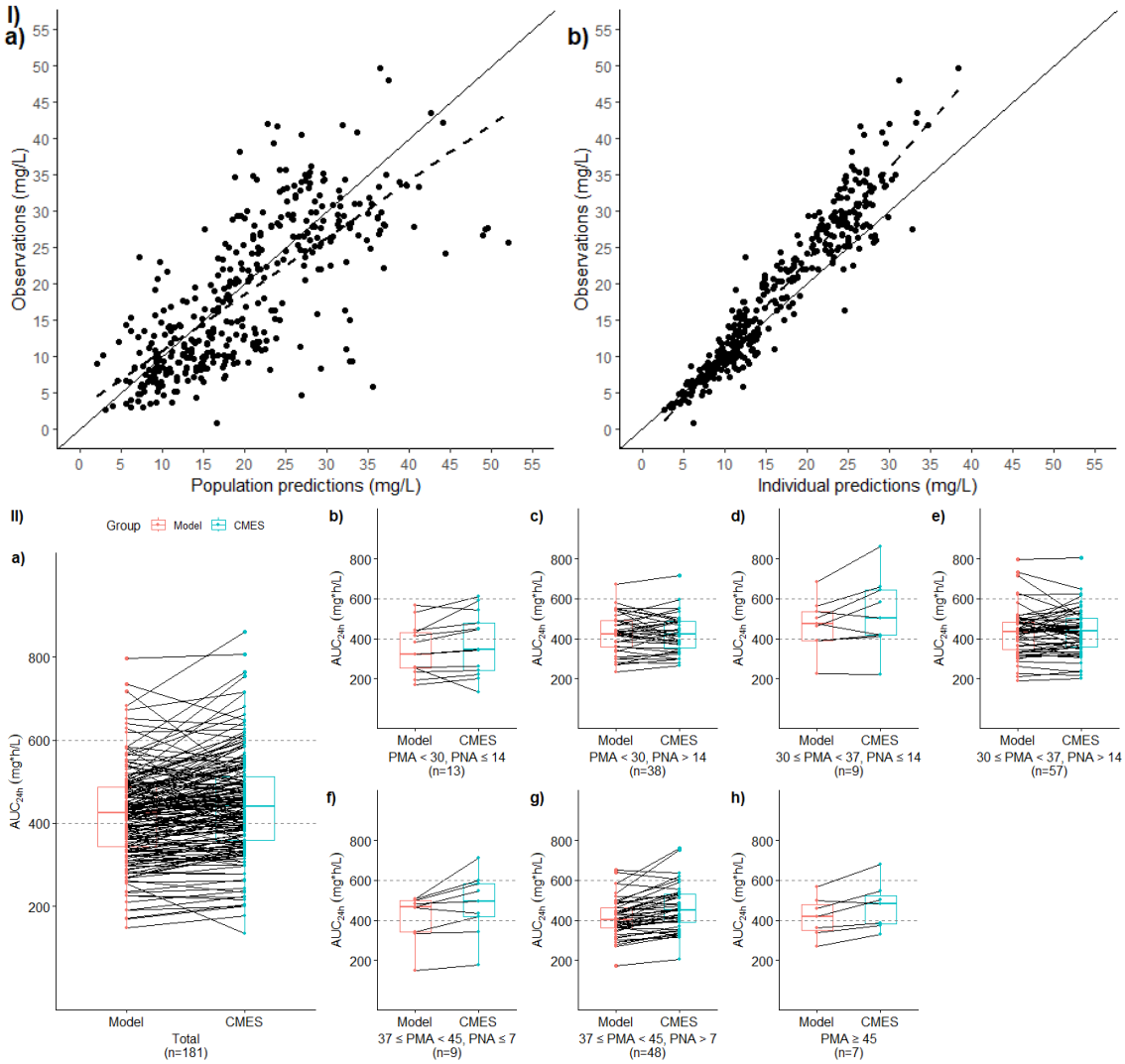
6) Jung et *al.* (31)



7) Kimura et *al.* (32)



8) Li et *al.* (34)


I)
a)
Observations (mg/L)
Population predictions (mg/L)
b)
Observations (mg/L)
Individual predictions (mg/L)
II)
Group Model CMES
a)
AUC24h (mg*h/L)
Model CMES
Total
(n=181)
b)
PMA < 30, PNA ≤ 14
(n=13)
c)
PMA < 30, PNA > 14
(n=38)
d)
30 ≤ PMA < 37, PNA ≤ 14
(n=9)
e)
30 ≤ PMA < 37, PNA > 14
(n=57)
f)
37 ≤ PMA < 45, PNA ≤ 7
(n=9)
g)
37 ≤ PMA < 45, PNA > 7
(n=48)
h)
PMA ≥ 45
(n=7)

9) Oudin et *al.* (37)

