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Optimisation of vancomycin exposure in neonates based on the best level of evidence

THESE

préparée sous la direction du Professeur Thierry Buclin
(avec la co-direction de la Professeure Chantal Csajka et
la collaboration du Docteur Eric Giannoni)

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par

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Optimisation of vancomycin exposure in neonates based on the best level of evidence

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Abstract

There is no consensus regarding optimal dosing of vancomycin in term or preterm neonates. Various available dosing recommendations are based on age, kidney function and/or body weight to define a starting dose. Our objectives were (i) to develop a comprehensive population PK model of vancomycin in a large cohort of neonates and (ii) to evaluate and compare the performances of current dosing approaches with respect to target attainment, using simulations based on our model. This will serve the purpose to recommend the best dosing approaches among existing regimens in the early and later phases after treatment initiation as a complementary approach to therapeutic drug monitoring (TDM).

A total 405 neonates provided 1831 vancomycin concentrations measured during routine TDM. A one-compartment model with linear elimination incorporating covariates such as age, kidney function and body weight was developed (NONMEM®). The final model was applied to simulate in our population vancomycin exposure resulting from 20 dosing guidelines identified in the literature. Proportions of patients within and above target exposure were used as a performance measure. Target attainment meant area under the curve/minimal inhibitory concentration (AUC_{24}/MIC) ratio of 400-700 h and trough concentration of 10-20 mg/L, both on days 1 and 7.

Most current vancomycin dosing regimens fail to ensure target attainment in a majority of neonates. Insufficiently dosed regimens should be avoided, especially in centers with widespread coagulase negative Staphylococci. Adding a loading dose to simple regimens is best recommended to increase the proportion of early target attainment. Complex regimens seem to marginally improve exposure.

Optimisation of efficacy while minimizing toxicity of vancomycin in neonates is needed. The application of a simple dosing regimens like NNF7 or the Neofax Hi-Dose regimens, with a 25 mg/kg loading dose for severe infections, or the SmPC regimen should be recommended to ensure the highest proportion of target attainment after 24 hours. TDM should then be carried out, to account for residual unexplained variability in vancomycin elimination.

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Introduction

Vancomycin, a glycopeptide antibiotic, is frequently administered to neonates for nosocomial Gram positive infections. [1] It is subject to important interindividual pharmacokinetic (PK) variability, mostly explained by variations in renal function and volume of distribution (V) in neonates. This might lead to either poor antibacterial coverage or concentration-dependent nephrotoxicity. [2, 3] Emergence of vancomycin resistant strains has become a major concern, emphasizing the need for adequate vancomycin exposure. Therapeutic drug monitoring (TDM) of vancomycin is largely justified in this population, but requires a certain turnaround time. [4, 5] By definition, it cannot be used for initial dosage decisions, which can only rely on appropriate guidelines.

Several PK models have already described factors that mostly influence vancomycin clearance (CL) in neonates, [6] such as body weight (WT), serum creatinine (SCr), gestational age (GA), postnatal age (PNA) or postmenstrual age (PMA). Various dosing recommendations have been issued, but most of them were not validated prospectively, and there is at present no consensus about the most appropriate initial dosage regimen for vancomycin. Recent observations report that current dosing guidelines often result in subtherapeutic plasma levels in neonates considering trough concentrations (C_{min}). [7, 8] Model-based algorithms are increasingly called to improve dosing decisions in neonates. [9, 10]

The objectives of this study were (i) to develop enhanced comprehensive population PK model of vancomycin in a large cohort of neonates and (ii) to perform model-based simulations to evaluate and compare the performance of current dosing guidelines with respect to target attainment. Dose recommandations reported in the literature, provided by international neonatal guidelines, or used in tertiary care neonatal intensive care units (NICUs) throughout Switzerland were evaluated and compared. We aimed to address current concerns for increased bacterial resistance and to facilitate harmonization of neonatal dosing regimens, with the goal of enhancing efficacy while minimizing toxicity of vancomycin in neonates.

Materials & Methods

Population

Our study retrospectively included all neonates with at least one plasma vancomycin determination admitted consecutively in the NICU of Lausanne University Hospital over a time period of 10 years (from December 2006 to April 2016). Neonates with missing information on drug administration or sampling times or unclear dose schedule were excluded. For all patients, sex, GA, PNA, birth weight (BW), small for gestational age status (SGA), WT at sampling time, Apgar

score at 1 and 5 minutes, umbilical arterial and venous pH, serum creatinine (SCr) and exposure to antenatal steroids were recorded. PMA was defined as the sum of GA and PNA.

Vancomycin measurements were retrieved using the NICU clinical information system (MetaVision®, iMDsoft, Massachussetts, USA) and the local TDM database. Vancomycin was always administered intravenously over 1 hour using an infusion pump (DPS Orchestra, Fresenius). Initial vancomycin dosage was 10-15 mg/kg in most cases, with further dosing guided by TDM (either at 4 and 12 hours following the 1st dose or at trough under steady-state conditions). Concentrations were measured at the discretion of NICU physicians, based on recommendations of clinical pharmacologists.

Serum vancomycin concentrations were determined by fluorescent polarization immunoassay (FPIA, Cobas Integra 400 Plus, Roche Diagnostics). Lower limits of detection and quantification of the method were 0.74 and 3.2 mg/L respectively (coefficient of variation (CV) for imprecision was 1.9-4.1%). SCr concentrations were measured by the Jaffe Gen. 2 compensated method (Cobas 8000 / c702, Roche Diagnostics) standardized according to IDMS-traceable method. This retrospective study was approved by the local ethics committee of Vaud.

Development of Population Pharmacokinetic Model

A population PK analysis was performed using non-linear mixed effect modelling (NONMEM® version 7.3, ICON Development Solutions, Ellicott City, MD, USA) to characterize vancomycin exposure over time in a large neonatal population. Details about methods are provided in Supplemental material. Based on existing models of vancomycin in neonates, only covariates deemed relevant for dosage adjustment were considered, namely GA, PNA, PMA, SCr, gender, small for gestational age (SGA), Apgar and antenatal steroids. An allometric scaling with current WT was implemented on CL and V [11], while the effect of GA, PNA, PMA and gender were tested on both parameters. SCr, SGA, antenatal steroids were tested on CL only. Although the impact of co-medications on vancomycin CL has been shown in some PK model, they were not investigated in the present study as they were not considered relevant for dosage adjustment.

Model evaluation

The predictive performance of the final model was assessed by standard validation techniques (see Supplemental material). An external dataset of 78 neonates was used for model evaluation (Table 2).

Comparison of previously published population PK models

In order to compare our model with previously published analyses, available neonatal PK models for vancomycin were reviewed. [6, 12] The criteria for comparison were similar demographic characteristics and intermittent administration, whereas models based on different populations or performed with patient under extracorporeal membrane oxygenation were excluded. Papers lacking proper model description were excluded too. Details about model selection are available in Supplemental material. Each selected model was used to predict vancomycin concentrations using the external dataset employed to validate our model. Accuracy (bias) and precision (variability) of prediction with respect to actual observations were estimated through mean prediction error (MPE) and root mean squared error (RMSE), respectively and compared to our model.

Simulations to evaluate and compare current dose recommendations:

Vancomycin dosing regimens in neonates were retrieved from international guidelines, from published dosing algorithms and from the 9 tertiary care NICUs (NICU-CH 1 to 9) of Switzerland. The selected dosing guidelines are summarized in Table 1. [13-23] A dosing algorithm directly derived from our model (based on WT, SCr and PMA and allowing dosing intervals of 4, 6, 8, 12, 24 and 48 hours) that selected dose and dosing interval to maximize the probability of target attainment was also simulated, to establish the best possible dosing performance ideally achievable.

The final model for vancomycin with covariates was applied to the original dataset to predict concentrations over 7 days of treatment following each dosage regimen. AUC_{24} was derived by numerical integration in NONMEM® over the first 24 hours and after 7 days of treatment (assumed to have reached the steady-state). Trough concentrations (C_{min}) were also predicted at similar timepoints. The primary measure for efficacy and safety was the ratio of AUC_{24} over MIC (minimal inhibitory concentration), currently considered as the gold standard determining efficacy and safety. A MIC of 1 mg/L was considered by default, corresponding to the cutoff most usually determined for vancomycin-sensitive pathogens. Minimal target was defined as $AUC_{24}/MIC > 400$ h [1]. An $AUC_{24}/MIC > 700$ h was considered as the upper threshold, based on studies observing increased nephrotoxicity with AUC_{24} above 700 – 800 mg · h/L in adult and pediatric patients, respectively [24, 25]. Frymoyer *et al* recently demonstrated that a C_{min} of 10 mg/L, more conveniently assessed in clinical settings, was associated with a high probability to achieve an $AUC_{24}/MIC \geq 400$ h. C_{min} was therefore considered as a secondary marker of efficacy, with a target interval of 10- 20 mg/L. [26] Tkachuk et *al* although observed in a review that lower C_{min} of 6 -10 mg/L may be able to achieve $AUC_{24}/MIC > 400$ h. [27] Proportions of neonates found within and above target exposure (AUC_{24}/MIC 400 h to 700 h and > 700 h, respectively) were calculated for each of the tested regimens. Similar proportions were computed as well as for a trough

concentration target (C_{min} of 10 – 20 and > 20 mg/L, respectively). As a sensitivity analysis to further enhance reproducibility of results, the same simulations were carried out with the externally validated model from Frymoyer *et al*. [26]

Results

Analysis Dataset

Out of the 1947 vancomycin concentrations collected from 409 patients, 116 samples and 4 patients were excluded. A total of 1831 vancomycin concentrations and 405 patients were thus included in the analysis to develop the population PK model, with a median of 4.5 concentrations per patient. Patients demographics of the dataset for model building and external validation are detailed in Table 2. Raw observations are available as Supplementary material in Figure 4.

Developed Population PK Model

Vancomycin concentrations were best described with a one-compartment model. The allometric exponent describing the influence of WT on CL was estimated to be 1.4 (structural model) and 0.438 (final model), which significantly improved the model compared to the classic value of 0.75 (ΔOF=-332; $p<0.001$) in the structural model. The allometric exponent of V was estimated to 1.05, not significantly different from the literature value of 1 (ΔOF=-2.8), at which it was then fixed. [28] The age dependency of CL was best described using a sigmoid E_{max} function representing a maturation function (MF), in which $MF=(PMA^{HILL})/(PMA^{HILL} + T_{50}^{HILL})$ with T_{50} of 46.4 weeks representing the PMA when 50% of maturation of CL has been reached, and a Hill coefficient of 3.54 (ΔOF=-515; $p<0.001$). This MF best describes maturation of kidney function in neonates, since PMA includes GA (development during pregnancy) but also PNA (postnatal maturation). The inclusion of SCr using an inverse function further improved the description of concentration data (ΔOF=-307; $p<0.001$), in line with vancomycin being mainly excreted through the kidneys. The final model is summarized in Table 3.

