Population pharmacokinetic meta-analysis of individual data to design the first randomized efficacy trial of vancomycin in neonates and young Infants

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Running title : Population pharmacokinetic meta-analysis of vancomycin in neonates

Abstract

Objectives

In the absence of consensus, the present meta-analysis was performed to determine an optimal dosing regimen of vancomycin for neonates.

Methods

A “meta-model” using NONMEM with 4894 concentrations from 1631 neonates was built and Monte Carlo simulations were performed to design an optimal intermittent infusion, aiming at reaching a target AUC_{0-24} of 400 mg*h/L at steady state in at least 80% of neonates.

Results

A two-compartment model best fitted the data. Current weight, post-menstrual age (PMA) and serum creatinine were the significant covariates for clearance (CL). After model validation, simulations showed that a loading dose (25 mg/kg) and a maintenance dose (15 mg/kg twice daily if < 35 weeks PMA and 15 mg/kg three times daily if ≥ 35 weeks PMA) achieved the AUC_{0-24} target earlier than a standard “Blue Book” dosage regimen in more than 89% of the treated patients.

Conclusions

The results of a population meta-analysis of vancomycin data have been used to develop a new dosing regimen for neonatal use and assist in the design of the model-based, multinational European trial, NeoVanc.

102 **Introduction**

103 Vancomycin is one of the most widely used antibiotics in the world for the treatment of
104 serious Gram-positive infections. It is a high molecular weight complex glycopeptide
105 which inhibits the cell wall synthesis of Gram-positive bacteria by the formation of stable
106 complex murein pentapeptides, thereby causing inhibition of further peptidoglycan
107 formation. It became the treatment of choice for staphylococcal infections, when
108 staphylococcal strains developed resistance to treatment with penicillin. It was then
109 replaced by methicillin in the 1960s, but when the incidence of late onset neonatal sepsis
110 increased due to coagulase negative and methicillin-resistant staphylococci, the use of
111 vancomycin re-emerged and it is today the treatment of choice for many staphylococcal
112 infections.[1,2]

113 According to recent surveys,[3-7] neonatal dosage recommendations for vancomycin are
114 highly variable, and include a range of single or multiple clinical factors, such as
115 gestational age (GA), post-natal age (PNA), postmenstrual age (PMA), weight and
116 creatinine clearance. Even internationally recognised dosing guidelines gave different
117 dosing recommendations, either as continuous (CVA) or intermittent intravenous (IVA)
118 vancomycin administration. However, although vancomycin is one of the most studied
119 antibiotics in neonates,[2,8-10] population pharmacokinetic (popPK) and pharmacokinetic–
120 pharmacodynamic (popPKPD) approaches have had limited success in leading to a clear
121 consensus on the optimal dosing regimen to use in routine clinical practice. This is partly
122 because the models and results are dependent on study / centre-related factors, including
123 differences in the covariates that were incorporated in the final analysis. The present
124 study aimed to conduct a meta-analysis of published individual pharmacokinetic data and
125 to build a popPKPD model that would take into account all available variables, as part of
126 the programme of work to plan the NeoVanc trial.[11]

127

128

129 **Methods**

130 **Identification of individual patient data**

131 Published PK or PK/PD studies were identified through databases (PubMed, Embase)
132 in 2014, according to the following screening criteria (PK study, vancomycin, neonates
133 and infants,114 single and multicentre studies, all countries. The investigator
134 responsible for the publication was contacted, invited to participate in the present study
135 and provided individual vancomycin dose and concentration data and associated
136 covariates. Additional, non-published, routine Therapeutic Drug Monitoring (TDM) data
137 from our center (hospital Robert Debré – Paris – France) were also used. All data were
138 anonymised before transfer with a pre-defined data sharing agreement, according to
139 Good Clinical and Laboratory Practices.

140

141 **Requested covariates and individual information**

142 The following dataset of mandatory variables was collected to ensure that individual
143 patient data could be included in the pooled model.

144 *Vancomycin administration information*: dosing history for each infant (time of start of
145 infusion, time of end of infusion and doses), continuous or intermittent infusion,
146 vancomycin concentrations and exact sampling day and time.

147 *Demographic covariates:* gestational age, postnatal age, birth weight, current weight (at
148 sampling), gender.

149 *Information on co-medications* was not collected and not analysed as it was available in
150 only a limited number of neonates.

151 *Biological covariates:* serum creatinine concentrations

152 *Study-related covariates:* analytical method used to quantify vancomycin (FPIA EMIT,
153 PENTINIA or CMIA CLIA), creatinine assay method (Jaffé or enzymatic) and
154 corresponding units.

155 **Data analysis**

156 PK data were made available on a standard Microsoft Office Excel spreadsheet (CIC,
157 1426, Hôpital Robert Debré) and formatted for subsequent modelling using NONMEM V
158 7.2 (Icon Development Solutions, USA).