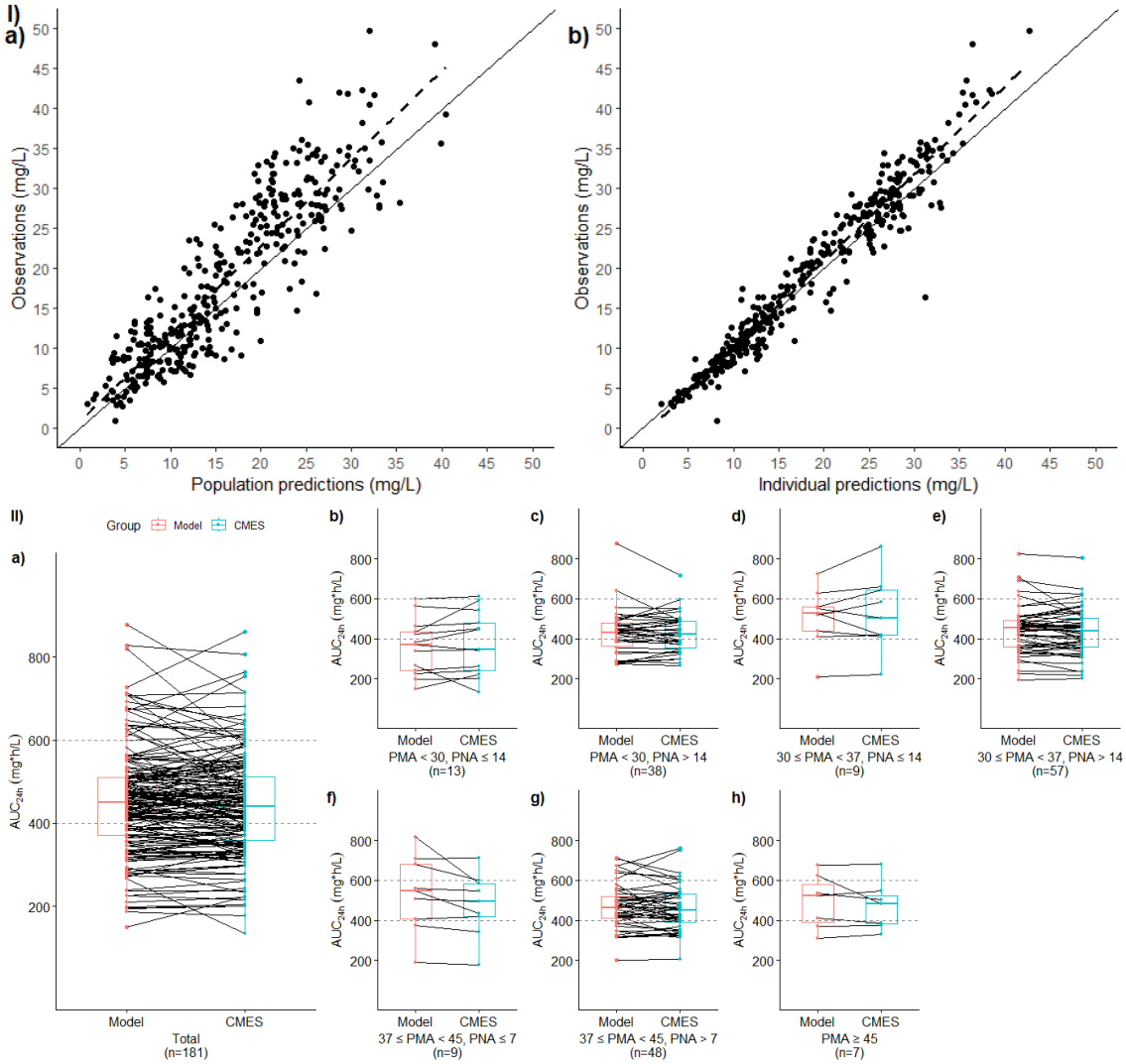
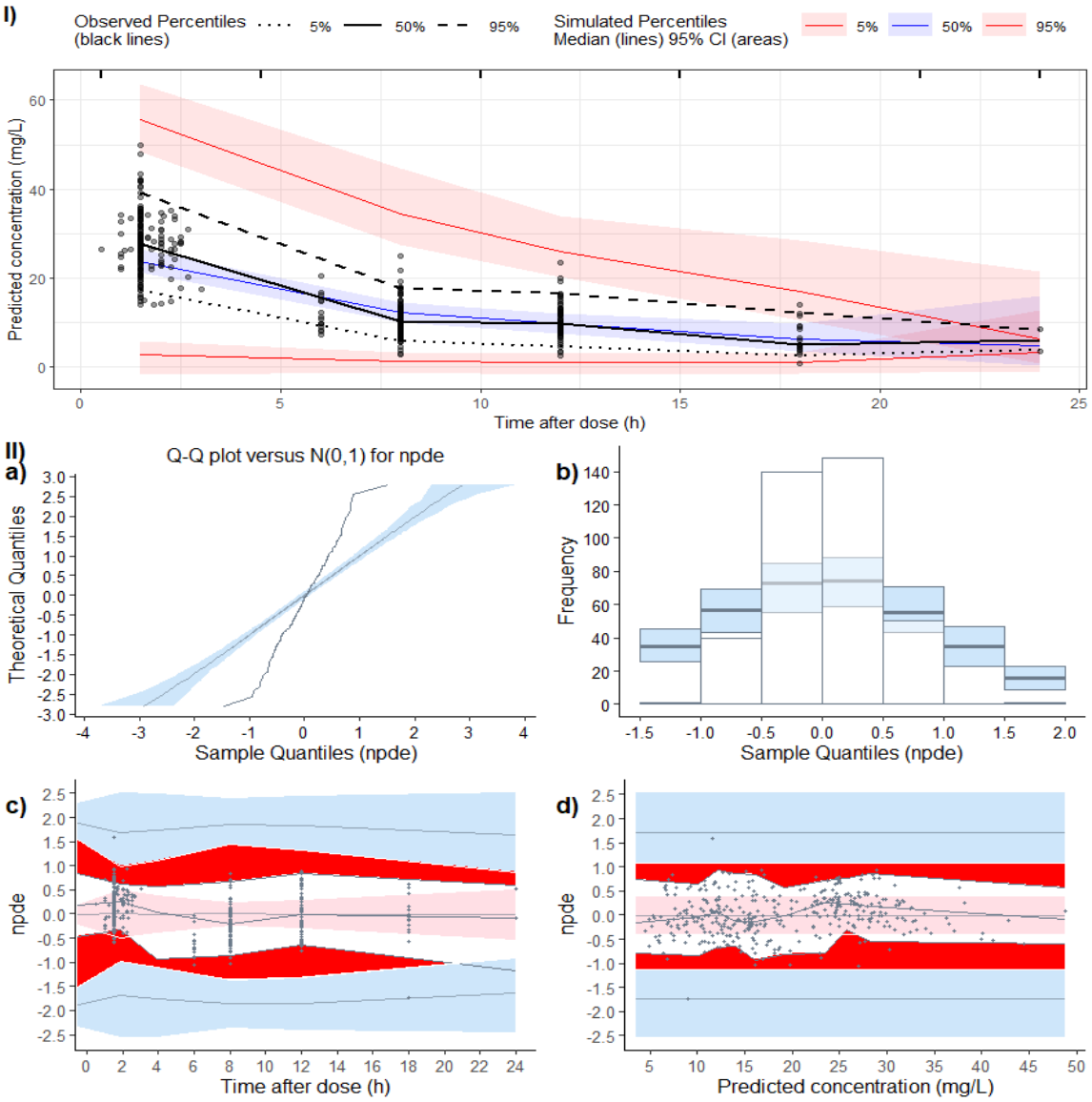
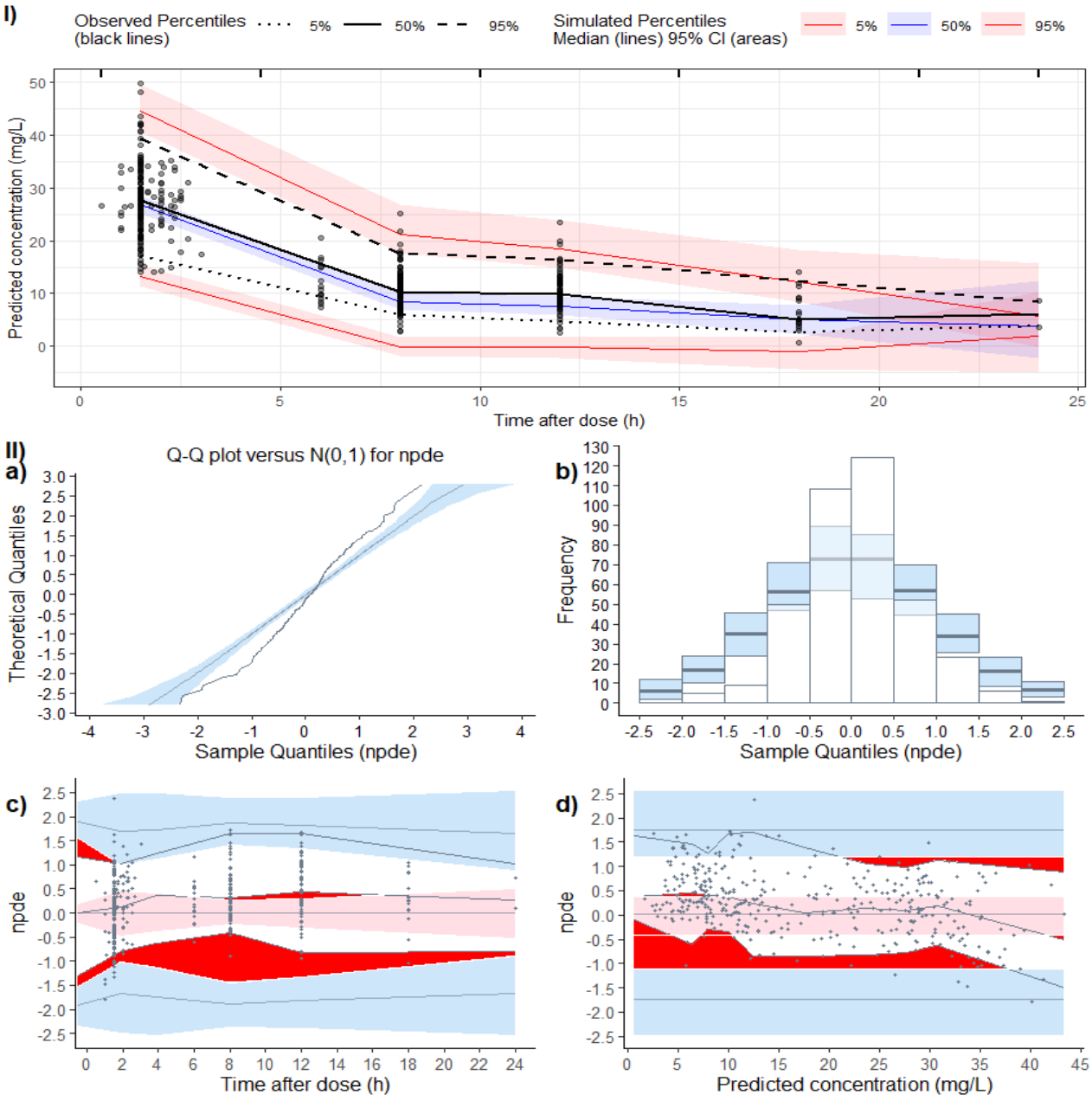


Figure 1. – I) Goodness-of-fit plots using the complete (P+T) dataset - Observations versus **a)** Population or **b)** Individual predictions - Identity function is represented as a solid line, Trend as a dashed line. **II)** Boxplots of Bayesian (Model) versus reference equation-based AUC_{24h} (CMES) - **a)** Total - **b)** PMA $<$ 30, PNA $\leq$ 14 **- c)** PMA $<$ 30, PNA $>$ 14 **- d)** 30 $\leq$ PMA $<$ 37, PNA $\leq$ 14 **- e)** 30 $\leq$ PMA $<$ 37, PNA $>$ 14 **- f)** 37 $\leq$ PMA $<$ 45, PNA $\leq$ 7 **- g)** 37 $\leq$ PMA $<$ 45, PNA $>$ 7 **- h)** PMA $\geq$ 45, where postmenstrual age (PMA) is expressed in weeks and postnatal age (PNA) in days - AUC_{24h}: 24-hour area under the concentration-time curve, where therapeutic target is delimited by dashed lines