Model evaluation

The parameter estimates of the final population PK model were within the bootstrap 95% CI and differed less than 3% from the median bootstrap parameters, indicating the acceptability of the model. The structural, final model parameters and bootstraps results are presented in Table 3 (and Table 4 in Supplementary material), goodness of fit plots in Figure 5, results of pcVPC in Figure 1, and normalized prediction error (NPDE) in Supplemental material (Figure 6). The external validation showed a small and unsignificant bias of 0.01 (CI95%: -0.05;0.07) in the individual predictions, with an imprecision of 37%.

Comparison of previously published population PK models

Seventeen out of twenty-two PK models initially identified were excluded according to our criteria. Included models and their PK parameter estimates used for comparison are reported in Table 5 (in Supplemental material). [16, 26, 29, 30]. The models from Frymoyer *et al*, *Mehrorta et al* and Kimura *et al* had a negligible or non significant bias with a mean prediction error of -0.05 (IC 95%:-0.10;-0.01), 0.01 (-0.03;0.04) and 0.06 (0.00;0.13) respectively, and a precision of 29%, 19% and 40% respectively. Our model had a mean prediction error of 0.01 (IC 95%: -0.05;0.07) and a precision of 37%. Considering the validity of our model, we kept it for simulation studies. Frymoyer *et al* model was further used to test the reproducibility of results, since it also used a MF and was externally validated. Comparison of observed concentrations versus individual predictions using our final model or Frymoyer et al model is available in Figure 9 (Supplemental material).

Simulations to evaluate and compare current dose recommendations

Results of the simulations of the 20 different dosing regimen are summarized in Figures 2 and 3. Considering early exposure on 1st day, the median proportion of patients with an AUC_{24}/MIC in the defined target across all regimens was 42% (IQR: 28-69%). The median proportion of AUC_{24}/MIC above 700 and under 400 was 1% (IQR: 0 – 3%) and 52% (IQR: 29-71%), respectively. The median proportion of patients with a C_{min} between 10-20 mg/L was 32% (IQR: 24 - 45%), while it was 9% (IQR 5 – 20%) for a C_{min} under 5 mg/L and 12% (IQR: 1 - 27%) for a C_{min} over 20 mg/L.

Janssen *et al* dosing algorithm [15] provided the best exposure on day 1 (73% within target and 20% over). The SmPC regimen ranks close with 71% within target (0.25% over). The NNF7 and Neofax (Hi-Dose) brought 69 % of the patients in the defined target, with 1-2% of patients above 700 mg·h/L. The flat 15 mg/kg every 8 h used in our hospital achieved a close performance (65% within target and 30% over). The highest proportion of patients with a C_{min} between 10 – 20 mg/L was produced by the Dutch children formulary, the SmPC, NICU-CH3 and regimen of Neofax (Hi-Dose) with respectively 58, 53, 51 and 50% within the therapeutic target.

Regarding exposure after 7 days, the median proportion of patients with an AUC_{24h}/MIC in the defined target was 48% (IQR: 43-52%). The median AUC_{24}/MIC above and under target were 20% (IQR: 8 - 25%) and 32% (IQR: 19-43%), respectively. The best regimens were Grimsley *et al*, Neofax (Hi-Dose), Capparelli *et al* and NNF7 with respectively 66, 57, 57 and 56% within target. The median proportion of C_{min} in the defined target was 38% (IQR: 32 - 41%), while it was 8% (IQR 6 – 19%) for a C_{min} under 5 mg/L and 24% (IQR: 7 - 36%) for a C_{min} over 20 mg/L. The

guidelines issued from Grimsley *et al* ranked first followed by the Neofax (Hi-Dose), and NICU-CH6 (Hi-Dose) with respectively 51, 48 and 46% of patients brought within the therapeutic target.

Using our model to simulate a best case scenario, exposure could be further improved to reach optimal exposure in 94% of patients (day 1) and 73% (day 7). A supplemental file with the latter model-based regimen is provided. Adding a loading dose of 25 mg/kg to the NNF7 regimen also significantly improved exposure on 1st day, with 77% patients within target and 15% over. Finally, simulations carried out with Frymoyer *et al* model similarly demonstrated suboptimal exposures with most regimens (Figure 7 and 8 in Supplemental material). Final ranking was slightly different, the dosing regimens of Janssen *et al* and of our center (NICU-CH7) were best on day 1, while NICU-CH6 (Hi-Dose), Neofax (Hi-Dose), one of Lexicomp's regimen (Hi) and NNF7 were best after 7 days (according to AUC_{24}/MIC).

Discussion

The problematic adequacy of current dosing regimens of vancomycin to reach therapeutic targets in neonates has already been emphasized. [7-9] Despite numerous authors urging for revision of current guidelines, a consensual, optimized regimen is still not available and actual practice remains largely dominated by heterogenous and empirical approaches. [31]

The results of this study illustrate the large diversity in vancomycin dosage regimens used and confirm that most recommended regimens will not ensure adequate antimicrobial coverage, considering targets for AUC_{24}/MIC of 400 to 700 h or a C_{min} between 10 and 20 mg/L. These results further support the need for global harmonization and optimization of vancomycin dosing regimens in neonates, to prevent both the development of bacterial resistance and the occurrence of nephrotoxicity resulting from overexposure. An overall lower ability to achieve C_{min} targets was observed, probably explained by the incomplete overlap between C_{min} and AUC_{24}/MIC in this population. Indeed, it was recently shown that the target AUC_{24}/MIC attainment could be reached with C_{min} between 6-10 mg/L. AUC_{24}/MIC remains the gold standard for efficacy. [27]

Coagulase negative *Staphylococcus* (CoNS) is a leading pathogen in neonatal sepsis, accounting for the majority of central line-associated nosocomial sepsis episodes. [32] In our NICU, vancomycin is administered for empirical treatment of hospital-acquired late-onset sepsis, and for target treatment of methicillin-resistant CoNS (MRSE) and *Staphylococcus aureus* (MRSA). Therapeutically, CoNS are challenging due to the large proportion of methicillin-resistant strains and increasing numbers of isolates with reduced susceptibility to glycopeptides. [33] According to EUCAST, the median MIC distribution for MRSE is 2 mg/L (range 0.5 – 4 mg/L), higher than for MRSA, and is drawing attention to the need for adequate exposure to avoid the emergence of resistant strains.

The therapeutic window for vancomycin has not been defined specifically in neonates and has been extrapolated from adult studies. An AUC_{24}/MIC ≥ 400 h (for a MIC of 1 mg/L), widely accepted as the best predictor of vancomycin efficacy for MRSA infection, was chosen as the cut-off for efficacy. [1] The upper boundary for target window was based on studies observing increased nephrotoxicity with AUC_{24} above 700 mg·h/L in adult and pediatric patients [24, 25], considered a reasonable threshold by recent data. [34]

Rapidly reaching therapeutic window according to AUC_{24}/MIC has been associated with better outcome in adults [35]. As already mentioned, adding a loading dose allows the attainment of therapeutic window and steady-state more rapidly. For instance, a loading dose of 25 mg/kg implemented into the NNF7 regimen increased from 69 to 77% the proportion of patients in the target concentration range after 24 hours of treatment. SmPC, Janssen *et al* and Frank Shann recommend a loading dose, which should be considered in all neonates with severe infection.

Interestingly, prescribing 15 mg/kg every 8 hours without adjustment to PMA nor SCr, brings a majority of neonates within target on day 1, but will lead to overexposure after several days of treatment. Using the simple dosing regimen issued from the SmPC for vancomycin (i.e. a loading dose of 15 mg/kg, a maintenance dose of 10 mg/kg, every 12 hours for a PNA < 7 days and every 8 hours for a PNA > 7 days) puts 71% of patients within target, with <1% over it at 24 h. These results rank close to the complex dosage adjusments from Janssen *et al* (73%), NNF7 (69%) or Neofax Hi-Dose (69%). Of note, the Neofax (Hi-Dose) and NNF7 regimens are stratified according to PMA and/or PNA, using up to seven categories. The complex dosing algorithm from Janssen *et al* [15] includes 19 levels based on PNA and WT following a loading dose. All these regimens are thought to provide adequate drug levels in up to 69 % of patients on the first day of treatment. Overstratification of neonates characteristics appears therefore pointless to reduce unexplained variability of vancomycin PK.

After 7 days, the proportion of exposure predicted within the target was globally low according to our simulations. Grimsley *et al* regimen [16] was the most performant to achieve adequate exposure in 66% of neonates, followed by Neofax (Hi-Dose), Capparelli *et al* and NNF7 for approximately 56-57% of cases. Neofax (Hi-Dose) and NNF7 regimens also brought approximately 20% of patients over the target, except for the regimens of Grimsley *et al* and Capparelli *et al* based on SCr that led to potentially less toxic exposures (6-10%). Janssen *et al* dosing algorithm brought 42% of patients within the target in terms of AUC_{24}/MIC and 25% over it. A major drawback of the latter regimen for steady-state is the absence of integration of SCr as a covariate. Furthermore, its complexity only marginally improves exposure.

Finally, only few dose regimens allow maintaining drug concentrations within the targets from the start of the treatment over several days. High doses at treatment start induce overexposure after one week of treatment, due to drug accumulation or induced nephrotoxicity and inversely too low

doses underexpose neonates on the first days of treatment. This advocates for performing TDM at several timepoints in cases requiring ≥ 3 days of vancomycin treatment.

A dosing strategy of vancomycin in neonates should be based on the combination of GA and PNA (i.e. PMA) [36] but also SCr, as these parameters take into account the evolution of body composition, hence of volume of distribution and renal function. Discarding most low-dose regimens and adding a loading dose to a simple table-based regimen appears sufficient to optimize early exposure, in the absence of apparent renal failure. Based on these results, we would recommend to use rather simple dosing regimens like NNF7 or the Neofax (Hi-Dose) regimens, with a 25 mg/kg loading dose for severe infections, or the SmPC regimen, to ensure the highest proportion of target attainment after 24 hours. In our opinion, TDM before the fourth dose should still be carried out, to account for residual unexplained variability in vancomycin elimination (notably maturation).

While prospective validation of these optimized algorithms remains needed, efforts should be put to update guidelines recommending low-dose vancomycin and move to a consensus to decrease variability in terms of doses, dosing interval and total daily doses observed so far. [31]

In a constructed best-case scenario tool derived from our model (available as Supplemental file), aiming to reach the therapeutic interval of 400 – 700 h, it was possible to bring a higher proportion of patients (94% and 73% on day 1 and 7, respectively), similarly to the recently published model-based algorithm *Neo-Vanco* of Frymoyer *et al* [9] (and available at: http://neovanco.insight-rx.com/neo-vanco/). Model-based approach appears as a tailored option to account for the important variability among the neonatal population and increase the proportion of adequate exposure. Still, adequate exposure in everyone may not be attained in all children, especially after 7 days, further stressing the need for TDM. A model-based dosing algorithm for continuous vancomycin administration was already prospectively evaluated in neonates and increased exposure from 41 to 72% in a French cohort. [10] Switching from intermittent to continuous iv infusions is considered as an option to reduce variability in concentration, but precludes the use of the iv line for most others medications.