159 A first order conditional estimation (FOCE) method with interaction was used to estimate
160 PK parameters and their variability. One and two compartment models with first order
161 elimination were tested to estimate clearance (CL), central volume of distribution (V1),
162 peripheral volume of distribution (V2) and intercompartmental clearance (Q) using the
163 appropriate ADVAN subroutines. Inter-individual variability of the pharmacokinetic
164 parameters was best described with an exponential model and was expressed as $\theta_i =$
165 $\theta_{mean} * e^{\eta_i}$, where θ_i represents the parameter value of the ith subject, θ_{mean} the typical value
166 of the parameter in the population and η_i the variability between subjects, which is
167 assumed to follow a normal distribution with a mean of zero and variance ω^2.

168 Covariate analysis followed a forward and backward selection process. The likelihood
169 ratio test was used to test the effect of each variable on model parameters. The effects
170 of current weight, gestational age, postnatal age, postmenstrual age, serum creatinine
171 concentration, analytical methods of vancomycin and creatinine, and ethnicity were
172 investigated as potential covariates affecting PK parameters. During the first step of
173 covariate model building, a covariate was included if a significant ($p<0.05$, $\chi 2$ distribution
174 with one degree of freedom) decrease (reduction>3.84) in the objective function value
175 (OFV) from the basic model was obtained. All the significant covariates were then added
176 simultaneously into a 'full' model. Subsequently, each covariate was independently

177 removed from the full model. If the increase in the OFV was higher than 6.635 ($p<0.01$,
178 χ^2 distribution), the covariate was retained in the final model.
179 Model validation was based on graphical and statistical criteria. Goodness-of-fit plots,
180 including observed (DV) *versus* population prediction (PRED); DV *versus* individual
181 prediction (IPRED); conditional weighted residuals (CWRES) *versus* time and CWRES
182 versus PRED were initially used for diagnostic purposes. The stability and performance
183 of the final model was also assessed by means of a nonparametric bootstrap with re-
184 sampling and replacement. Re-sampling was repeated 200 times and the values of
185 estimated parameters from the bootstrap procedure were compared with those estimated
186 from the original data set. The entire procedure was performed in an automated fashion,
187 using Perl-speaks-Nonmem (PsN v2.30). The final model was also evaluated graphically
188 and statistically by normalised prediction distribution errors (NPDE). One thousand
189 datasets were simulated using the final population model parameters. NPDE results were
190 summarized graphically by default as provided by the NPDE R package (v1.2): (i) QQ-
191 plot of the NPDE; (ii) histogram of the NPDE. The NPDE is expected to follow the N (0,
192 1) distribution.[12]
193 Monte Carlo simulations for dosage optimisation were performed to evaluate different
194 weight adjusted (mg/kg) dosing regimens for three predefined neonatal groups:
195 postmenstrual age (PMA) <29, 29-35 and >35 weeks. Drug exposure was simulated 100
196 times for each set of patients including only the Caucasian patients. Area under the curve
197 between 0 and 24h on the first treatment day (AUC_{0-24h}) and AUC_{24h} at steady state
198 (AUC_{SS-24h}) were calculated for each simulated patient. The parameter estimates obtained
199 from the final model were used to estimate the target attainment rate for an AUC_{24h} of
200 ≥400 mg*h/L with the standard dosage regimen recommended in the "Blue Book" [13] and
201 to define the optimal dosing regimen able to attain this target in 80% of patients. The

current dosage recommendations and a loading dose followed by a maintenance dose administered as an intermittent infusion were evaluated in the 3 PMA groups.

Results

Study population.

A total of 1631 neonates and infants from 15 studies were included (Table 1). Their PMA and current weight (CW), expressed as mean (standard deviation) were 33.3 (5.7) weeks and 1785 (1127) grams, respectively. Overview of the individual PK trials is presented in Table 2. We refer to the original studies for additional factual information.[14-26]

Population PK analysis

Model building

A total of 4894 concentrations from 1631 patients were included in the population analysis. A two-compartment model with first-order elimination best fitted the data; both the OFV and the residual variability were lower than with a one-compartment model.

Covariate analysis

Allowing separate estimates for each analytical method in the residual variability caused a significant drop in the OFV of 113.5 units. Body weight was the most important clinical covariate following a systematic covariate analysis, associated with a drop in the OFV of 3367.1 units after incorporating it into the basic model using estimated allometric coefficients for CL, V_1 and V_2. A further decrease in the OFV of 244.5 units was achieved by including PMA on CL and serum creatinine concentrations gave a further reduction (ΔOFV 1087.9 units). The model was further improved (ΔOFV 65.5 units) by introducing a conversion factor between the Jaffé and enzymatic assay methods for creatinine.

226 Ethnicity (Malaysian patients) was identified as a sixth covariate (ΔOFV 302.1 units) on
227 CL. The final model had the following structure:

228 $$CL = 0.0680 \times (CW/1350)^{0.863} \times RM \times RF \times F_{Jaffé\text{-}Enzymatic} \times F_{race}$$

229 where CW is current weight, RM reflects renal maturation and RF reflects renal function.
230 The population PK parameters of the final model are presented in Table 3.