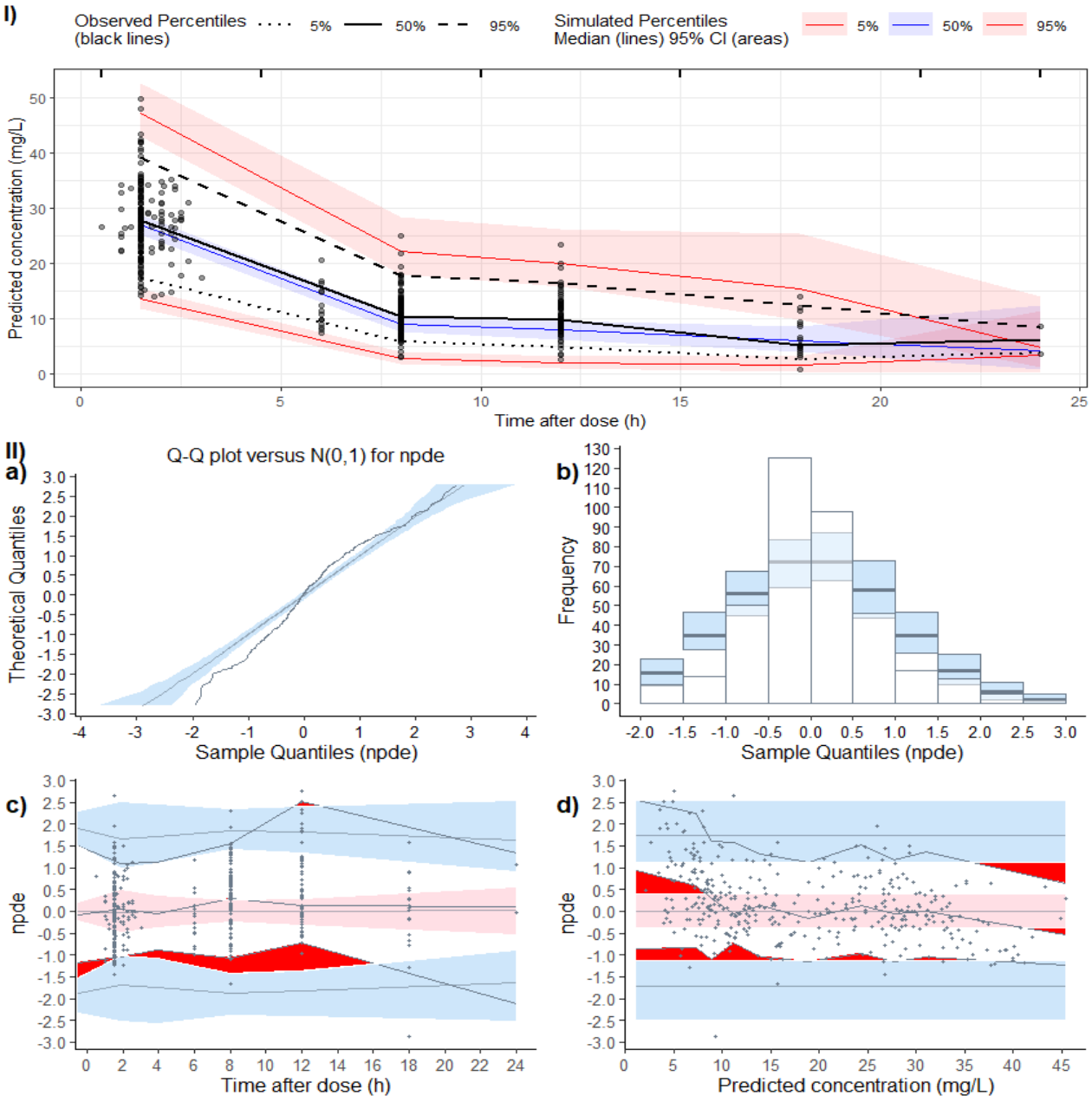
1) Alsultan et *al.* (21)



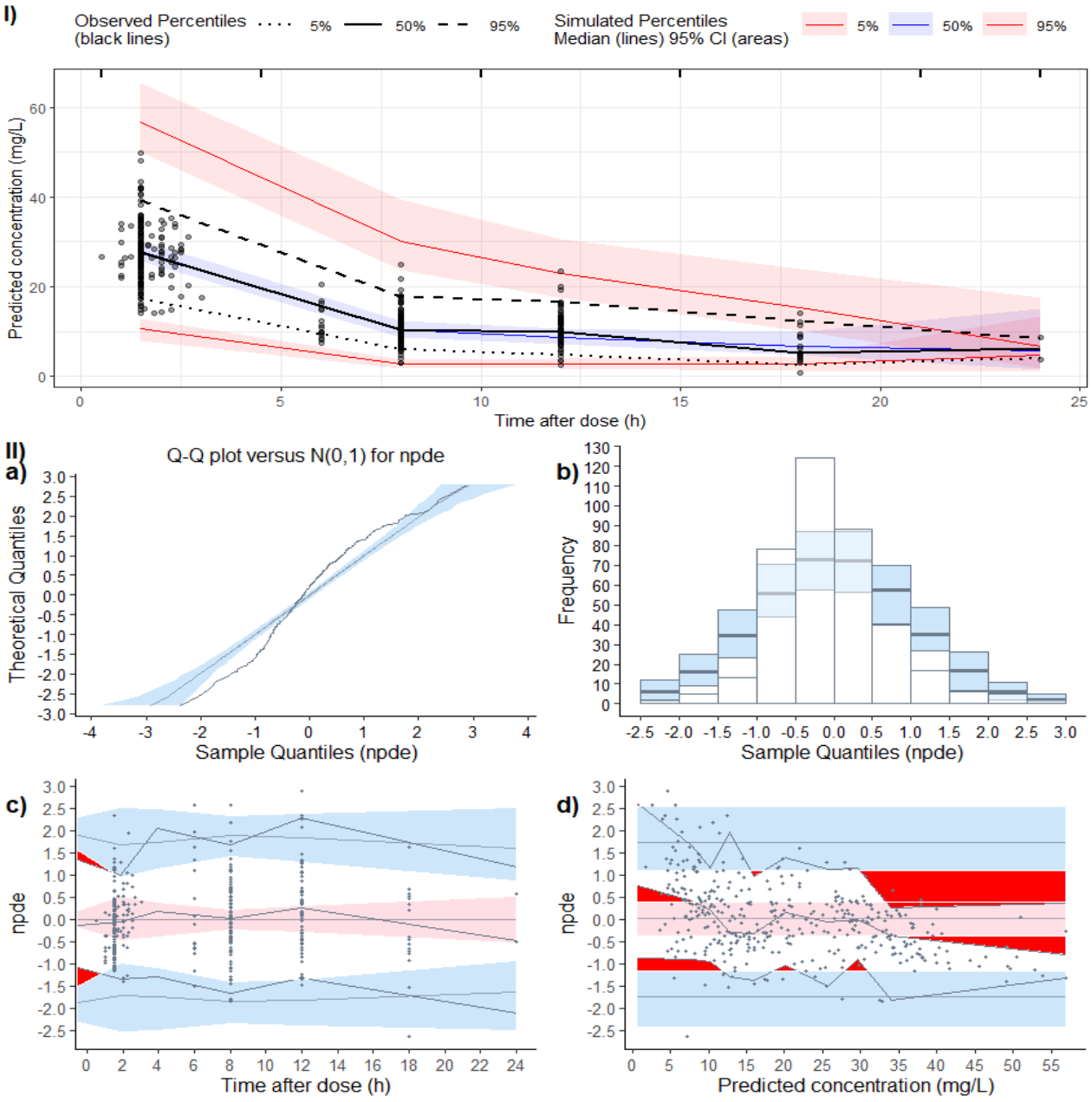
2) Capparelli et *al.* (22)



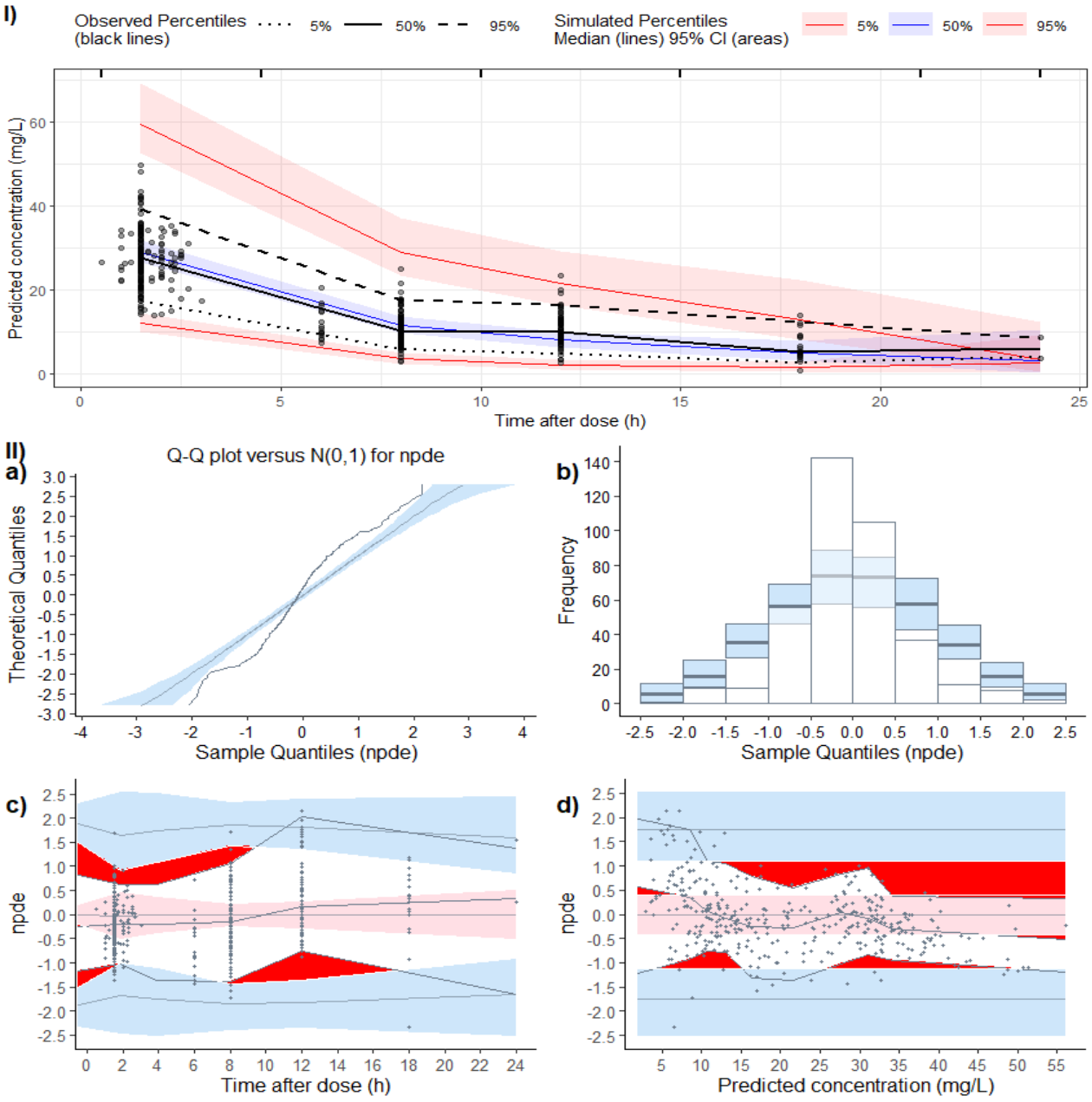
3) Chen et *al.* (23)