This study has several assets and limitations. Our pharmacokinetic analysis used the largest ever cohort of term and preterm neonates exposed to vancomycin, to our knowledge. Apart from WT and age uniformatly used to adjust dosage regimens, it reinforces the need to integrate SCr in dosage adjustment to avoid vancomycin accumulation due to renal dysfunction. AUC_{24}/MIC at an early stage and after 7 days of treatment were evaluated in a large number of dosing regimens, including recently published ones. The main limitations of our study are the retrospective design of our data collection and the lack of prospective validation of the newly proposed regimens. In addition, potential biases related to the problematic performance of the Jaffé SCr assay method and of vancomycin measurement were not accounted for during model building [37]. The omission

of potential effects of comedications in the model is another limitation, calling for its cautious application to support dosage decisions in patients receiving e.g. NSAIDs or diuretics. [38]

In conclusion, the comparison of 20 different algorithms indicates that most current regimens are suboptimal to reach the AUC_{24}/MIC predefined target of 400 – 700 h or C_{min} of 10 – 20 mg/L in neonates. The low-dosed regimens should definitely be discarded, especially in centers harboring methicillin-resistant CoNS. Complex regimens comprising many levels of dose stratification do not seem useful, and are not suitable in the clinical setting. Using NNF7 or Neofax Hi-Dose regimens with a loading dose appears as a commendable option for severe infections, as it significantly improves early exposure, as well as the SmPC regimen, that ranks close in terms of early target attainment. Model-based approaches emerge as another promising option, as it allows first dose individualization. TDM before the fourth dose should still be carried out, to account for residual unexplained variability in cases of $\geq$ 3 days of therapy. Prospective work, such as NeoVanc, an European ongoing trial, will help better defining concentration-effect relationships against Gram positive pathogens and confirm or help recommending optimal vancomycin dosing regimens based on clinically relevant outcomes.

Authors' contributions

KD, MG, PA, SB, AF, WZ contributed to the literature search and data collection. KD, TB, CC, EG, AF, MP contributed to study design. KD, MG, SB, PA, TB, CC participated in data analysis and interpretation. KD wrote the manuscript, MG, PA, EG, SB, WZ, AF, MP, TB, CC critically reviewed the manuscript.

No conflict of interest are reported.

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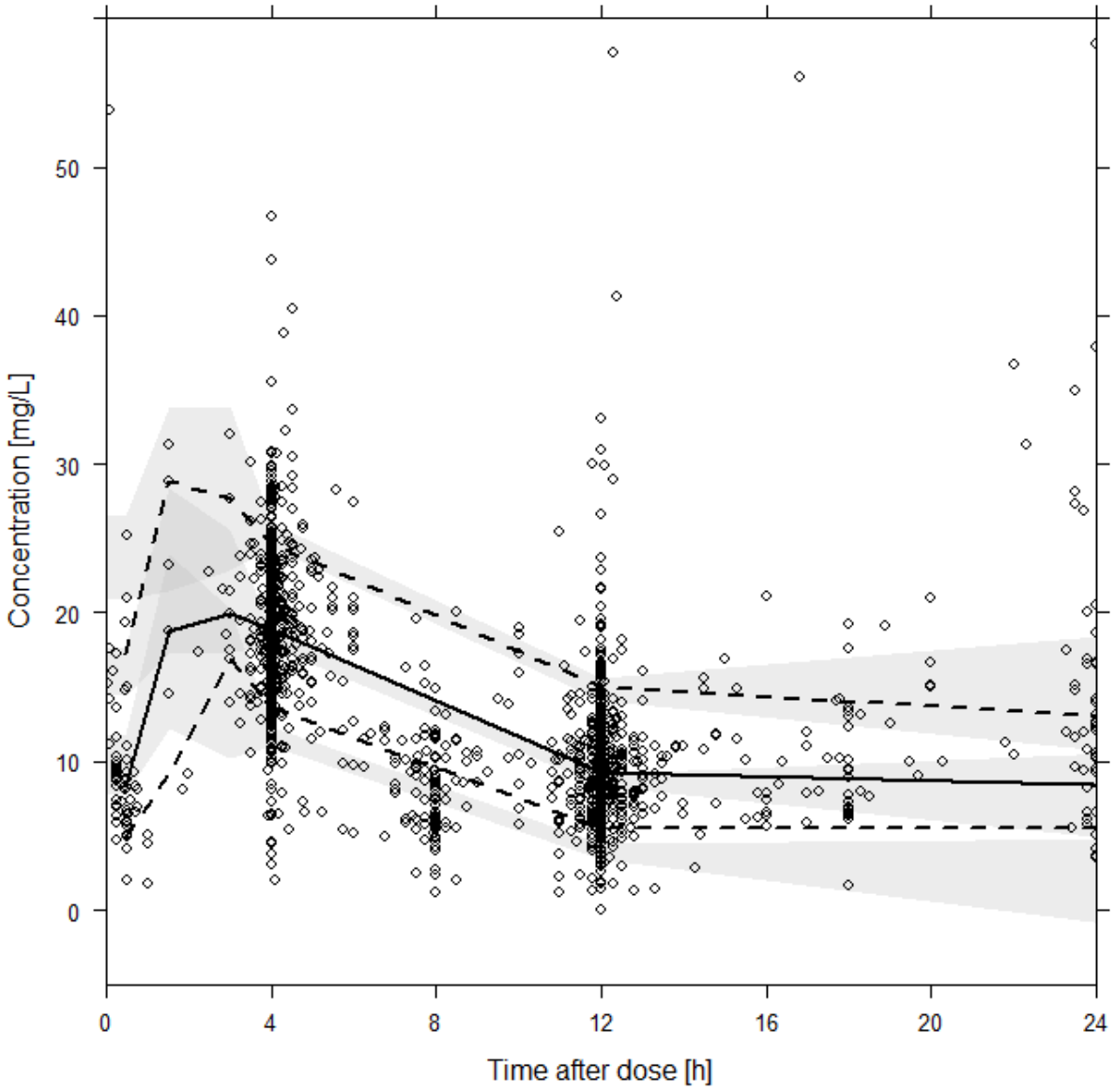
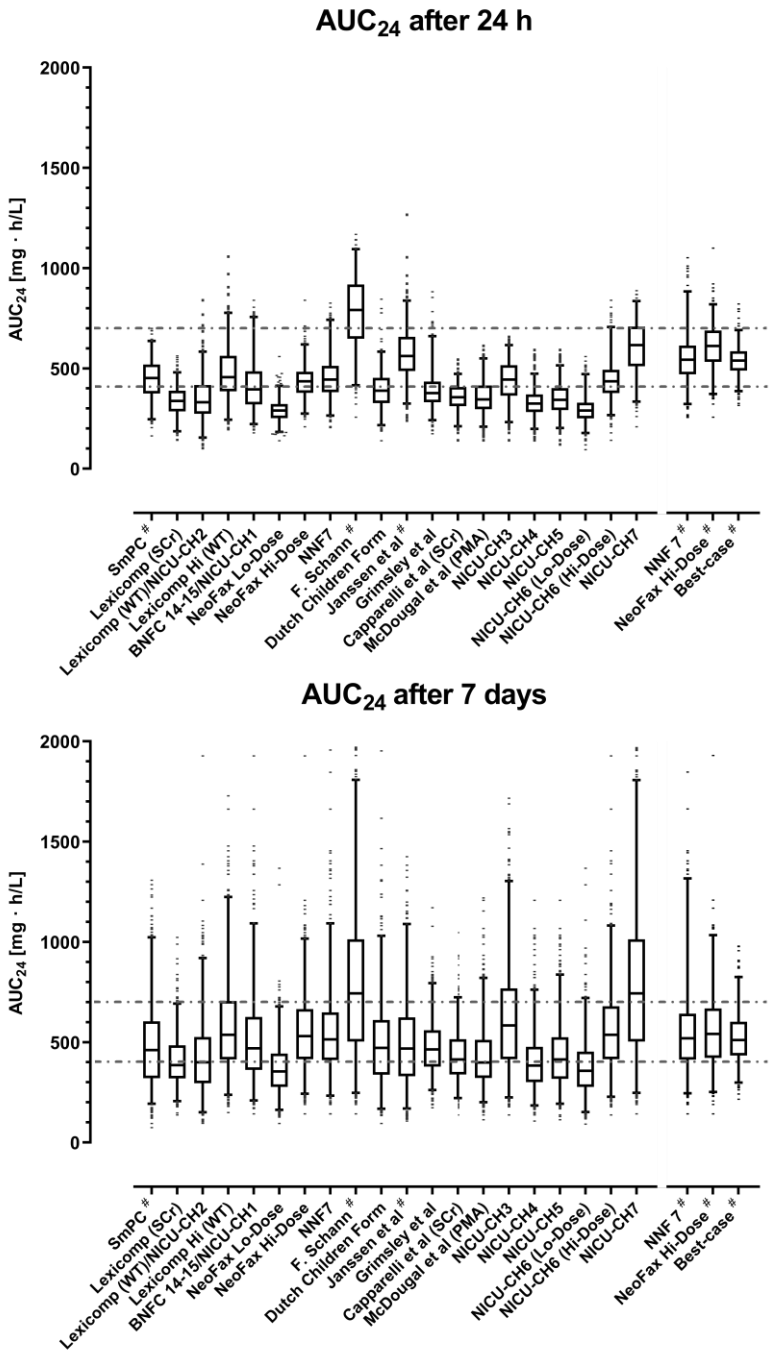
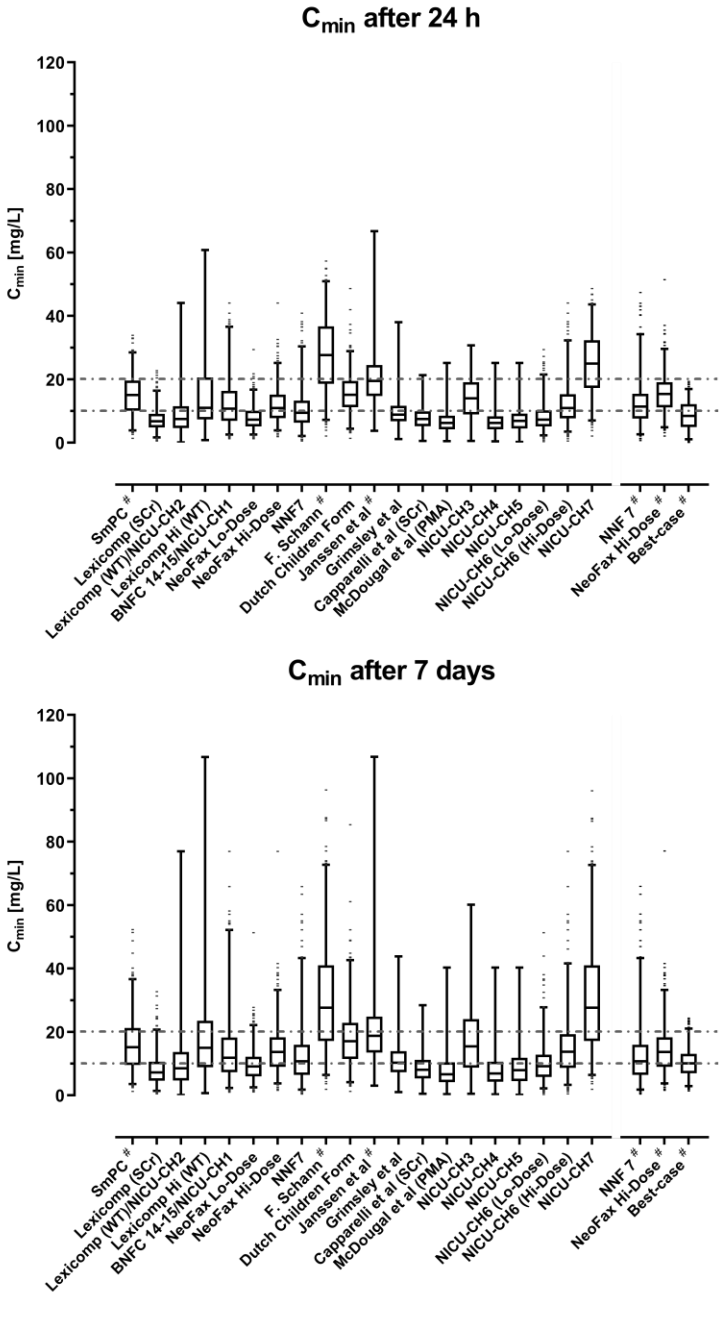