231 *Model evaluation*

232 Model diagnostics showed acceptable goodness-of-fit for the final model. Predictions
233 were unbiased and no trends were observed in the diagnostic plots of CWRES versus
234 time. The NPDE distribution and histogram were consistent with the theoretical N (0, 1)
235 distribution and density, indicating a good fit of the model to the individual data (Figure
236 1). The mean and variance of the NPDEs were 0.09 and 0.98, respectively. Visual
237 predictive checks (VPCs) of the final model for all neonates and in subgroups of neonates
238 <29 weeks (L), 29-35 weeks (M) and >35 weeks (H) are shown in Fig. 2 (A and B). The
239 plots confirm that the average predicted concentrations matched the observed
240 concentrations and that the variability was well estimated in the 3 subgroups.

241 In addition, the median PK parameter estimates resulting from the bootstrap procedure
242 closely agreed with the respective values from the final population model, indicating that
243 the final model was stable (Table 3).

244 ***Dosing optimisation.***

245 Dosing optimisation was conducted in the Caucasian population. Monte Carlo simulations
246 were performed to evaluate different mg/kg dosing regimens for the three neonatal
247 groups.

248 With the standard vancomycin dosing regimen at steady-state, the percentage of
249 neonates reaching the target $AUC_{ss0\text{-}24}$ of ≥400 mg*h/ was 74.0% and the percentage
250 exposed to an $AUC_{ss0\text{-}24}$ above 700 mg*h/L was 23.0% when considering all age groups.

251 When considering only neonates <29 weeks PMA, the corresponding values fell to 27.7%
252 and 1.1% respectively (Table 4).
253 With a loading dose of 25 mg/kg followed by the optimal maintenance dose of 15 mg/kg,
254 either 'q12h' if ≤35 weeks PMA or 'q8h' if >35 weeks PMA, the percentage of neonates
255 reaching the target AUC_{ss0-24} of 400 mg*h/L was 89.3% while the percentage exposed to
256 an AUC_{ss24h} over 700 mg*h/L was 33.3% when considering all age groups. When
257 considering only neonates <29 weeks PMA, the corresponding values increased to 95.0%
258 and 45.5% respectively (Table 5). The target attainment rate on the first day of treatment
259 increased from 42.6% with the standard regimen to 88.9% with the loading dose strategy.
260

261 **Discussion**

262 To the best of our knowledge, this is the largest meta-analysis that has assessed the
263 population PK of vancomycin in neonates and young infants aged less than 3 months.
264 The analysis has combined vancomycin concentrations linked to key demographic and
265 biological covariates from 15 pharmacokinetic studies conducted in 7 different countries.
266 Monte-Carlo simulations showed that the current dosage regimen was not suitable for the
267 treatment of staphylococcal infection and that the optimal vancomycin dosing regimen
268 should include a loading dose of 25 mg/kg for all neonates, irrespective of their PMA,
269 followed by a maintenance dose adapted to their PMA.
270 Although widely used for many years, important questions remain on how to optimise
271 vancomycin dosing in neonates.[2,8,9] In the absence of prospective evaluation, most
272 neonatal units have developed local dosing recommendations, resulting in variable
273 exposures that may lead to poor efficacy, induction of resistance or toxicity[3]
274 Consequently, vancomycin dosage regimens adapted to neonates require harmonisation,
275 taking into account the impact of developmental pharmacology on disposition and PK

276 parameters from very preterm neonates through term neonates to older children.[27] This
277 issue is central and initiatives from both the FDA and EMA are currently being undertaken
278 to revise vancomycin dosing.[28,29]
279 Drug pharmacokinetics and dynamics need to be linked to explicative individual
280 characteristics either constitutional (age, weight, genetics, etc.) or environmental
281 (pathology, drug interactions, etc.). In this context, population modelling allows
282 assessment and quantification of sources of variability in drug exposure and response in
283 the target population, even under sparse sampling conditions [30-32] The present study has
284 confirmed the impact of serum creatinine and vancomycin assay methods as predictors
285 of vancomycin concentrations in neonates.[33,34] Additional covariates, such as
286 ventilation,[35] co-administered drugs (e.g. aminoglycosides or ibuprofen), ECMO,[37] whole
287 body cooling,[38] as well as centre or country dependent effects linked to ethnic,
288 environmental and nutritional differences, were not explored in the current study, as they
289 were not available in all data sets. However, it is recognised that they may also contribute
290 to PK variability in neonates.
291 Model-based approaches to characterise drug PK/PD have been recommended as
292 powerful tools for overcoming the practical and ethical challenges associated with dose
293 selection for neonatal indications.[39,40] For vancomycin, a model tailored dose had already
294 been demonstrated to increase substantially the target attainment rate of vancomycin in
295 treated neonates.[10] However, there were few neonates less than 29 weeks gestational
296 age in that study and centre-effects could not be eliminated. These limitations were
297 addressed in the present PK meta-analysis, which was conducted by pooling 4894
298 vancomycin concentrations from 1631 neonates. Although robust parameter estimates
299 were obtained with this strategy, different strategies may be necessary when data are
300 heterogenous.[41]