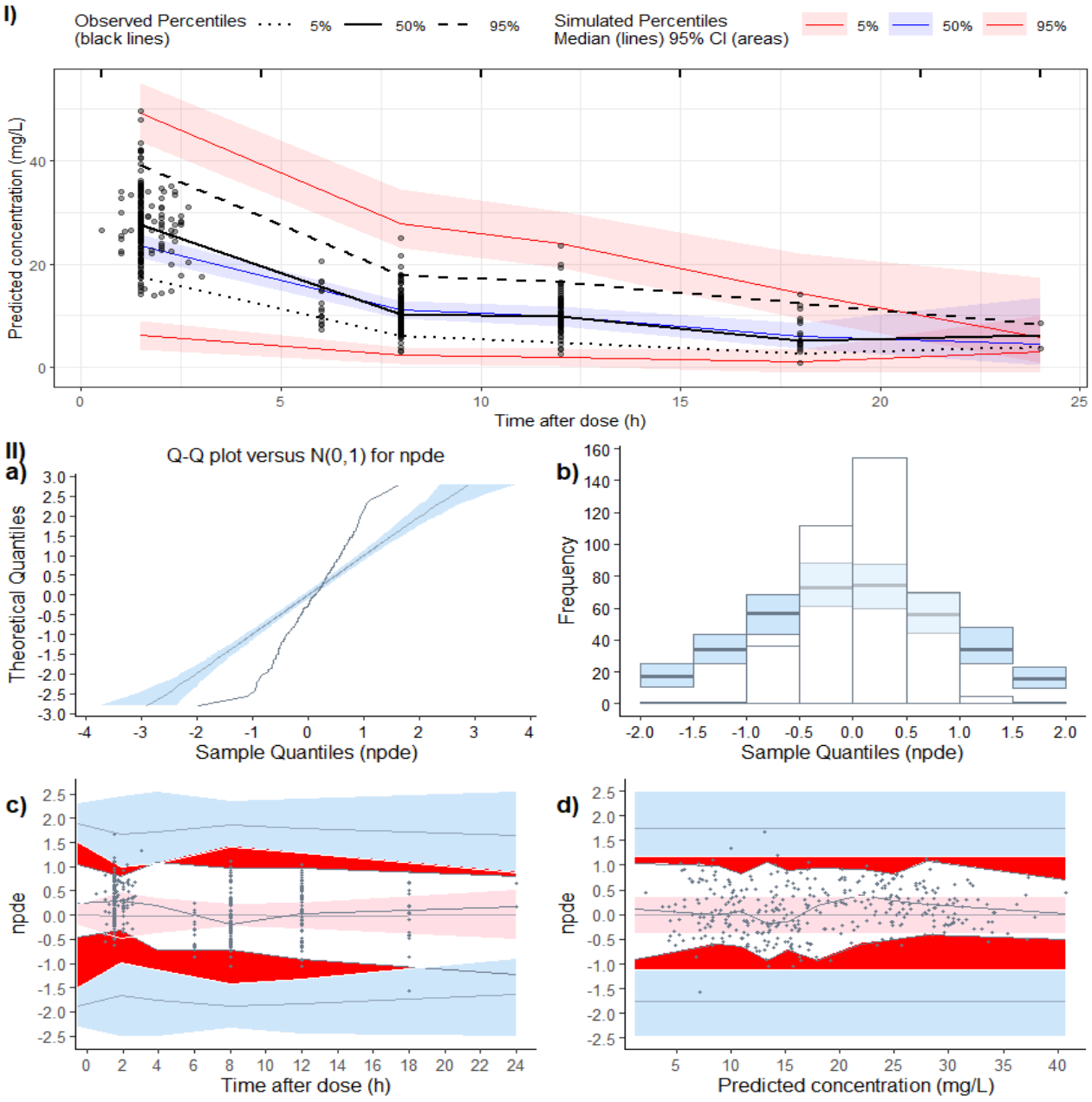
4) Cristea et *al.* (13)



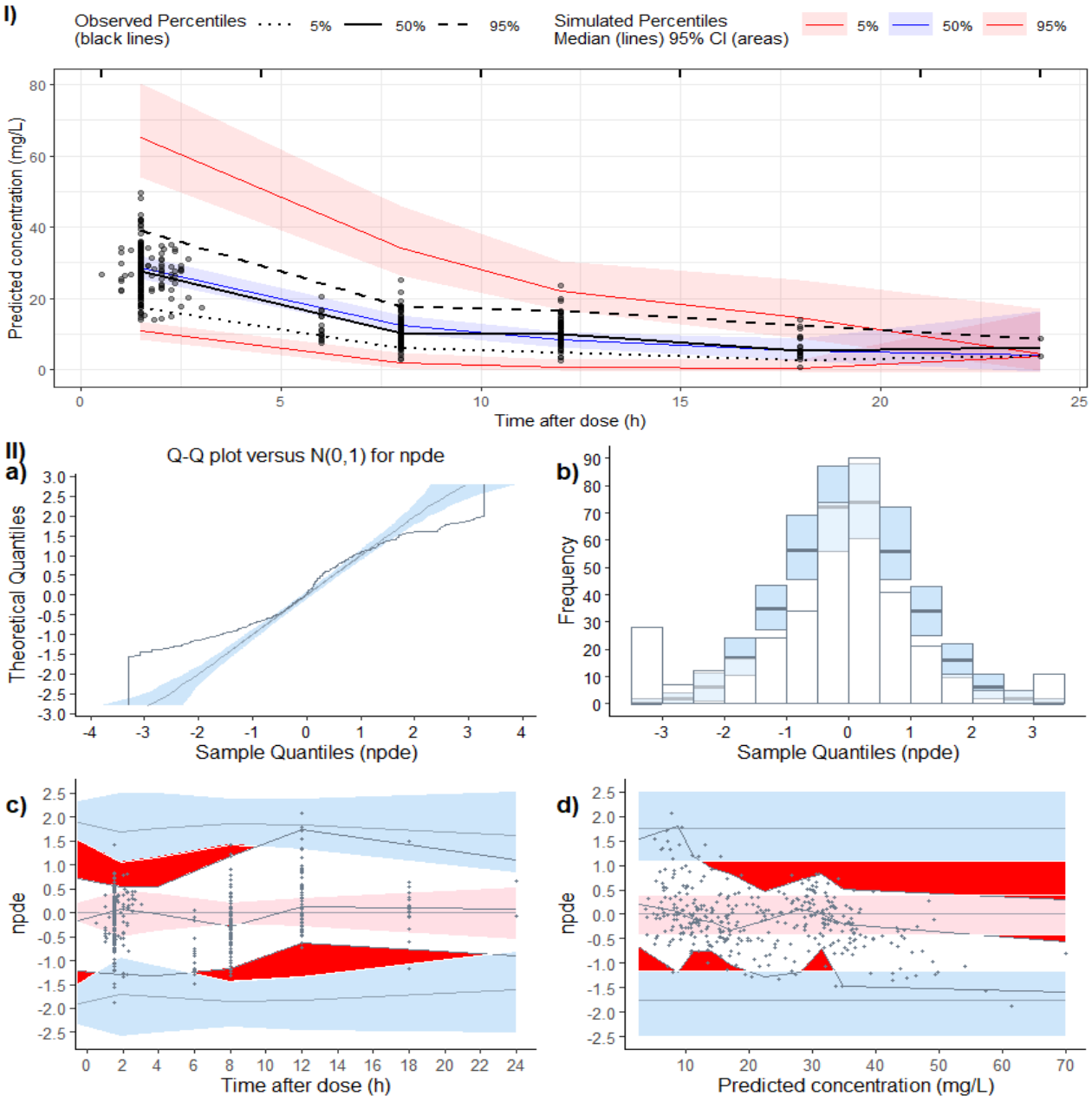
5) Germovsek et *al.* (27)