Figure 1 Prediction-corrected Visual Predictive Check of the final model with vancomycin prediction-corrected concentrations (circles) and median prediction corrected concentrations (solid line) and 95% confidence interval (semi-solid line). Grey fields represent the model-based percentile 90% confidence interval.

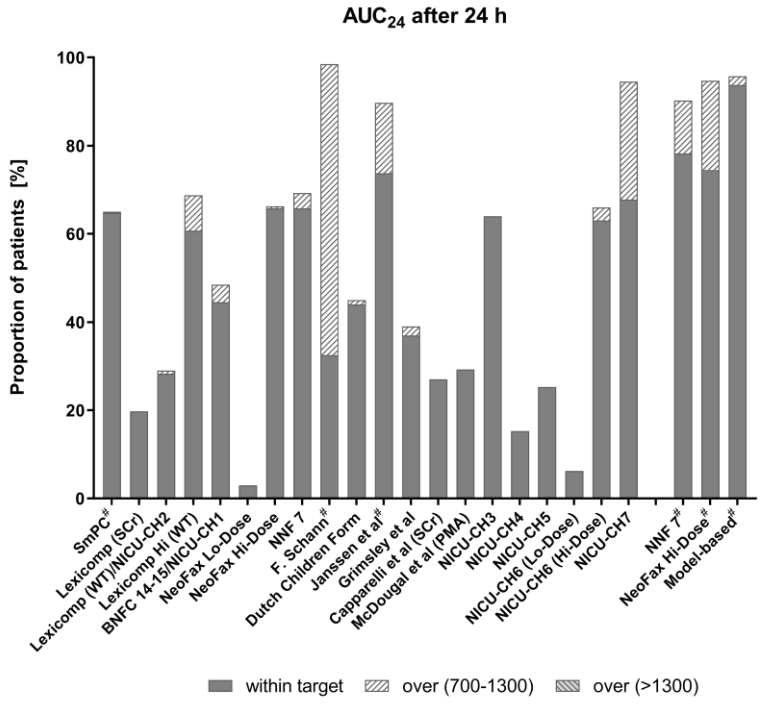

AUC24 after 24 h
AUC24 [mg · h/L]
2000
1500
1000
500
0
SmPC #
Lexicomp (SCr)
Lexicomp (WT)/NICU-CH2
Lexicomp HI (WT)
BNFC 14-15/NICU-CH1
NeoFax Lo-Dose
NeoFax Hi-Dose
NNF7
F. Schann #
Dutch Children Form
Janssen et al #
Grimsley et al
Capparelli et al (SCr)
McDougal et al (PMA)
NICU-CH3
NICU-CH4
NICU-CH5
NICU-CH6 (Lo-Dose)
NICU-CH6 (Hi-Dose)
NICU-CH7
NNF 7 #
NeoFax Hi-Dose #
Best-case #
AUC24 after 7 days
AUC24 [mg · h/L]
2000
1500
1000
500
0
SmPC #
Lexicomp (SCr)
Lexicomp (WT)/NICU-CH2
Lexicomp HI (WT)
BNFC 14-15/NICU-CH1
NeoFax Lo-Dose
NeoFax Hi-Dose
NNF7
F. Schann #
Dutch Children Form
Janssen et al #
Grimsley et al
Capparelli et al (SCr)
McDougal et al (PMA)
NICU-CH3
NICU-CH4
NICU-CH5
NICU-CH6 (Lo-Dose)
NICU-CH6 (Hi-Dose)
NICU-CH7
NNF 7 #
NeoFax Hi-Dose #
Best-case #

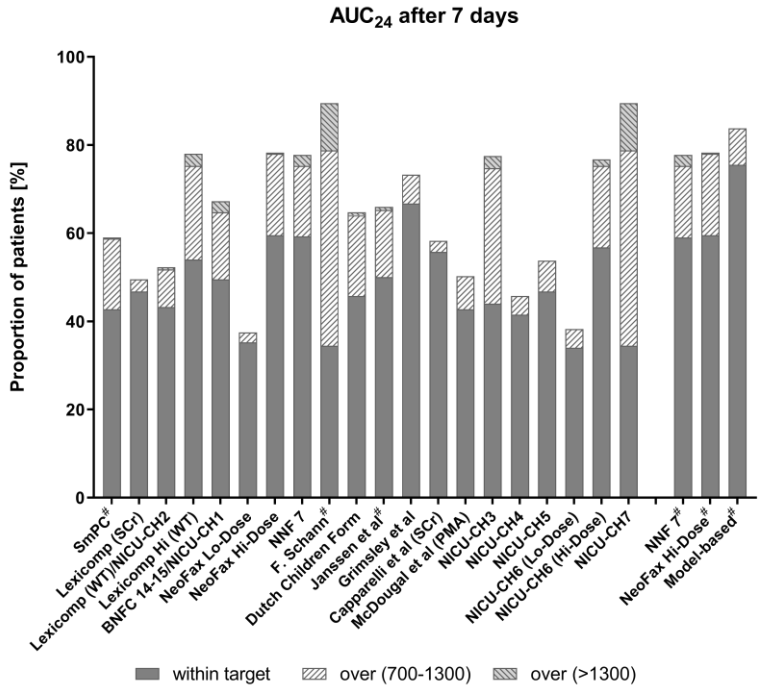
(a)



(b)

Figure 2: Results of simulated dosing regimens according to the AUC_{24} (a) and C_{min} (b): the semi-solid lines represent the lower and upper boundary of the therapeutic AUC_{24} target of 400 – 700 mg · h/L (a) or C_{min} target of 10 – 20 mg/L (b). Boxes represent the median and interquartile range of AUC_{24} or C_{min} for vancomycin according to the regimen after 24 hours of treatment (top) and at steady-state (bottom). Whiskers represent the 2.5 and 97.5 percentiles. Detailed dosing regimens are available in Table1. Regimens with a loading dose are tagged with #. On the right of each figure is represented results from simulations of NNF 7 and Neofax Hi-Dose regimens with a 25 mg/kg loading dose and the best-case scenario


AUC24 after 24 h
Proportion of patients [%]
100
80
60
40
20
0
SmPC#
Lexicomp (SCr)
Lexicomp (WT)/NICU-CH2
Lexicomp Hi (WT)
BNFC 14-15/NICU-CH1
NeoFax Lo-Dose
NeoFax Hi-Dose
NNF 7
F. Schann #
Dutch Children Form
Janssen et al#
Grimsley et al
Capparelli et al (SCr)
McDougal et al (PMA)
NICU-CH3
NICU-CH4
NICU-CH5
NICU-CH6 (Lo-Dose)
NICU-CH6 (Hi-Dose)
NICU-CH7
NNF 7#
NeoFax Hi-Dose #
Model-based#
within target
over (700-1300)
over (>1300)


AUC24 after 7 days
Proportion of patients [%]
100
80
60
40
20
0
SmPC#
Lexicomp (SCr)
Lexicomp (WT)/NICU-CH2
Lexicomp Hi (WT)
BNFC 14-15/NICU-CH1
NeoFax Lo-Dose
NeoFax Hi-Dose
NNF 7
F. Schann #
Dutch Children Form
Janssen et al#
Grimsley et al
Capparelli et al (SCr)
McDougal et al (PMA)
NICU-CH3
NICU-CH4
NICU-CH5
NICU-CH6 (Lo-Dose)
NICU-CH6 (Hi-Dose)
NICU-CH7
NNF 7#
NeoFax Hi-Dose #
Model-based#
within target
over (700-1300)
over (>1300)

(a)