301 For vancomycin, exposure, measured by AUC_{0-24}, is the PK/PD parameter influencing
302 efficacy and emergence of resistance,[42-44] but also influencing toxicity. Nephrotoxicity is
303 a multifactorial, well-identified risk of high vancomycin exposure and high trough
304 concentrations.[45] AUC_{0-24} or corresponding trough levels can vary widely and
305 independently, since the trough depends on both the daily dose and the frequency of
306 administration, whereas AUC_{0-24} only depends on the daily dose. Consequently, in the
307 present study, simulations were performed to evaluate the current dosage regimen[13] and
308 to optimize efficacy by determining the target attainment rate and exposure to vancomycin
309 measured by the AUC_{0-24h}. A target AUC_{0-24h} of at least 400 mg*h/L was selected as an
310 AUC_{0-24}/MIC ratio of 400 has been associated with favourable treatment outcomes in
311 adults, assuming that bacterial strains have a vancomycin MIC ≤1 mg/L.[43,46] Simulations
312 of the current dosage recommendation (see table 5) were performed after the first dose
313 and at steady-state. Our results showed that the current daily dose was too low for all
314 neonatal age groups but particularly for neonates <29 weeks, as less than 30% of
315 neonates reached the steady-state target. As a loading dose strategy is recommended in
316 adult settings in order to reduce the time needed to reach the target AUC_{0-24} [47,48]
317 simulations were then performed with a loading dose and optimal maintenance doses in
318 all age groups, based on weight and PMA. Increasing the maintenance dose to 15 mg/kg
319 'q12h' instead of 'q24h' was also tested in the group <29 PMA weeks to optimise dosage.
320 These modifications led to an increase in the target attainment rate after the first dose
321 and at steady-state in all age groups.
322 Nephrotoxicity is a recognized side-effect of vancomycin treatment, although its safety
323 profile is considered favorable. The risk of nephrotoxicity primarily increases with high
324 vancomycin exposure and duration of administration.[45,49] In studies in adults and
325 children,[45] reported incidence varied widely, from 5% to 43%, occurrence increased with

326 longer durations of administration with a range of 4.3 to 17 days and nephrotoxicity was
327 reversible in the majority of cases. In neonates, most studies were not sufficiently
328 powered to detect nephrotoxicity and, when reported, renal impairment was frequently
329 associated with concomitant administration of nephrotoxic drugs.[50]
330 Therefore, optimising exposure while reducing duration of administration would maximise
331 clinical efficacy while minimising toxicity and selection of resistance.
332 The upper AUC_{24h} limit remains a matter of debate. "Usual" AUC_{24h} values of 700 or 800
333 mg*h/L have been used in both adults [46,51,52] and children,[48] however, more extreme
334 values have also been reported, with breakpoints for nephrotoxicity of <600 or >1300
335 mg*h/L.[51,53] In the absence of specific neonatal data, a value of 700 mg*h/L was used in
336 the present study. With our simulated dosage regimen, 89% of neonates reached the
337 predetermined $AUC_{ss\text{-}24h}$ target and 21.0% had an $AUC_{ss\text{-}24h}$, over 800 mg*h/L; this was
338 slightly higher that the percentage expected with the dosing regimen that is currently
339 used. Additional TDM is necessary to individualise therapy for patients at risk of high
340 exposure rates.
341 The simulated drug regimens presented here in the different neonatal age groups
342 resulted in higher percentage of patients who would reach the target for efficacy but
343 also higher percentage of patients who would have vancomycin concentrations over the
344 nephrotoxicity threshold of 15-20 mg/L, reported both in adults and children. [24,54,55] This
345 potential higher risk of nephrotoxicity requires further evaluation, but in our recent
346 patient-tailored vancomycin dose study in 190 neonates, no patient developed
347 nephrotoxicity after model-based TDM although the AUC0-24h reached 1200 mg·h/L in
348 some patients.[10]
349 The simulated vancomycin regimens were developed as the pre-clinical component of
350 the FP7 NeoVanc programme. As our final objective is to maximise clinical efficacy and

351 minimise toxicity and selection of resistance by increasing exposure and reducing
352 length of treatment, our data are now being taken forward in a RCT of the optimised
353 regimen in which the duration of vancomycin therapy is reduced to 5 days, compared to
354 a standard dosing regimen and administration for 10 days. The NeoVanc RCT trial was
355 evaluated by experts at the EC, a pediatric Investigation Plan was validated by EMA
356 and regulatory authorities and a DSMD closely monitors patients and data. Due to
357 multifactorial variability in vancomycin disposition, drug monitoring is being performed
358 in patients included in the two arms to further guide dosing[56] , although a trough level is
359 not a very good predictor of AUC_{24h}.[57,58] Our RCT will also provide information on
360 additional factors specific to neonates that may contribute to toxicity, including
361 hypovolemia, concurrent nephrotoxic drug use.
362

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Authors' contributions

EJA, WZ, SL, MS designed research

KA, EVC, VB, AT, NS, BM, YLL, RM, JEP, IL, JS, HN, JNA provided data and revised the manuscript

WZ and SL analysed data

EJA wrote the first version of the manuscript

EJA, WZ, AT, IL and MS revised it.