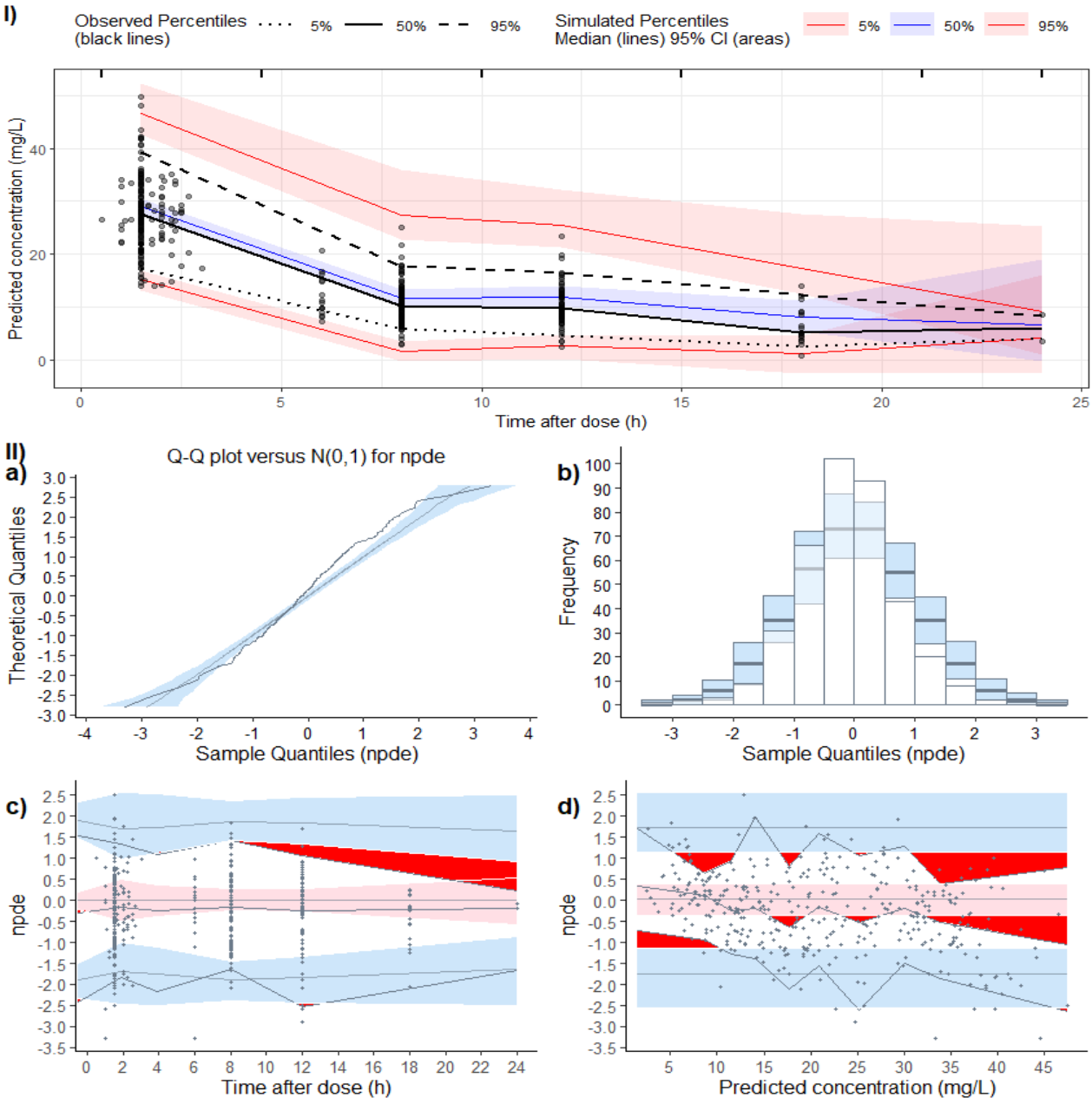
6) Jarugula et *al.* (30)



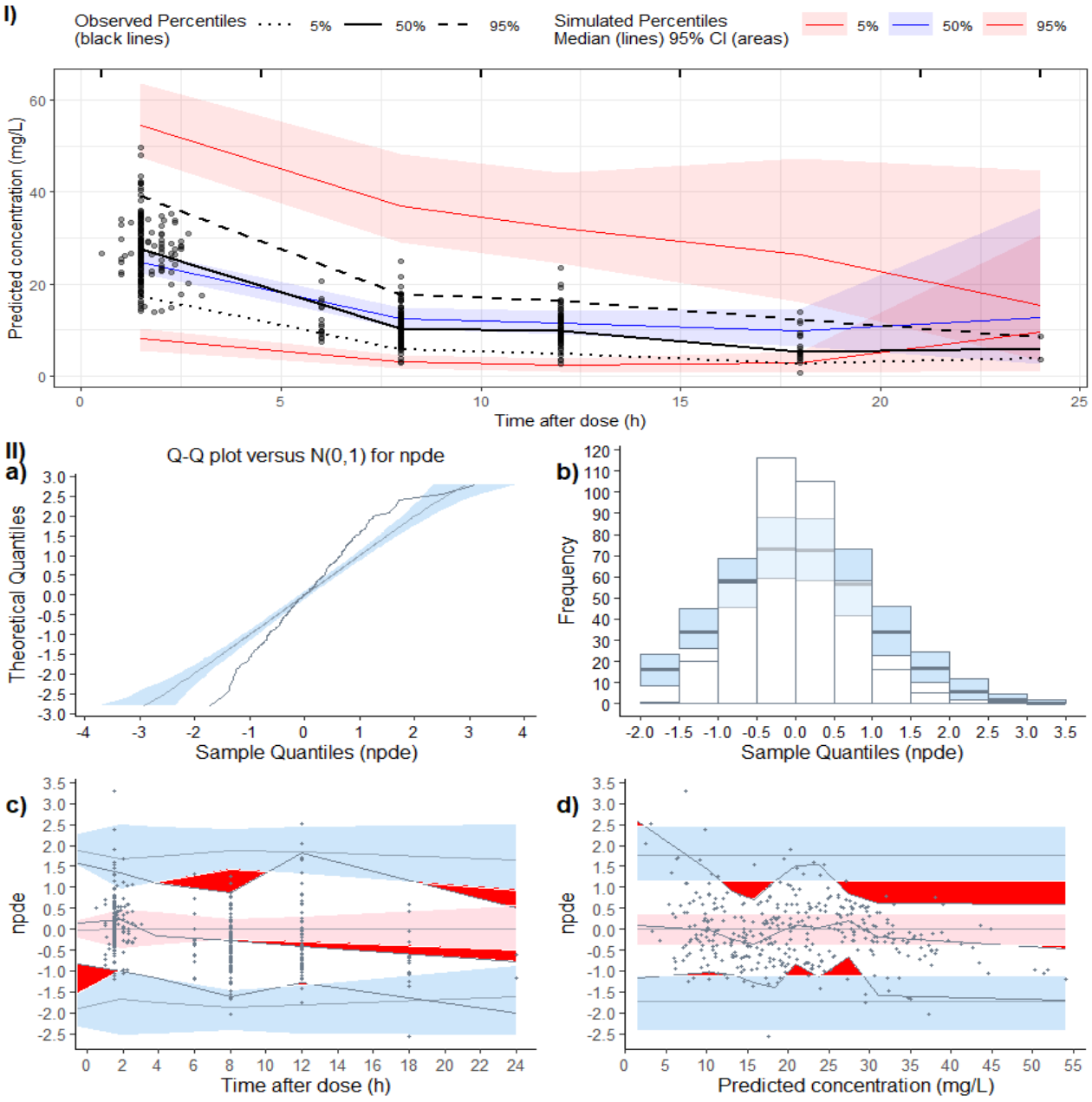
7) Jung et *al.* (31)



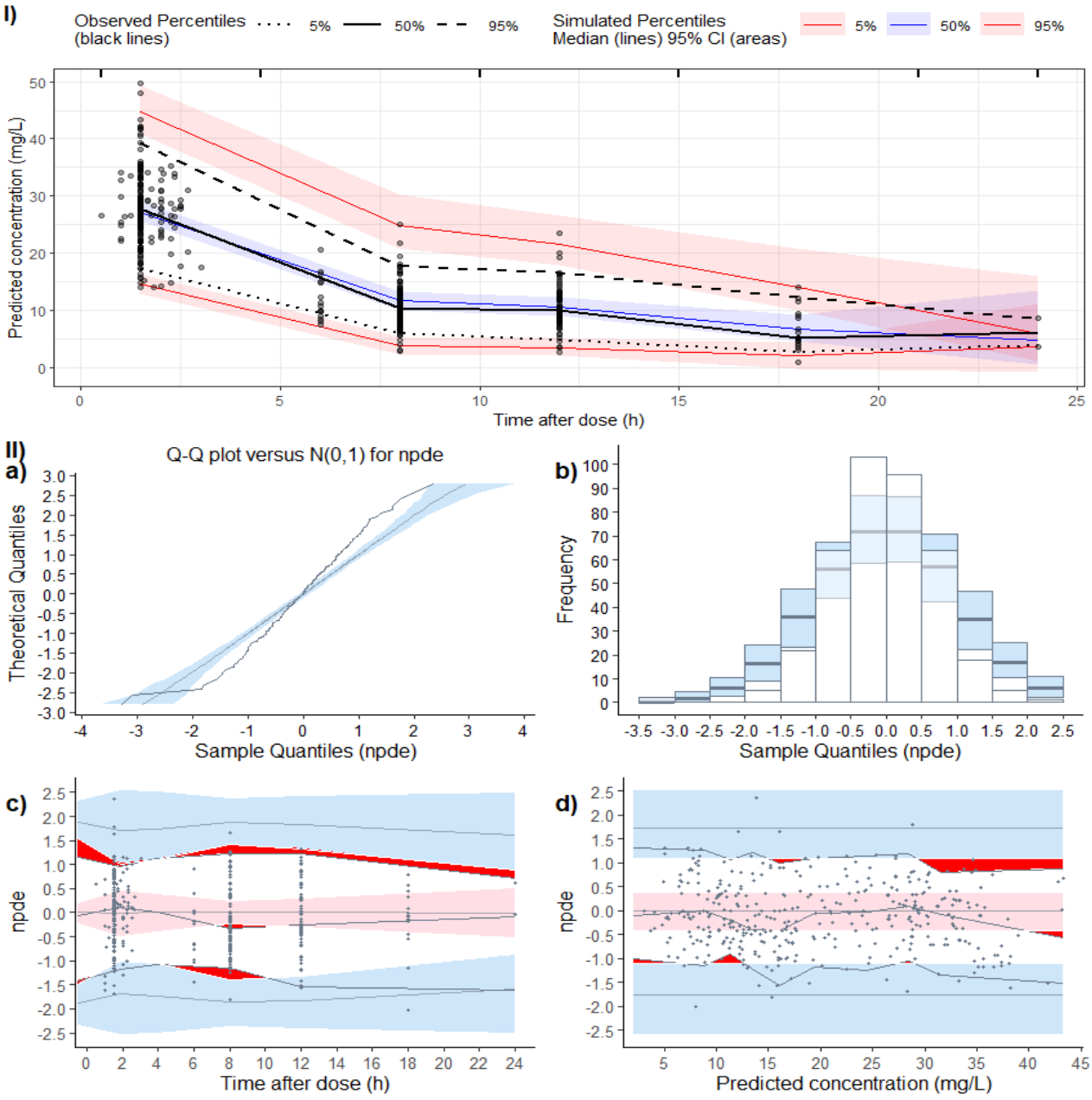
8) Kimura et *al.* (32)