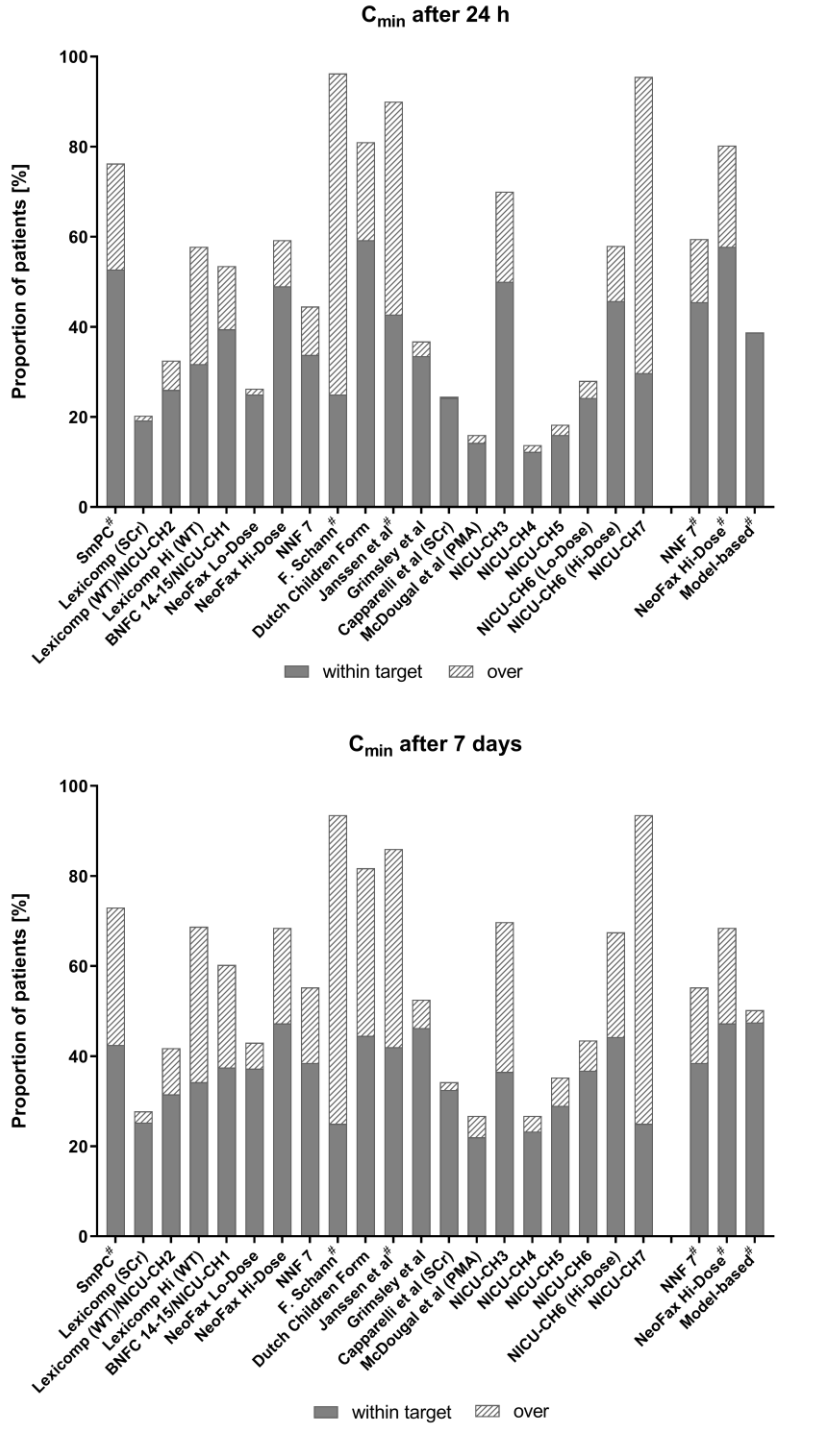


Figure 3 Proportion of patients within or over targets according to AUC_{24} (a) and C_{min} (b): The proportion of patients with a therapeutic exposure of 400 – 700 mg · h/L for AUC_{24} (a) or 10 – 20 mg/L for C_{min} (b) is represented in plain dark gray. The proportion of patients with exposure over 700 mg · h/L for AUC_{24} or 20 mg/L for C_{min} is represented with light gray stripes. Regimens with a loading dose are tagged with $^{\#}$. Detailed dosing regimens are available in Table 1.

Reference	GA (week)	PMA (week)	PNA (day)	Current weight (kg)	Creatinine	Loading dose (mg/kg)	Dose (mg/kg)	Interval (h)
SmPC [19]			< 7			15	10	12
			≥ 7			"	"	8
Lexicomp (SCr) [21]	≥ 29				< 0.7 mg/dL	-	15	12
Nelson (2015)	≥ 29				0.7-0.99	-	20	24
Redbook (2015)	≥ 29				1.0-1.29	-	15	24
	≥ 29				1.3-1.59	-	10	24
	≥ 29				≥ 1.6	-	15	48
	< 29				< 0.5	-	15	12
	< 29				0.5-0.79	-	20	24
	< 29				0.8-1.09	-	15	24
	< 29				1.1-1.39	-	10	24
	< 29				≥ 1.4	-	15	48
			> 60			-	15	8
Lexicomp (WT) [21]			≤ 7	< 1.2		-	15	24
Redbook (2009)			≤ 7	1.2-1.99		-	"	18
NICU-CH2 (Aarau)			≤ 7	≥ 2.0		-	"	12
			> 7	< 1.2		-	"	24
			> 7	1.2-1.99		-	"	12
			> 7	≥ 2.0		-	"	8
Lexicomp Hi (WT) [21]			≤ 28	< 1.2		-	15	18
Redbook (2009)			< 7	1.2-2		-	"	12
			< 7	> 2		-	"	8
			≥ 7	1.2-2		-	"	8
			≥ 7	> 2		-	"	6
British National Formulary (2014-15) [20]		< 29				-	15	24
NICU-CH1 (Bern/St-Gallen)		29 - 35				-	"	12
		> 35				-	"	8
Neofax Lo-Dose (Hi-Dose)# [13]		< 30	≤ 14			-	10 (or 15 Hi-Dose)	18
Harriet Lane 2012		< 30	> 14			-	" (or " Hi-Dose)	12
Sanford		30-36 6/7	≤ 14			-	" (or " Hi-Dose)	12
		30-36 6/7	> 14			-	" (or " Hi-Dose)	8
		37-44 6/7	≤ 7			-	" (or " Hi-Dose)	12
		37-44 6/7	> 7			-	" (or " Hi-Dose)	8
		≥ 45				-	" (or " Hi-Dose)	6
Neonatal Formulary [14] **(NNF7)**		< 30				-	20	24
		30-33 6/7				-	"	18
		34-37 6/7				-	"	12
		38-44 6/7				-	15	8
		≥ 45				-	10	6
Frank Schann [22]						25	15	8
Dutch Children Form [23]			< 7	< 2.5		-	10	12
			≥ 7	< 2.5		-	10	8
			< 7	≥ 2.5		-	8	6
			7-28	≥ 2.5		-	12	6
			≥ 28	≥ 2.5		-	15	6
Janssen *et al* [15]			0-7	≤ 0.7		16	5	8
			0-7	0.7-1.0		16	7	8

			0-7	1.0-1.5		16	9	8
			0-7	1.5-2.5		16	7.5	6
			0-7	> 2.5		16	9	6
			8-14	≤ 0.7		20	7	8
			8-14	0.7-1.0		20	9	8
			8-14	1.0-1.5		20	12	8
			8-14	1.5-2.5		20	10	6
			8-14	> 2.5		20	12	6
			14-28	≤ 0.7		23[§]	8	8
			14-28	0.7-1.0		23[§]	14	8
			14-28	1.0-1.5		23[§]	15	8
			14-28	1.5-2.5		23[§]	13	6
			14-28	> 2.5		23[§]	15	6
			> 28	< 2.5		18	8	6
			> 28	2.5-5.0		24	10	6
			> 28	5.0-10.0		27	13	6
			> 28	> 10.0		30	15	6
Grimsley *et al* [16]					< 30 µmol/L	-	20	8
					30-39	-	20	12
					40-49	-	15	12
					50-59	-	12	12
					60-79	-	15	18
					≥ 80	-	15	24
Capparelli *et al* [17]					≤ 0.6 mg/dL	-	15	12
					0.61-0.99	-	20	24
					1.0-1.29	-	15	24
					1.3-1.69	-	10	24
					≥ 1.7	-	15	48
McDougal *et al* [18]		< 27				-	18	36
		27-30 6/7				-	16	24
		31-36 6/7				-	18	18
		≥ 37				-	15	12
NICU-CH3 (Chur)						-	15	12
NICU-CH4 (Basel)		< 30				-	15	24
		30-37 6/7				-	"	18
		≥ 38				-	"	12
NICU-CH5 (Geneva)	< 27					-	15	24
	27-34 6/7					-	"	18
	35-42 6/7					-	"	12
	≥ 43					-	"	8
NICU-CH6 (Zürich / Luzern)[#]		< 30	< 15			-	10 (or 15 Hi-Dose)	18
		< 30	≥ 15			-	" (or " Hi-Dose)	12
		30-37	< 15			-	" (or " Hi-Dose)	12
		30-37	≥ 15			-	" (or " Hi-Dose)	8
		≥ 37	< 8			-	" (or " Hi-Dose)	8
		≥ 37	≥ 8			-	" (or " Hi-Dose)	12
NICU-CH7 (Lausanne)						-	15	8

[§] if PNA 21-28 days then loading dose = 26 mg/kg; [#] 2 regimens according to severity of infection (Lo-Dose / Hi-Dose)

Table 1 Evaluated dosing regimens for intermittent vancomycin: Intermittent vancomycin dosing regimens for neonates as retrieved from international guidelines [13, 14, 19-23], published dosing algorithm for neonates [15-18] retrieved from a literature review and dosing regimens used in 9 Swiss NICUs (NICU-CH 1 to 7).

	Dataset for model building			Dataset for model validation	
	Median	**IQR**	**min-max**	**Median**	**IQR; min-max**
No. of subjects	405	-	-	78	-
No. of vancomycin concentrations	1831	-	-	112	-
Median vancomycin dose per kg [mg/kg]	13.7	10.0-16.1	2.0-222.2	11.4	7.4-16.9;2.5-42.8
No. of vancomycin samples per patient	4.5	2.0-6.0	1.0-19.0	1.4	1-2;1-4
Time after dose [h]	8.8[#]	4.0-12.0	0.02-64	60	41.3-72.0;17.8-455
Gestational age [weeks]	29	26.7-34.9	24-42.1	29	27-33;25-42
Preterm (N)	331	26.4-30.7	24-36.9	68	7.0-31.4;24.6-36.1
Full term (N)	74	38.1-40.3	37-42.1	10	38.1-39.9;38-42
Birth weight [g]	1050	790-2170	462-4330	1040	883-1550;540-4810
No. of male [%]	231 (57%)	-	-	-	-
Apgar at 1 min	5	2-8	0-10	-	-
Apgar at 5 min	8	6-9	0-10	-	-
Postnatal age [days]	12.3*	5-14	0-146	14	7.0-16.8;3-27
Postmenstrual age [weeks]	32	28.3-36.5	24.6-61.0	31	29.0-34.4;26.3-43.6
Weight at drug administration [g]	1100	800-2170	462-5660	1145	868-1618;570-4900
Serum creatinine [µmol/L][§]	54	31-68	5-276	46[¶]	35.0-61.0;21.0-174
No. small for gestational age (SGA)	88 (22%)	-	-	37 (47%)	-

* 65% had a PNA ≥ 7 days; § for missing values of SCr, closest available measure was carried forward or backward within a 48 h interval before or following vancomycin concentrations measurements; [#] 785 concentrations were at peak (between 0–4 h after the end of infusion), 882 between 4h – 12h after the end of infusion, 139 between 12 – 24h and 25 after 24 hours. [¶] Enzymatic method

Table 2: Population demographics of the dataset used for model building and simulations and for model validation: median of the population is reported with interquartile range (IQR) and minimum and maximal values. Postmenstrual age equals gestational age plus postnatal age. Three missing values of SCr values.