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563 **Figure Legend**
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566 **Figure 1**: Goodness-of-fit plots: **A)** Population predicted (PRED) versus observed
567 concentrations (DV); **B)** Individual predicted (IPRED) versus DV; **C)** Conditional weighted
568 residuals (CWRES) versus time; **D)** CWRES) versus PRED, Normalised prediction
569 distribution errors: **E)** QQ-plot of the distribution of the Normalised Prediction Distribution
570 Errors (NPDE) versus the theoretical N (0,1) distribution; **F)** Histogram of the distribution
571 of the NPDE, with the density of the standard Gaussian distribution overlaid.
572
573 **Figure 2:** Validation of the model by use of a visual predictive check (VPC) Visual
574 predictive check after continuous (CVA: 2A) and intermittent (IVA) vancomycin
575 administration. Comparison of the 5th (bottom dashed line), 50th (solid line), and 95th (top
576 dashed line) percentiles obtained from 1,000 simulations and the observed data (circles)
577 for vancomycin concentrations in premature neonates <29 weeks (L), 29-35 weeks (M)
578 and >35 weeks (H). Open circles represents individual observed concentrations.
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588 **Table 1**
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590
591 **Demographic characteristics of the 1631 neonates and infants included**
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	Number (%)	Mean (SD)	Median (min-max)
Patients	1631		
Race	1463 (89.7) Caucasian 116 (7.1) Malaysian 52 (3.2) Japanese		
GA (weeks)		31.2 (5.0)	30.0 (22.3 - 42.1
PMA (weeks)		33.3 (5.7)	32.0 (23.3 - 52.4)
PNA (days)		16 (15)	11 (1 - 90)
Current weight (g)		1785 (1127)	1350 (415 - 11370)
Serum creatinine concentration (μmol/L)		59.2 (32.0)	53.9 (6.2 – 353.6)
Vancomycin treatment			
Continuous infusion	295 (18.1)		
Intermittent infusion	1336 (81.9)		

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595 **Table 2**

596 **Presentation of the studies included in the vancomycin meta-analysis**

Study	N of patients (N=1631)	PK study	Adminis -tration	Location	Creatinine method	Vancomycin method	Ref
1	59	Single center	IVA	Glasgow, UK	Jaffé	FPIA	14
2	294	Multi centers (4)*	IVA	San Diego, US	Jaffé	EMIT and FPIA	15
3	35	Single center	IVA	Glasgow, UK	Jaffé	FPIA	16
4	210	Single center	IVA	Leuven, Belgium	Jaffé	PETINIA	17
5	116	Single center	IVA	Kuala Lumpur, Malaysia	Jaffé	FPIA	18
6	66	Single center	CVA	Marseille, France	Enzymatic	EMIT	19
7	61	Single center	CVA	Marseille, France	Enzymatic	EMIT	20
8	125	Single center	IVA	Memphis, US	Enzymatic	EMIT	21
9	55	Single center	CVA	Glasgow, UK	Enzymatic	CMIA	22
10	78	Single center	IVA	Paris, France	Enzymatic	EMIT AND FPIA	23
11	113	Multi centers (3)*	CVA	Paris, France	Enzymatic	PETINIA AND FPIA	24
12	199	Single center	IVA	Leuven, Belgium	Enzymatic	PETINIA AND FPIA	25
15	68	Single center	IVA	Tartu, Estonia	Enzymatic	FPIA	26
13	52	Single center	IVA	Tokyo, Japan	Enzymatic	CLIA	NP
14	100	Single center	IVA	Valencia, Spain	Enzymatic	FPIA	NP

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598 *: Number of centers was given for multi centers study

599 **NP**: not published; **CVA**: Continuous intravenous Vancomycin Infusion; **IVA**: Intermittent
600 intravenous Vancomycin infusion; **PETINIA**: particle enhanced turbidimetric inhibition
601 immunoassay **FPIA**: fluorescence polarization immunoassay method; **EMIT**: enzyme-
602 multiplied immunoassay method; **CMIA**: chemiluminescent microparticle immunoassay;
603 **CLIA**: chemiluminescent immunoassay; **CREA:** serum creatinine concentration in
604 µmol/L; **PMA:** postmenstrual age in weeks.