9) Li et *al.* (34)


I)
Observed Percentiles (black lines)
5%
50%
95%
Simulated Percentiles Median (lines) 95% CI (areas)
5%
50%
95%
Predicted concentration (mg/L)
Time after dose (h)
II)
a)
Q-Q plot versus N(0,1) for npde
Theoretical Quantiles
Sample Quantiles (npde)
b)
Frequency
Sample Quantiles (npde)
c)
npde
Time after dose (h)
d)
npde
Predicted concentration (mg/L)

10) Mehrotra et *al.* (35)



11) Oudin et *al.* (37)

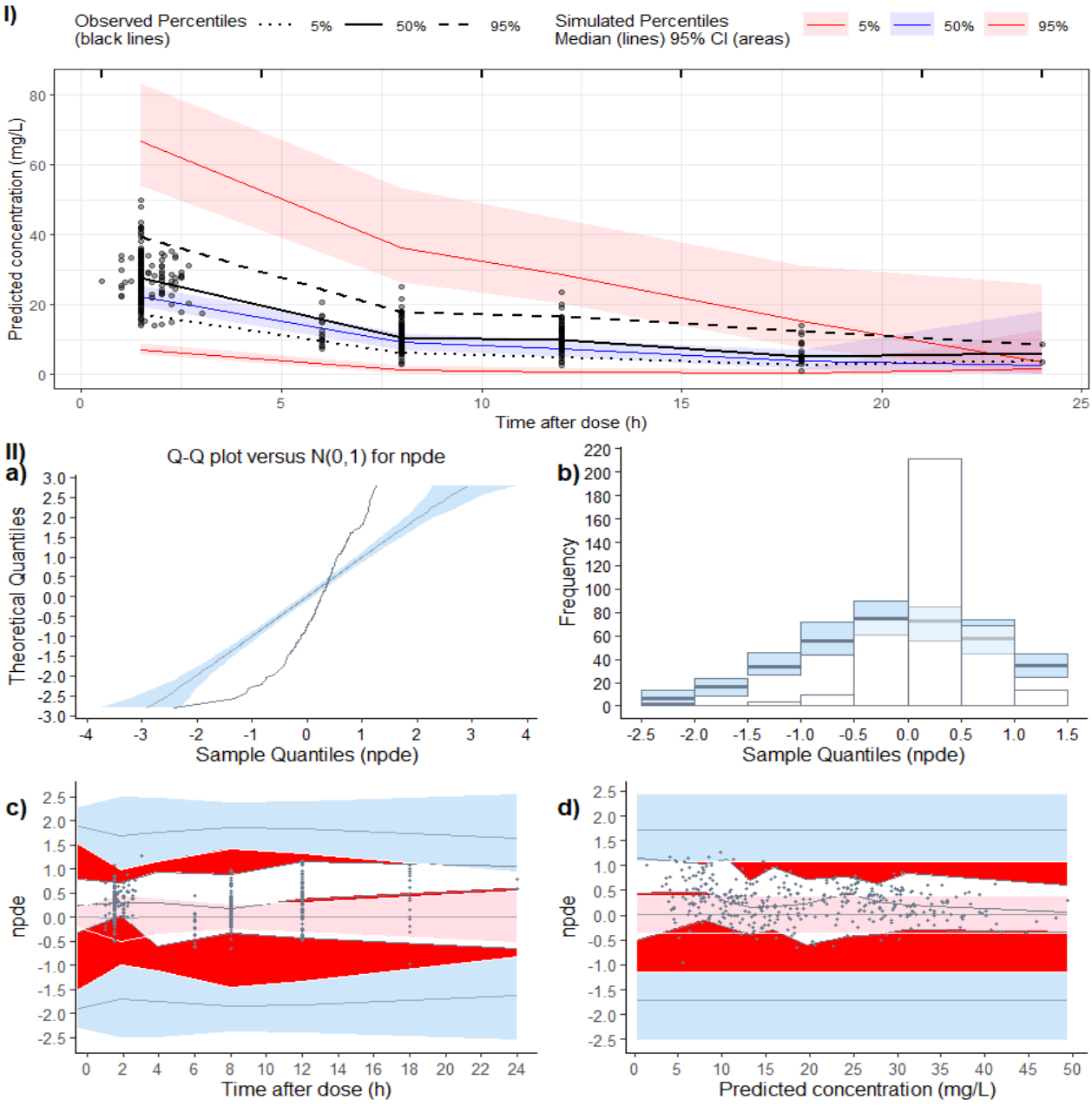
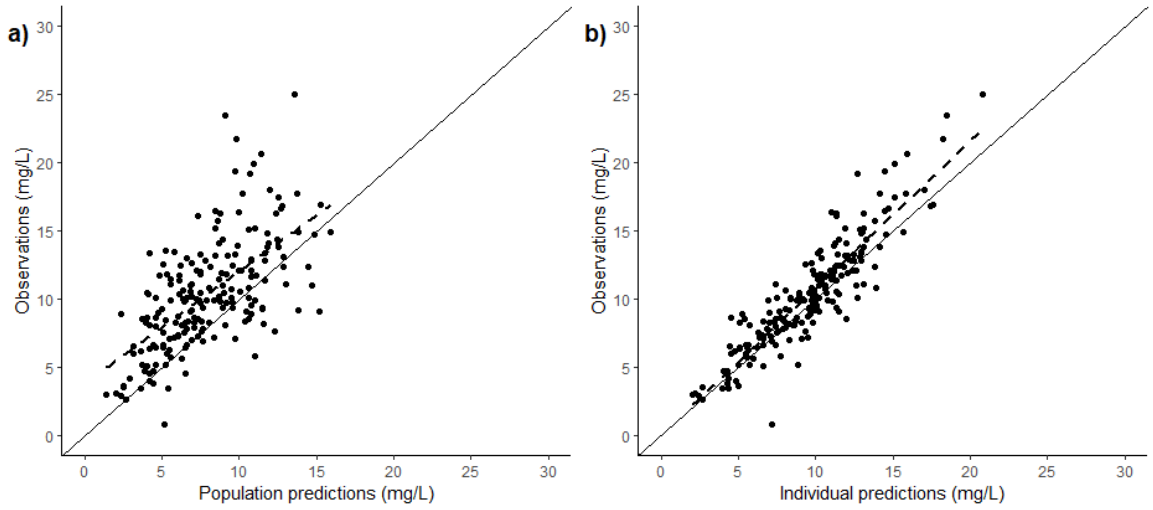


Figure 2. – I) Visual Predictive Check (VPC) - Simulated percentiles are presented as colored areas (pink for 5th and 95th, blue for the median). The corresponding percentiles of the observed data are shown as black lines (dashed lines for 5th and 95th, solid line for the median). **II)** Normalized Prediction Distribution Errors (NPDE) – **a)** Q-Q plot of NPDE – **b)** Histogram of NPDE – **c)** NPDE versus time after dose – **d)** NPDE versus predicted concentration - All plots include simulated percentiles presented as colored areas (blue

for 2.5^{th} and 97.5^{th}, pink for the median). The corresponding percentiles of the observed data are shown as black lines. Red shaded areas indicate deviations of the observed percentiles from the simulated percentiles

1) Capparelli et *al.* (22)



2) Mehrotra et *al.* (35)

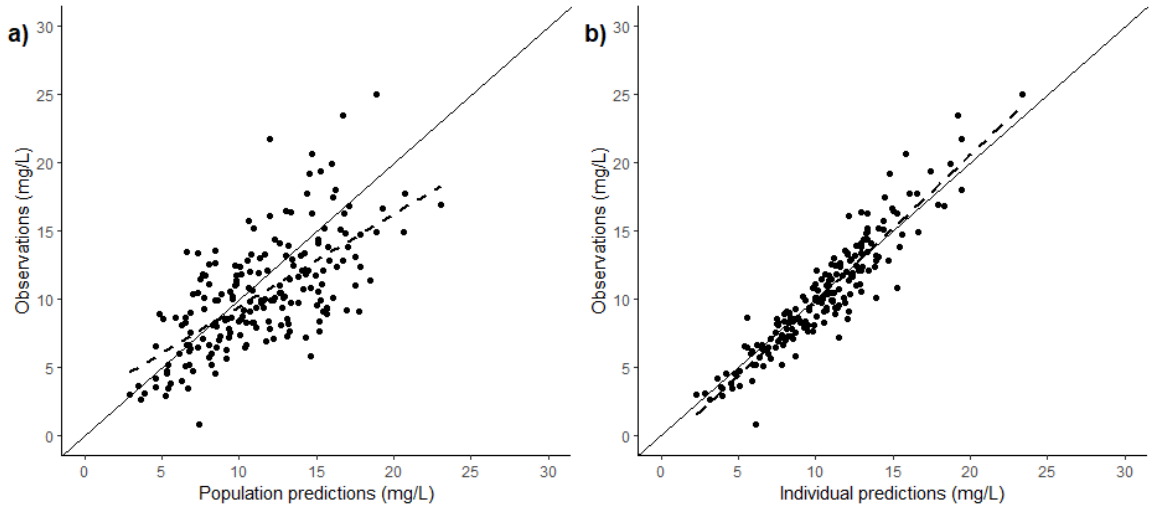


Figure 3. – Goodness-of-fit plots using the truncated (T) dataset - Observations versus **a)** Population or **b)** Individual predictions - Identity function is represented as a solid line, Trend as a dashed line