	Structural model		Final model			
Parameter	**Estimate**	**RSE(%)**	**Estimate**	**RSE(%)**	**BSV(%)**	**RSE(%)**
CL (L/h)	0.0517	3	0.273	17	22.6	8
V (L)	0.631	2	0.628	2	-	-
θ_{WT}	1.4	4	0.438	18	-	-
T50	-	-	46.4	-	-	-
Hill	-	-	3.54	14	-	-
θ_{SCr}	-	-	0.473	15	-	-
σ_{prop} (CV%)	0.28	7	0.236	6	-	-
σ_{add} (CV%)	2.35	13	1.98	12	-	-

CL: clearance, V: volume of distribution of a patient of 1.0 kg, the rounded median population body weight (WT_{median}), σ_{prop}: exponential residual error, σ_{add}: additive residual error, θ_{WT}: effect of body weight expressed as $(WT/WT_{median})^{\theta WT,}$ θSCr: effect of SCr expressed as $(SCr_{median}/SCr)^{\theta SCr}$; T50: value of PMA when 50% of maturation of CL has been reached and Hill: slope of sigmoid model described in the maturation function MF = $(PMA^{HILL})/(PMA^{HILL} + T50^{HILL})$,
SCr_{median} = 54 µmol/L, RSE = relative standard error of the estimate defined as SE estimate/estimate, expressed as a percentage (SE estimate directly retrieved from the NONMEM output file), BSV = between-subject variability.

Final model:

$$CL = \theta_{CL} \cdot \left(\frac{WT}{WT_{median}}\right)^{\theta WT} \cdot \left[\left(\frac{SCr_{median}}{SCr}\right)^{\theta SCr}\right] \cdot \left[\left(\frac{PMA^{Hill}}{PMA^{Hill} + T50^{Hill}}\right)\right]$$

$$V = \theta_V \cdot \left(\frac{WT}{WT_{median}}\right)^{1}$$

Which means that for a patient of 2.0 kg, PMA 34 weeks, SCr 40 µmol/L, vancomycin CL is 1.78 L/min. For instance, the influence of an increase of 1 kg on CL will be : +0.34 L/min (CL: 2.12 L/min), an increase in 1 week of PMA on CL: +0.14 L/min (CL: 1.91 L/min), an increase of 50 µmol/L of SCr on CL: -0.57 L/min (CL: 1.21 L/min).

Table 3: Parameter estimates for the structural and final pharmacokinetic model: according to the final model, for a patient of 2.0 kg, PMA 34 weeks, SCr 40 µmol/L, vancomycin CL is 1.78 L/min. For instance, the influence of an increase of 1 kg on CL will be : +0.34 L/min (CL: 2.12 L/min), an increase in 1 week of PMA on CL: +0.14 L/min (CL: 1.91 L/min), an increase of 50 µmol/L of SCr on CL: -0.57 L/min (CL: 1.21 L/min).

SUPPLEMENTAL MATERIAL

Methods

A population PK analysis was performed using non-linear mixed effect modelling (NONMEM® version 7.3, ICON Development Solutions, Ellicott City, MD, USA), using a first order conditional estimation with interaction. One- and two-compartment models with linear elimination were compared. Interpatient variability was assigned on CL and V and the residual intraindividual variability was estimated using a combined additive and proportional error model. The selection of models was based on the difference of objective function value (OFV) and visual goodness-of-fit graphics. Considering an approximated chi-square distribution of the OFV, a statistical difference of OFV > 10.83 points ($p < 0.001$) was considered significant.

The influence of continuous variables were tested using linear, exponential or power functions. The allometric exponent describing the influence of WT on CL was estimated, whereas the power function describing WT on V was fixed to 1. A maturation function with a sigmoid maximum effect was used to describe CL according to PMA. [11] Dichotomous covariates were tested using an indicator variable for the absence or presence of the variable.
The stability of the final model was assessed by means of the bootstrap method implemented in Perl speak to NONMEM (PsN, version 4.8.1). [39] Median parameters values with their 95% confidence interval (CI95%) were derived from 2000 replicates of the initial dataset and compared with the original estimates. Prediction-corrected visual predictive checks (pcVPC) were also performed using PsN-Toolkit and Xpose4 (version 4.3.5, Uppsala, Sweden) [40] by simulations based on the final PK estimates using 1000 individuals to calculate median concentration-time profile and 95% prediction intervals (PI95%). The predictive performance of the pharmacokinetic model was evaluated by calculation of the normalized prediction distribution errors (NPDEs), simulating each original observation 3000 times. The NPDEs and their distributions were then computed. Accuracy and precision of the model were estimated through mean prediction error (MPE) and root mean squared error (RMSE) using log-transformed concentrations. [41] Eventually, an independent set of 78 premature and term newborns was employed for external model validation. Individual post hoc concentrations were derived from the final model to assess the accuracy and the precision by means of the mean prediction error (MPE) and the root mean squared error (RMSE), using log-transformed concentrations. [41]

Comparison of previously published population PK models

The inventory of vancomycin PK models were retrieved from Marsot A et al [6] and Wilbaux M et al. [12]. Seventeen out of the 22 neonatal PK models were excluded for the following reasons. The models were either based on only preterm populations [42-46], older children [47-49], continuous infusion [50, 51] or performed with patient under extracorporeal membrane

[52]. Model only included weight as covariate [53], or with lacking detailed PK model description [54-57] were excluded as well. Lastly, one model was excluded due to unusual model building methodology (interindividual variability added in the last step after covariate analyses) [58].

Results

Initially, 1947 vancomycin concentrations were collected from 409 patients. Of these, 116 samples and 4 patients were excluded due to inconsistencies in the reported administered dose, unclear dose schedule or dialysis. A total of 1831 vancomycin concentrations and 405 patients were finally included in the analysis, with a mean of 4.5 concentrations per patient.

Patients demographics are detailed in Table 2. Mean GA was 29 weeks, with 74 (18%) full term neonates and 331 (82%) preterms. BW and WT at drug administration were available for all patients. The mean PNA was 12.3 days (range 0-146 days), with 65% with a PNA $\geq$ 7 days. Eighty-eight patients (22%) were SGA, with a BW inferior to percentile 10 on growth charts. SCr levels available within 24 hours of vancomycin administration and measurements. Thirty-seven patients had no SCr levels available around that timeframe. For three patients, SCr levels were missing and replaced by the median SCr of the studied population. For the others, more remote SCr levels were used (range: 36 hours to 11 days). The median dose was 13.7 mg/kg administered every 6 to 48 hours. One patient who was accidently overdosed secondary to a dilution error received 222 mg/kg instead of 22 mg/kg. Regarding sampling times, 785 concentrations were measured at peak (between 0–4 h after the end of infusion), 882 between 4h – 12h after the end of infusion and 139 between 12 – 24h and 25 after 24 hours. Thirty-six patients had serum vancomycin concentration below the limit of quantification (LOQ of 3.2 mg/L), value that were replaced by half the LOQ of 1.6 mg/L. Two observations were below the limit of sensitivity of the method and replaced by 0.

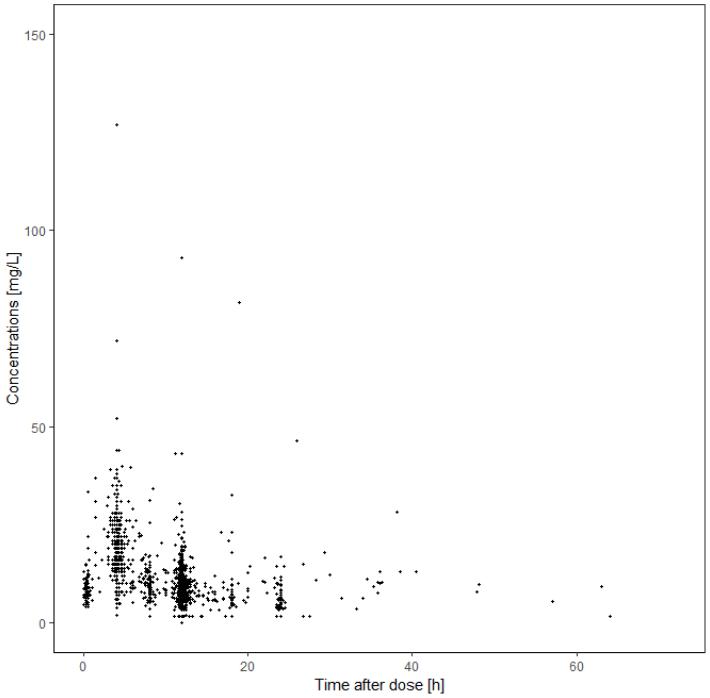


Figure 4: Vancomycin concentrations versus time after dose: raw observations for a median dose of 13.7 mg/kg (IQR: 10.0-16.1, range 2.0-222.2 mg/kg).