605 In our population, 1350 gram, 32 weeks and 52 μmol/L are the median current weight
606 (day of the study), postmenstrual age, and serum creatinine concentration values,
607 respectively.
608

609 **Table 3: Population pharmacokinetic parameters of vancomycin and Bootstrap**
610 **results (n = 500)**
611

Parameters	Full data set		Bootstrap	
	Final	RSE(%)	Median	2.5th - 97.5th
Central volume of distribution V_1 (L)				
$V_1 = \theta 1 \times (CW/1350)^{\theta 2}$				
$\theta 1$	0.728	1.5	0.714	0.414 – 0.742
$\theta 2$	1.13	3.0	1.12	0.596 – 1.200
Peripheral volume of distribution V_2 (L)				
$V_2 = \theta 3 \times (CW/1350)^{\theta 4}$				
$\theta 3$	0.358	11.1	0.335	0.185 – 0.474
$\theta 4$	1.15	14.9	1.25	0.75 – 1.93
Intercompartmental clearance (Q) (L/h)				
$Q = \theta 5 \times (CW/1350)$				
$\theta 5$	0.0301	12.5	0.0361	0.0248 – 1.190
Clearance (L/h)				
$CL = \theta 6 \times (CW/1350)^{\theta 7} \times RM \times RF \times F_{Jaffé\text{-}Enzymatic}$				
$\theta 6$	0.0680	1.3	0.0686	0.0664 – 0.0717
$\theta 7$	0.863	5.3	0.895	0.787 – 0.968
$RM = (PMA/32)^{\theta 8}$				
$\theta 8$	0.544	30.3	0.544	0.143 – 0.816
$RF = (1/ F_{Jaffé\text{-}Enzymatic} \times CREA/54)^{\theta 9}$				
$\theta 9$	0.666	3.6	0.655	0.598 – 0.718
$F_{Jaffé\text{-}Enzymatic}$				
$\theta 10$	0.720	2.8	0.716	0.682 – 0.756
F_{Race}				
$\theta 11$	0.724	2.8	0.710	0.646 – 0.757
Inter-individual variability (%)				
V_1	17.5	25.6	14.1	1.7 – 23.0
V_2	102.5	25	80.3	19.2 – 132.8
CL	18.2	21.6	15.2	2.2 – 21.0
Inter-occasion variability (%)				
CL	19.1	20.1	16.7	2.4 – 22.7
Residual proportional (%)				
FPIA	22.2	4.8	22.2	19.9 – 24.2
EMIT	20.9	7.3	21.1	18.0 – 24.0
PENTINIA	25.1	5.6	24.7	21.7 – 27.8
CMIA	10.7	21.2	10.6	5.7 – 14.2
CLIA	38.3	25.8	39.2	19.6 – 58.5
Residual additive (mg/L)				
FPIA	1.57	7.7	1.63	1.32 – 1.99
EMIT	1.53	16.7	1.54	0.94 – 2.08
PENTINIA	1.01	19.6	1.06	0.59 – 1.65
CMIA	2.02	26.1	2.07	0.71 – 2.78
CLIA	3.30	28.7	3.26	0.723 – 4.97

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615 **Table 4: Monte Carlo simulations of vancomycin standard dose regimen***

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PMA (weeks)	<29	29 - 35	>35	Total
Number of patients	335	618	510	1463#
Standard dose regimen (mg/kg)	15 OD	15 BID	15 TID	
First day				
$AUC_{0\text{-}24h}$ median (mg*h/L)	246	378	495	385
$AUC_{0\text{-}24h}$ 5th-95th (mg*h/L)	163-356	264-523	332-725	203-638
Target attainment rate (%)	1.5	39.0	81.0	45.1
$AUC_{0\text{-}24h}$ 400 - 700mg*h/L (%)	1.5	38.9	74.0	42.6
$AUC_{0\text{-}24h}$ >700mg*h/L (%)	0	0.1	7.0	2.5
$AUC_{0\text{-}24h}$ >800mg*h/L (%)	0	0	2.0	0.7
C_{min24h} median (mg/L)	3.8	9.0	14.3	9.0
C_{min24h} 5th-95th (mg/L)	0.2–8.7	2.9–18.4	4.8–30.8	1.6–24.0
C_{min24h} >20mg/L (%)	0	3.4	24.2	9.9
Steady state				
$AUC_{0\text{-}24h}$ median (mg*h/L)	338	536	654	520
$AUC_{0\text{-}24h}$ 5th-95th (mg*h/L)	203-547	323-893	368-1276	259-1028
Target attainment rate (%)	27.7	84.3	91.9	74.0
$AUC_{0\text{-}24h}$ 400 - 700mg*h/L (%)	26.6	65.5	49.4	51.0
$AUC_{0\text{-}24h}$ >700mg*h/L (%)	1.1	18.7	42.5	23.0
$AUC_{0\text{-}24h}$ >800mg*h/L (%)	0.5	10.0	29.6	14.7
C_{min24h} median (mg/L)	6.0	12.3	17.2	11.9
C_{min24h} 5th-95th (mg/L)	1.1–14.7	4.1–28.3	5.6–46.0	2.8–34.4
C_{min24h} >20 mg/L (%)	12.8	17.6	40.0	21.7