1) Capparelli et *al.* (22)

$$\boldsymbol{CL\ \left(\frac{L}{h}\right) = CW\ (kg) \times \left(\frac{0.028}{SCr\ \left(\frac{mg}{dL}\right)} + 0.000127 \times PNA\ (days) + 0.0123 \times\ GA28\right) + 0.006}$$

$$\boldsymbol{V_d\ (L) = 0.666 \times V_{ss}\ (L)}$$

$$\boldsymbol{Q\ \left(\frac{L}{h}\right) = 0.0334 \times CW\ (kg)}$$

$$\boldsymbol{V_{ss}\ (L) = 0.793 \times CW\ (kg) + 0.010}$$

2) Mehrotra et *al.* (35)

$$\boldsymbol{CL\ \left(\frac{L}{h}\right) = 0.18 \times (CW\ (kg) \times 2.5)^{0.75} \times \left(0.42 \times SCr\ \left(\frac{mg}{dL}\right)\right)^{0.7} \times \left(\frac{PMA\ (weeks)}{37}\right)^{1.4}}$$

$$\boldsymbol{V_d\ (L) = 1.7 \times (CW\ (kg) \times 2.5)^{1.0}}$$

Figure 4. – PK equations of **1) Capparelli et *al.*** (22), a two-compartment model, and **2) Mehrotra et *al.*** (35), a one-compartment model - CL: Clearance (L/h), Vd: Volume of distribution (L), Q: Intercompartmental clearance (L/h), Vss: Volume of distribution at steady-state, CW: Current weight, SCr: Serum creatinine, PNA: Postnatal age, GA28: 1 if gestational age (GA) $>$ 28 weeks or 0 if GA $\leq$ 28 weeks, PMA: Postmenstrual age

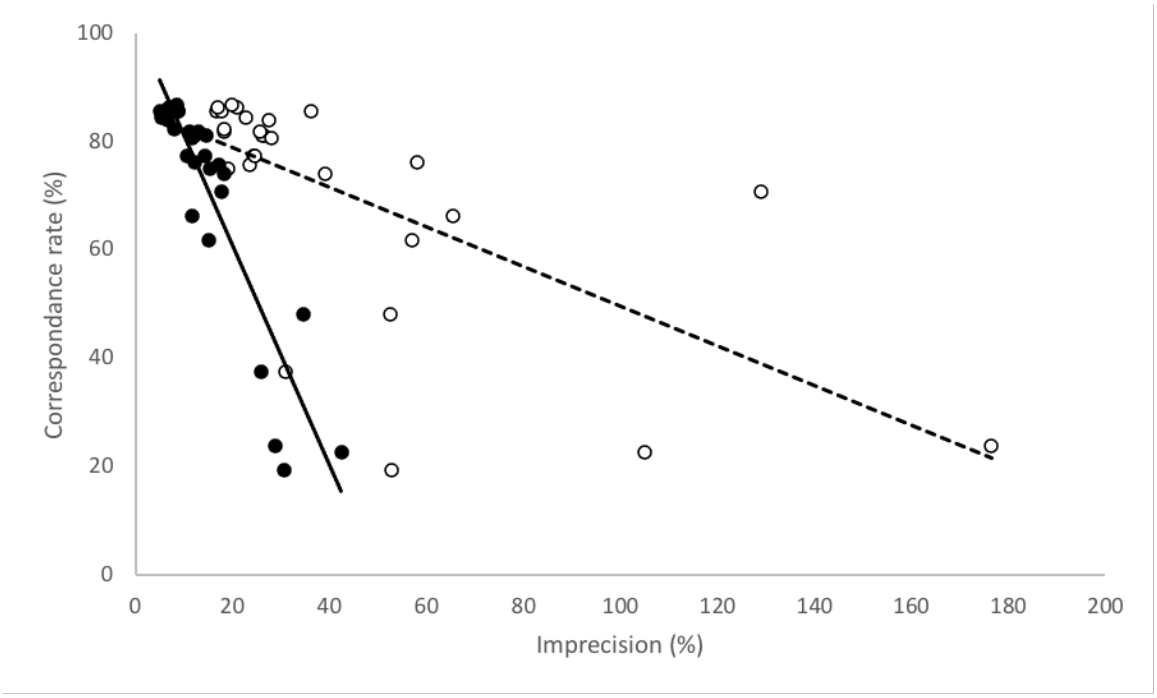


Figure 5. – Correspondence rates in relation to population (white circles, dashed line) and individual (black circles, solid line) imprecisions

Chapitre 4 - Discussion

Ce chapitre récapitulatif vise à comparer les deux études conduites au CHUSJ et au CMES, respectivement. Les similitudes et les différences entre les pratiques cliniques des centres sont mises en évidence afin de discuter de leurs impacts concrets sur l'évaluation externe des modèles PopPK de vancomycine en néonatalogie. Il convient de mentionner que ces éléments sont, encore une fois, majoritairement complémentaires à ce qui apparaît dans les deux articles inclus dans ce mémoire de maîtrise.

4.1. Deux centres et des similitudes

4.1.1. Une évaluation constante

Ces deux articles possèdent quelques points communs, en commençant par les modèles PopPK évalués à l'aide des populations néonatales du CHUSJ et du CMES. En effet, les 28 modèles ont été identifiés séquentiellement par le biais de revues de littérature publiées (45,47,48), couvrant la période comprise entre la création de la base de données PubMed et le 17 août 2020, suivi de deux mises à jour supplémentaires datant de janvier 2022 puis septembre 2023. Bien qu'une majorité des modèles PopPK testés soit issue des revues de littérature (45,47,48), les révisions subséquentes ont tout de même permis d'en ajouter huit nouvellement développés entre 2020 et 2023, un rythme d'environ trois modèles par année. En août 2024, un dernier survol a permis d'identifier un nouveau modèle évaluable (52). L'évaluation des mêmes modèles dans les deux centres entraîne une comparaison juste des performances prédictives au CHUSJ et au CMES, pour autant que les populations soient similaires.

4.1.2. Des populations comparables

L'étude porte seulement sur les nouveau-nés québécois traités en unité de soins intensifs de néonatalogie du CHUSJ et du CMES. Les critères de sélection des patients (inclusion et exclusion) appliqués ont été maintenus à travers les centres, donc il est vraisemblable que les populations néonatales soient comparables en vertu des facteurs démographiques et environnementaux propres à la province de Québec. En effet, on observe une absence de différences statistiquement significatives entre les principales covariables des nouveau-nés du CHUSJ et du CMES, quoique ceux du CMES soient généralement un peu plus âgés, hormis la créatinine sérique qui diffère entre les deux populations telle qu'illustré dans le **Tableau 1** ci-après. Les tests statistiques ont été effectués soit à l'aide du test U de Mann-Whitney pour les covariables continues ou bien du test χ^2 en ce qui concerne le sexe des patients.

Table 1. – Comparaison des populations néonatales du CHUSJ et du CMES

Caractéristiques (Unités)	CHUSJ	CMES	Valeur-p
Nombre de patients (Garçon/Fille)	63 (37/26)	72 (43/29)	1
Âge gestationnel (semaines)	27,0 [22,0-41,0]	28,0 [23,0-40,0]	,3096
Âge chronologique (jours)	18,7 [2,9-137,8]	21,4 [4,3-125,0]	,4735
Âge post-menstruel (semaines)	31,9 [25,0-50,6]	34,0 [24,3-49,0]	,1247
Poids (kg)	1,5 [0,7-4,7]	1,9 [0,5-6,6]	,3543
Poids à la naissance (kg)	0,9 [0,5-4,2]	1,1 [0,4-4,8]	,2989
Créatinine sérique (µmol/L)	45,3 [29,6-92,3]	36,8 [17,0-79,0]	$3{,}042 \times 10^{-5}$
Créatinine sérique (mg/dL)	0,5 [0,3-1,0]	0,4 [0,2-0,9]	$2{,}926 \times 10^{-5}$
Nombre de concentrations sanguines de vancomycine	144	380	NA
Durée de traitement (jours)	4 [2-32]	4 [2-16]	,5391

Médiane [minimum-maximum] - NA: Non applicable

4.2. Deux centres et des différences

4.2.1. Une surprise en bioanalyse

Au vu du **Tableau 1**, il semble étonnant que les deux populations, quasiment comparables en tout point, présentent une différence aussi significative dans leurs valeurs de SCr. En fait, ce décalage s'explique par des méthodes de quantification de la SCr divergentes, à savoir la méthode de Jaffé au CHUSJ contrairement à la méthode enzymatique au CMES. La méthode de Jaffé est une réaction colorimétrique entre la créatinine et un complexe picrate en milieu alcalin, sauf qu'elle est désormais couramment reléguée au profit de la méthode enzymatique étant plus précise et moins susceptible aux interférences (53).