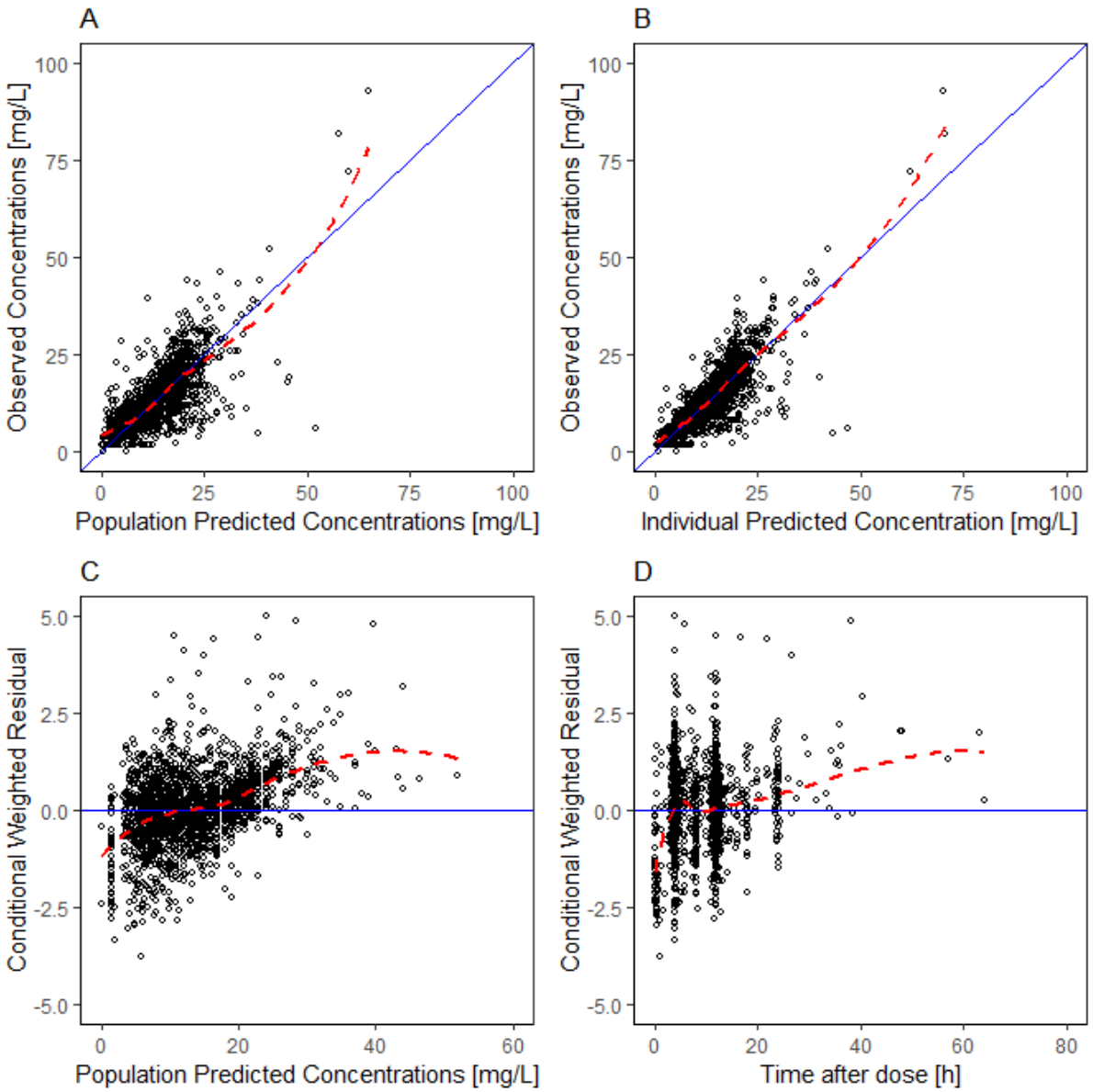
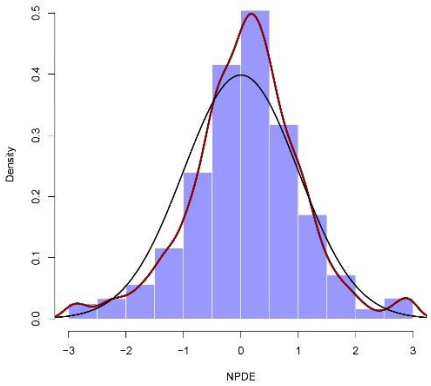
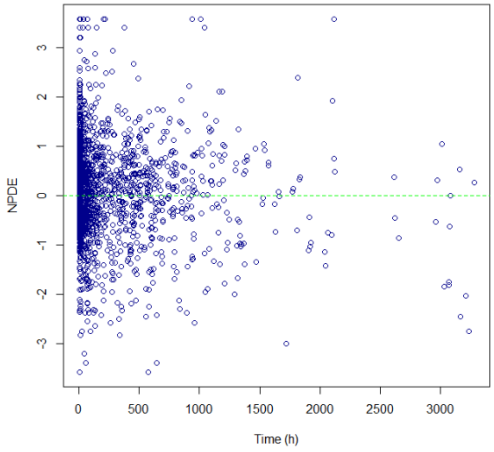


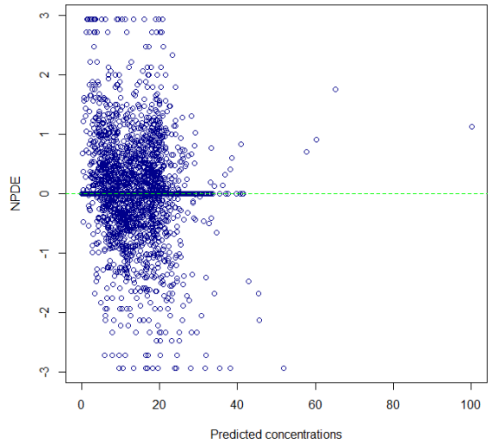
Figure 5: Goodness of fit plots of the final PK model: observed concentrations versus population predicted concentrations (A), versus individual predicted concentration (B), conditional weighted residual versus population predicted concentrations (C), versus time after dose (D). Smoothed lines are represented by dashed lines.



(a)



(b)



(c)

Figure 6: Normalized prediction error (NPDE): (a) distribution of residues, (b) NPDE versus time and (c) NPDE versus predicted concentrations.

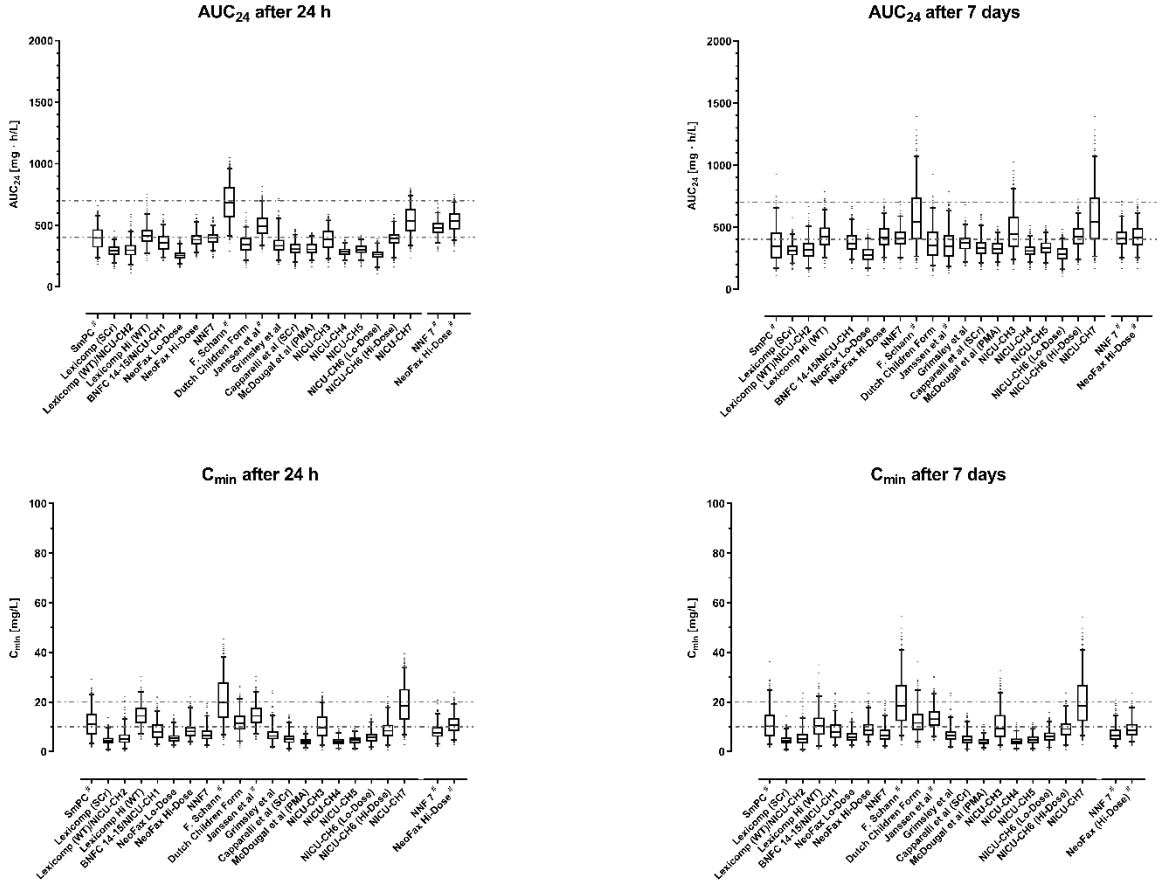


Figure 7: Results with Frymoyer *and colleagues'* model of simulated dosing regimens according to the AUC_{24} (top) and C_{min} (bottom): the semi-solid lines represent the lower and upper boundary of the therapeutic AUC_{24} target of 400 – 700 mg · h/L (top) or C_{min} target of 10 – 20 mg/L (bottom). Boxes represent the median and interquartile range of AUC_{24} or C_{min} for vancomycin according to the regimen after 24 hours of treatment (left) and at steady-state (right). Whiskers represent the 2.5 and 97.5 percentiles. Detailed dosing regimens are available in Table1. Regimens with a loading dose are tagged with #. On the right of each figure is represented results from simulations of NNF7 and Neofax Hi-Dose regimens with a 25 mg/kg loading dose.

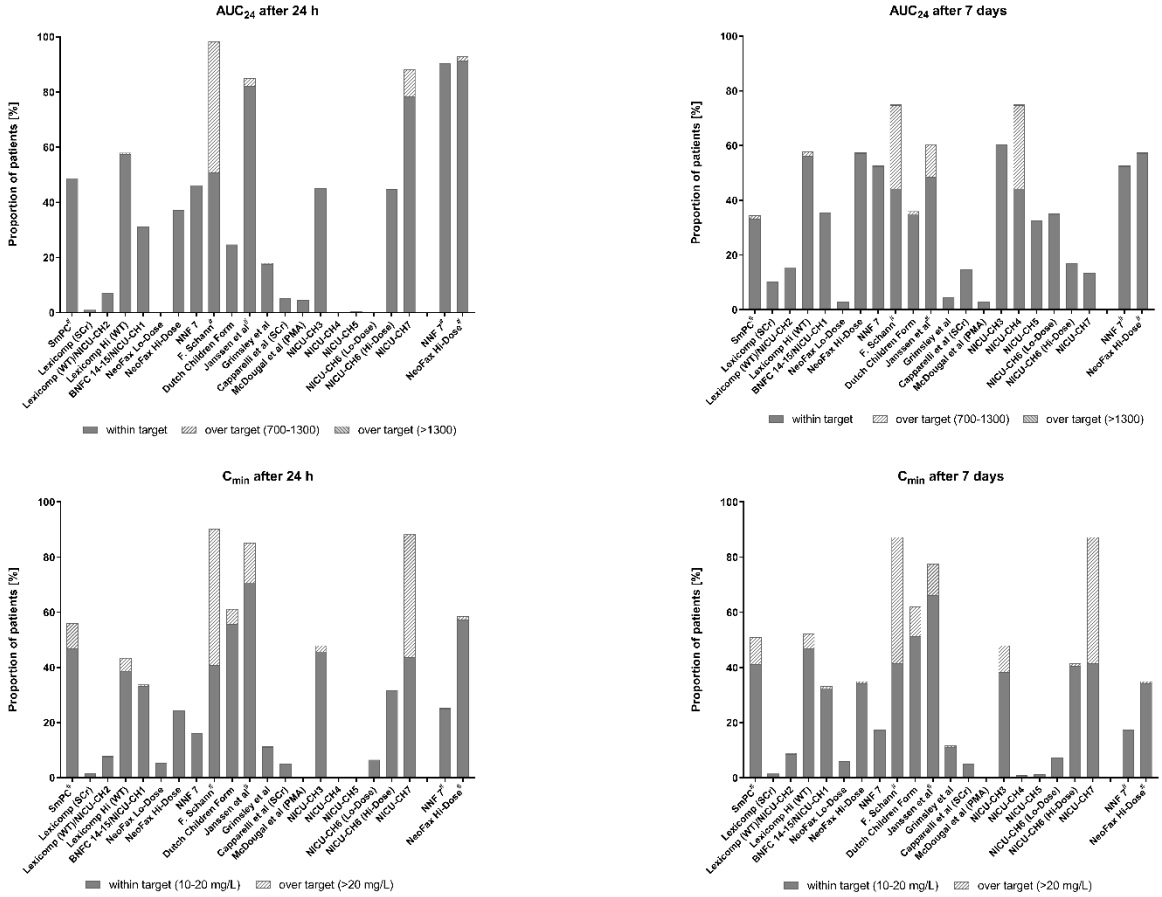


Figure 8: Proportion of patients within or over targets according to AUC_{24} (top) and C_{min} (bottom) using Frymoyer *et al* model: The proportion of patients with a therapeutic exposure of 400 – 700 mg · h/L for AUC_{24} (top) or 10 – 20 mg/L for C_{min} (bottom) is represented in plain dark gray. The proportion of patients with a potentially toxic exposure is represented with light gray stripes. Regimens with a loading dose are tagged with [#]. Detailed dosing regimens are available in Table 1.