617

618 * as indicated in the Blue Book (12),

619 # number of Caucasian patients,

620 $AUC_{0\text{-}24h}$: 24h Area Under the Curve at the first day,

621 C_{min24h} : trough level at the first day

622 $AUC_{ss\text{-}24h}$: 24h Area Under the Curve at steady-state,

623 $C_{minss\text{-}24h}$: trough level at steady-state

624 **Table 5: Monte Carlo simulation of vancomycin dosage regimen with a loading**
625 **dose 25 mg/kg following by optimal maintenance dose**
626

PMA (weeks)	<29	29 - 35	>35	Total
Number of patients	335	618	510	1463
Loading dose (mg/kg)	25	25	25	
Optimal maintenance dose (mg/kg)	15 BID	15 BID	15 TID	
First day				
$AUC_{0\text{-}24h}$ median (mg*h/L)	559	492	596	539
$AUC_{0\text{-}24h}$ 5th-95th (mg*h/L)	384-787	336-692	426-820	358-812
Target attainment rate (%)	87.8	83.0	93.2	88.9
$AUC_{0\text{-}24h}$ 400 - 700mg*h/L (%)	74.0	78.6	67.5	74.7
$AUC_{0\text{-}24h}$ >700mg*h/L (%)	13.7	4.4	25.7	14.2
$AUC_{0\text{-}24h}$ >800mg*h/L (%)	4.1	1.0	12.0	5.6
C_{min24h} median (mg/L)	14.4	10.7	15.5	13
C_{min24h} 5th-95th (mg/L)	5.3–28.0	3.6–22.5	5.2–34.7	4.3–29.0
C_{min24h} >20mg/L (%)	21.2	8.9	31.3	19.8
Steady state				
$AUC_{0\text{-}24h}$ median (mg*h/L)	677	529	656	600
$AUC_{0\text{-}24h}$ 5th-95th (mg*h/L)	401-1102	325-883	368-1293	348-1093
Target attainment rate (%)	95.0	83.5	92.5	89.3
$AUC_{0\text{-}24h}$ 400 - 700mg*h/L (%)	49.5	65.0	49.4	56.0
$AUC_{0\text{-}24h}$ >700mg*h/L (%)	45.5	17.6	43.1	33.3
$AUC_{0\text{-}24h}$ >800mg*h/L (%)	28.9	9.0	30.3	21.0
C_{min24h} median (mg/L)	17.5	12.2	17.5	15
C_{min24h} 5th-95th (mg/L)	6.5–38.0	4.0–28.5	5.6–46.1	4.9–37.6
C_{min24h} >20 mg/L (%)	39.3	17.6	41.5	30.9

627
628 $AUC_{0\text{-}24h}$: 24h Area Under the Curve at the first day,
629 C_{min24h} : trough level at the first day
630 $AUC_{ss\text{-}24h}$: 24h Area Under the Curve at steady-state,
631 $C_{minss\text{-}24h}$: trough level at steady-state