4.2.2. Des pratiques de STP distinctes

Outre les méthodes bioanalytiques permettant de quantifier les concentrations de SCr ou de vancomycine, les pratiques de STP propres à chaque centre ont un impact certain sur la performance prédictive des modèles PopPK évalués. Tout d'abord, les **Table S2** (CHUSJ) et **Supporting Information-Table S1** (CMES) montrent des disparités entre les intervalles d'administration des nomogrammes de doses initiales des deux centres. Ensuite, le CHUSJ se basait encore sur les recommandations issues des premières lignes directrices (23) au moment de la collecte des données de 2019 à 2020, donc la majorité des concentrations sont prélevées au creux. À l'inverse, le CMES avait instauré un STP basé sur les équations PK de premier ordre en 2016 de sorte qu'une grande proportion de patients donnait aussi bien des concentrations au creux qu'au pic entre 2018 et 2022. Une concentration au pic supplémentaire présente un avantage sans équivoque sur la performance prédictive des modèles PopPK, avec l'identification de 11 modèles prédictifs au CMES contre seulement cinq au CHUSJ. Parmi ces derniers, trois (54,55,56) performent aussi bien, voire mieux au CMES tandis que les deux autres (57,58) excèdent dorénavant les critères d'acceptabilité préétablis (46).

4.3. Des impacts concrets

4.3.1. Un manque d'information

Le modèle de Capparelli (54) possède une excellente performance prédictive à travers les deux populations. C'est un des rares modèles décrivant la PK de la vancomycine au moyen de deux compartiments en néonatalogie, même s'ils semblent idéaux en théorie (37,59). En réalité, un échantillonnage limité au creux uniquement n'engendre pas une description convenable d'un modèle à deux compartiments puisqu'il ne fournit pas les informations nécessaires à la caractérisation de la phase de distribution (28,60). Il est donc surprenant que ce modèle présente une bonne performance prédictive au CHUSJ considérant le petit nombre de concentrations aux pics; cependant, un grand nombre de patients (374) et de prélèvements (1103) ainsi qu'un échantillonnage diversifié, présenté dans le Tableau 2 de l'article référencé, contribuent plausiblement à la robustesse et à la transférabilité de ce modèle (54).

4.3.2. Des fois oui, des fois non

Contrairement au modèle de Capparelli (54), celui de Grimsley and Thomson (58) n'a pas présenté une bonne performance prédictive au CMES après s'être montré le plus prédictif au CHUSJ. Une singularité de ce modèle (58) réside dans l'équation de CL divisant le poids par la SCr; or, on se souvient que la valeur de SCr variait significativement entre les deux centres à cause des méthodes de quantification divergentes (**Tableau 1**). Ainsi, les valeurs de SCr plus faibles au CMES augmentent la CL pour un poids comparable, expliquant donc la forte tendance du modèle à sous-estimer les concentrations de vancomycine observées en clinique (58). Il est important de mentionner qu'une évaluation externe antérieure (61) avait déjà souligné l'impact non négligeable des différentes méthodes bioanalytiques de quantification du SCr sur la performance prédictive des modèles. Puisque la méthode de Jaffé était pratiquée au CHUSJ et dans le développement du modèle de Grimsley (58,61), il apparaît évident que des valeurs de SCr obtenues par la méthode enzymatique au CMES justifient sa performance prédictive inacceptable.

4.3.3. Pas si vite!

Heureusement, un groupe de recherche a développé l'**Équation 4** ci-dessous permettant de convertir les résultats de SCr obtenues d'une méthode à l'autre (53).

Équation 4. – $$SCr_{enzymatique} = 1,050 \times SCr_{Jaffé} - 0,122$$

où les valeurs de SCr sont toutes exprimées en mg/dL, indépendamment la méthode de quantification. En appliquant cette dernière à nos valeurs de SCr du CMES, la SCr médiane passe de 36,8 µmol/L (p = 3,042 x 10^{-5}) avec la méthode enzymatique à 43,6 µmol/L (p = ,9138) avec la méthode de Jaffé comparativement à 45,3 µmol/L au CHUSJ (53). D'après une analyse préliminaire, un tel ajustement des valeurs de SCr pour le CMES améliore la performance prédictive du modèle de Grimsley (58) qui affiche désormais l'imprécision la plus faible parmi tous les modèles testés, surpassant même ceux de Capparelli (54) et de Mehrotra (62) (**Table 2**). En effet, le biais baisse de -24,7% à -5,3% alors que l'imprécision suit cette tendance avec une diminution de 25,7% à 14,5%, comme l'illustrent les résultats rapportés dans le **Tableau 2** ci-dessous. Il serait intéressant d'appliquer ce modèle ajusté dans les simulations de Monte-Carlo pour le CMES, favorisant ainsi une comparaison plus juste des recommandations de doses initiales résultantes dans les deux centres (58).

Table 2. – Performance prédictive de Grimsley (58) selon méthode de quantification SCr

Méthode enzymatique	Biais (%)	Imprécision (%)	F_{20} (%)	F_{30} (%)	Correspondance (%)
Niveau de population	-24.7	25.7	35.0	61.3	81.8
Niveau individuel	-7.6	11.3	-	-	-
Méthode de Jaffé	Biais (%)	Imprécision (%)	F_{20} (%)	F_{30} (%)	Correspondance (%)
Niveau de population	-5.3	14.5	60.8	76.6	85.6
Niveau individuel	-1.2	8.1	-	-	-

4.3.4. Un nouveau manque de consensus

L'utilisation de modèles distincts entre le CHUSJ et le CMES dans le cadre des simulations de Monte-Carlo complique la comparaison des régimes de doses initiales recommandés. Un régime uniforme, commençant par une dose de charge de 15 mg/kg suivie de doses d'entretien de 11 mg/kg toutes les 8 heures, est proposé à l'aide du modèle de Grimsley (58) pour les nouveau-nés du CHUSJ. À l'inverse, des nomogrammes plus complexes sont prônés par les modèles de Capparelli (54) et de Mehrotra (62) au CMES. La pertinence des nomogrammes développés et des modèles devront être testés en pratique clinique, mais nos résultats démontrent clairement l'importance de l'évaluation externe en amont de l'implémentation clinique des recommandations des dernières lignes directrices (41).

Chapitre 5 - Conclusion

Cet ultime chapitre vient conclure le présent mémoire en discutant des prochaines étapes et possibilités futures en lien avec ce projet de recherche.

5.1. Un regard vers l'avenir

5.1.1. Des changements à prévoir

Ce projet a permis de confirmer notre hypothèse en identifiant trois modèles PopPK, soit un au CHUSJ (58) et deux autres au CMES (54,62), qui pourraient être intégrés en pratique clinique en vue de guider le STP tel que suggéré dans les dernières lignes directrices (41). L'objectif primaire a été atteint grâce à la proposition de nomogrammes de doses initiales spécifiques à chacun des trois modèles les plus prédictifs. Il a aussi permis d'explorer des objectifs secondaires permettant de renforcer les cibles thérapeutiques recommandées en comparant les paramètres de STP (creux/ASC_{24h}) aux issues d'efficacité et de toxicité au CHUSJ (**Chapitre 2**) ou de renseigner sur la faisabilité d'un plan de prélèvement limité en combinaison avec un modèle PopPK prédictif au CMES (**Chapitre 3**). Il reste encore du travail à faire avant d'implémenter une nouvelle pratique clinique concernant le STP de la vancomycine dans nos unités de soins intensifs de néonatalogie du Québec, mais ce mémoire jette les bases en décrivant une approche rigoureuse visant l'évaluation externe de modèles PopPK disponibles dans la littérature scientifique (44).

5.1.2. Des clarifications nécessaires

En effet, la méthode proposée pour identifier des modèles PopPK prédictifs possède une certaine flexibilité dans la mesure où les critères d'acceptabilité et cibles thérapeutiques peuvent être adaptés en fonction des besoins. En ce qui concerne l'évaluation externe, il n'existe actuellement pas de consensus sur les meilleures mesures ou leurs valeurs seuils

(63), de sorte que les critères d'acceptabilité peuvent varier d'une étude à l'autre. En lien avec les cibles thérapeutiques en pédiatrie, certains groupes suggèrent que les creux ont un meilleur pouvoir prognostic que l'ASC_{24h} (50,51), allant à l'encontre des plus récentes recommandations qui découlent principalement de données adultes (41). Bref, des zones grises nécessitent toujours plus de considération et de données probantes, mais celles-ci n'invalident pas notre étude puisque les différents éléments sont modulables.

5.1.3. IA peu d'avantages actuellement

Enfin, j'aimerais aborder les implications d'un sujet d'actualité en l'intelligence artificielle (IA) dans le domaine de la PK. Des algorithmes d'apprentissage automatique permettent d'agréger divers modèles PopPK en pondérant selon la performance prédictive de chacun (64,65). Bien que ces nouvelles approches soient intrigantes, pour l'instant les avancées semblent incrémentales par rapport aux procédures traditionnelles utilisées dans le cadre de ce projet de recherche (64-68). Il est vraisemblable que de tels algorithmes reposant sur l'IA se perfectionneront au fil des prochaines années; cependant, à l'heure actuelle, l'intérêt paraît anecdotique (64-68).

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