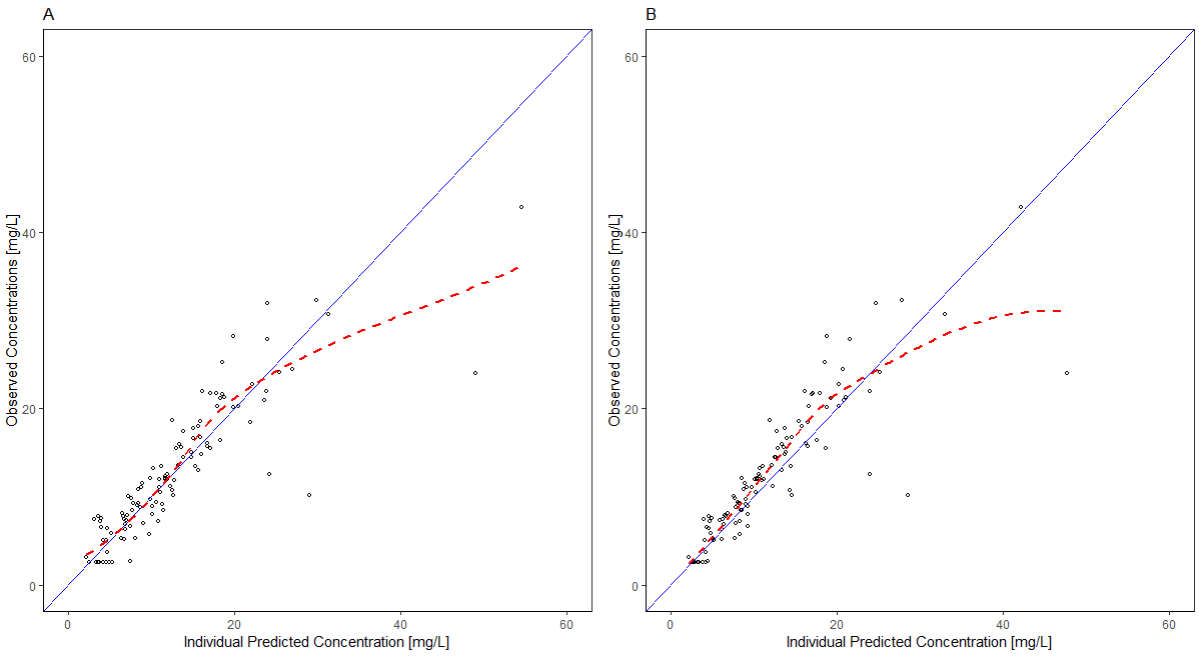


Figure 9: Observed concentrations versus individual predicted concentrations (external dataset): observed concentrations versus individual predicted concentrations using the external validation dataset for the final model (A) and Frymoyer et al model (B). Smoothed lines are represented by dashed lines.

	Population pharmacokinetics analysis				Bootstrap evaluation			
Parameter	**Estimate**	**RSE(%)**	**BSV(%)**	**RSE (%)**	**Estimate**	**$CI_{95\%}$**	**BSV(%)**	**$CI_{95\%}$**
CL (L/h)	0.273	17	22.6	8	0.271	(0.20;0.38)	22.2	(18.7;26.0)
V (L)	0.628	2	-	-	0.628	(0.61-0.65)	-	-
θ_{WT}	0.438	18	-	-	0.442	(0.28-0.58)	-	-
T50	46.4	-	-	-	46.4	-	-	-
Hill	3.54	14	-	-	3.52	(2.58;4.44)	-	-
θ_{SCr}	0.473	15	-	-	0.47	(0.34;0.61)	-	-
σ_{prop} (CV%)	0.236	6	-	-	0.23	(0.21;0.26)	-	-
σ_{add} (CV%)	1.98	12	-	-	1.97	(1.38;2.39)	-	-

Abbreviations: CL: clearance, V: volume of distribution of a patient of 1.0 kg, the rounded mean population body weight (WTmedian), σ_{prop}: exponential residual error, σ_{add}: additive residual error, θ_{WT}: effect of body weight expressed as $(WT/WTmedian)^{\theta WT}$; θSCr: effect of SCr expressed as $(SCr_{median}/SCr)^{\theta SCr}$; T50: value of PMA when 50% of maturation of CL has been reached and Hill: slope of sigmoid model described in the maturation function $MF = (PMA^{HILL})/(PMA^{HILL} + T50^{HILL})$, SCr_{median} = 45 µmol/L, RSE: Relative standard error of the estimate defined as SE estimate/estimate, expressed as a percentage, with SE estimate retrieved directly from the NONMEM output file. BSV: Between-subject variability. CI95%: 95% confidence interval.

Final model: $TVCL = \theta_{CL} \cdot \left(\frac{WT}{WT_{median}}\right)^{\theta_{WT}} \cdot \left[\left(\frac{SCr_{median}}{SCr}\right)^{\theta_{SCr}}\right] \cdot \left[\left(\frac{PMA^{Hill}}{PMA^{Hill} + T50^{Hill}}\right)\right]$ $TVV = \theta_{V} \cdot \left(\frac{WT}{WT_{median}}\right)^{1}$

Due to a significant correlation between CL and T50, the value of T50 obtained in the univariate analysis was used in the multivariate model and fixed. This value corresponds to the T50 found in the literature for a full term infant (T50 reached at a PMA range of 47.7–55.4 weeks). (29)

Table 4: Parameter estimates for the final pharmacokinetic model and bootstrap evaluation

	Grimsley (n=59)		Mehrorta (n=134)		Capparelli (n=374)		Frymoyer (n=249)		Kimura (n=19)		Our model (n=405)	
Postnatal age (weeks)	4.1		3.8		3.9		2.7		-		2.4	
Gestational age (weeks)	29		32.7		33.5		34		24.1-41.3		29 (24 - 42)	
Postmenstrual age (weeks)	-		36.5		-		39		27.1-50.4		32 (24 - 65)	
Birth weight (kg)	-		-		-		2		-		1.05	
Weight (kg)	1.52		2.5		2		2.9		0.71-5.2		1.1	
Median SCr	49 (µmol/L)		0.6 (mg/dL)		0.7 (mg/dL)		35.4 (µmol/L)		0.2-0.9 (mg/dL)		54 (µmol/L)	
Covariates on CL	WT	SCr (µmol/L)	WT, PMA	SCr (mg/dL)	WT	SCr (mg/dL)	WT, PMA	Scr (mg/dL)	WT	SCr (mg/dL)	WT, PMA	SCr (µmol/L)
Covariates on V	WT											
Model for CL	$\theta1 \cdot WT / SCr$		$CL = \theta1 \cdot (WT/2.5)^{0.75} \cdot (0.42/SCr)^{\theta2} \cdot (PMA/37)^{\theta3}$		$CL = WT \cdot (\theta1/SCr + \theta2 \cdot PNA \cdot [\text{if SCr} < 0.7] + \theta3 \cdot [\text{if GA} > 28])$		$CL = \theta1 \cdot (WT/2.9)^{0.75} \cdot MF \cdot (1/SCr)^{\theta2}$ $MF = 1/(1+[PMA/T50]^{-Hill})$		PMA ≥ 36 : $CL = \theta1 \cdot WT / SCr$ PMA < 36 : $CL = \theta2 \cdot WT / SCr$		$CL = \theta1 \cdot (WT/1000)^{\theta2} \cdot (SCr/60)^{\theta3} \cdot MF$ $MF = PMA^{Hill} / (PMA^{Hill} + T50^{Hill})$	
Model for V	$\theta2 \cdot WT$		$V = \theta4 \cdot WT / 2.5$		$V1 = \theta4 \cdot WT + \theta5$		$V = \theta3 \cdot (WT/2.9)$		$V = \theta3 \cdot WT$		$V = \theta4 \cdot WT$	
Model for Q					$Q = \theta6 * WT$							
Model for V2					$V2 = \theta7 * V1$							
Final PK parameters	$\theta1 = 3.56$ $\theta2 = 0.669$		$\theta1 = 0.18$ $\theta2 = 0.7$ $\theta3 = 1.4$ $\theta4 = 1.7$		$\theta1 = 0.028$ $\theta2 = 0.000127$ $\theta3 = 0.0123$ $\theta4 = 0.793$ $\theta5 = 0.01$ $\theta6 = 0.0334$ $\theta7 = 0.666$		$\theta1 = 0.345$ $\theta2 = 0.267$ $\theta3 = 1.75$ Hill = 4.53 T50 = 34.8		$\theta1 = 0.0344$ $\theta2 = 0.025$ $\theta3 = 0.61$		$\theta1 = 0.268$ $\theta2 = 0.438$ $\theta3 = 0.483$ $\theta4 = 0.629$ Hill = 3.57 T50 = 46	
Residual error (type & value)	add: 4.53		add: 5		prop: 14%, add : 3,4		prop: 20.5%, add: 1.3		add: 3.38		prop: 22.8%, add: 2.2	
IIV CL, V values (%)	22	18	25.3	21.8	32	16	21.6	10.9	25.8	22.3	22.6	-
External validation	-		-		Validation group (n = 67)		Validation group (n=243)		-		-	
Mean prediction error (MPE)	-0.29 (IC95%:-0.20;-0.38)		0.01 (IC95%: -0.03; 0.04)		-0.10 (IC95%: -0.04;-0.17)		-0.05 (IC95%: -0.10;-0.01)		0.06 (IC95%: 0.00;0.13)		0.01 (IC95%: -0.05;0.07)	
Root mean squared error (precision)	0.563 (76%)		0.178 (19%)		0.369 (45%)		0.257 (29%)		0.339 (40%)		0.315 (37%)	

Table 5. Comparison of previously comparable published models

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