Figure 1

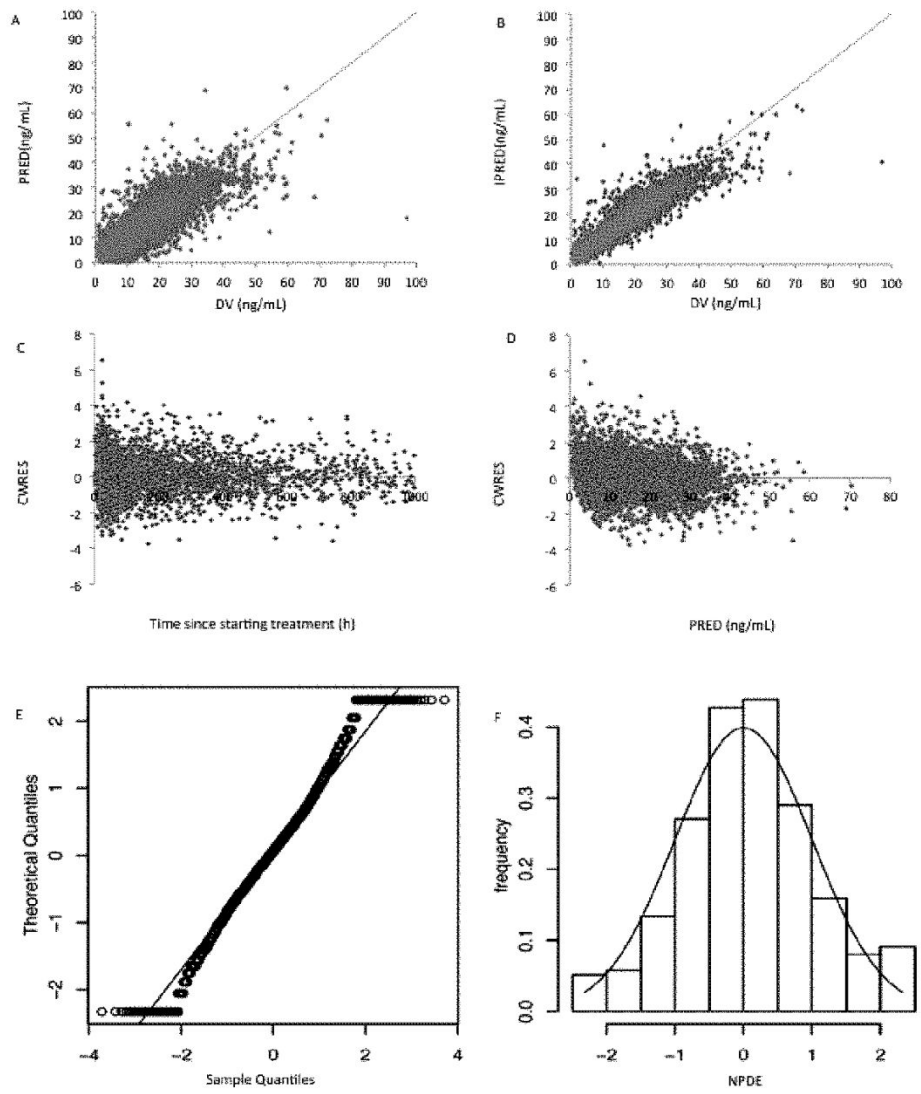

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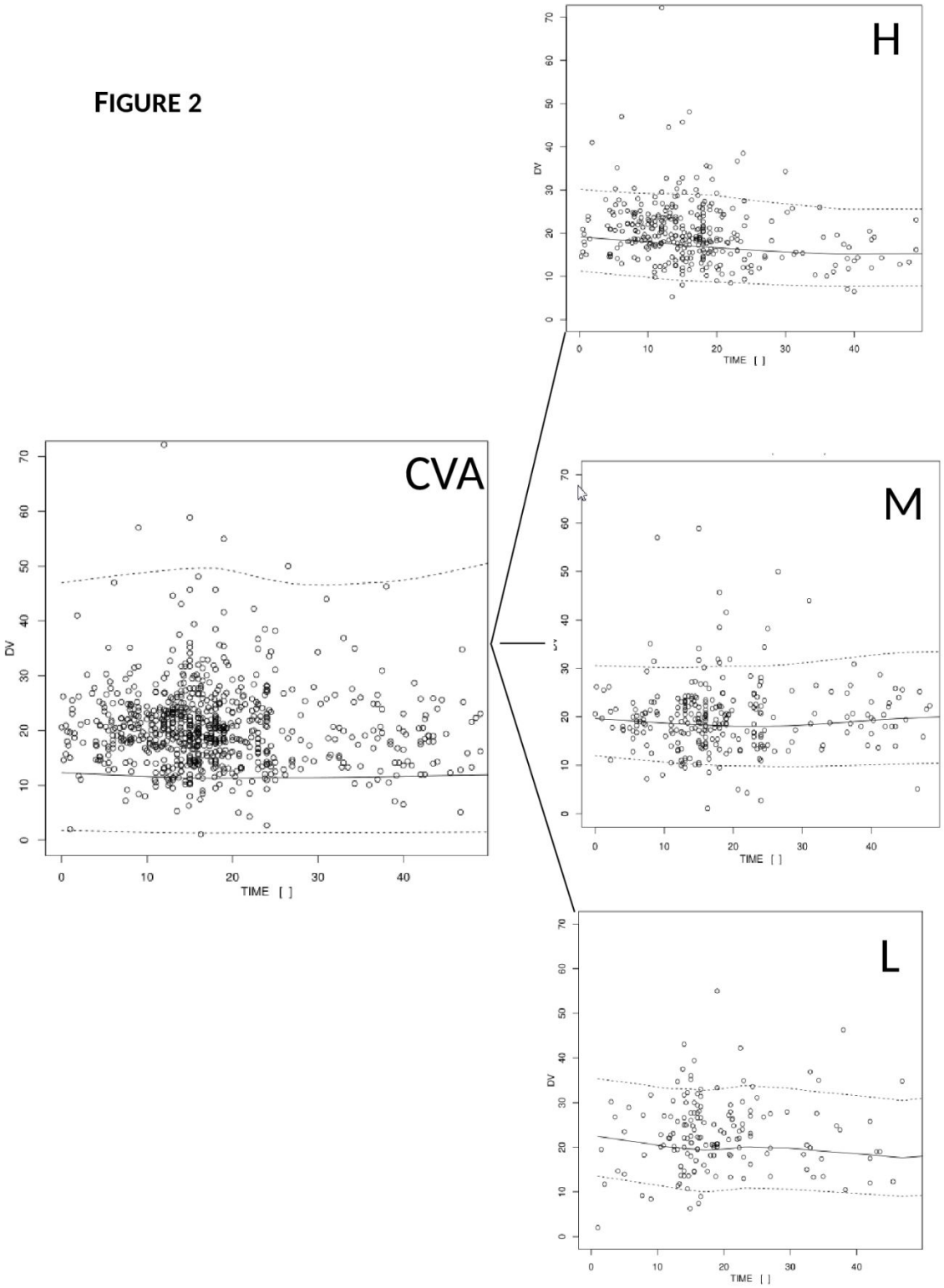
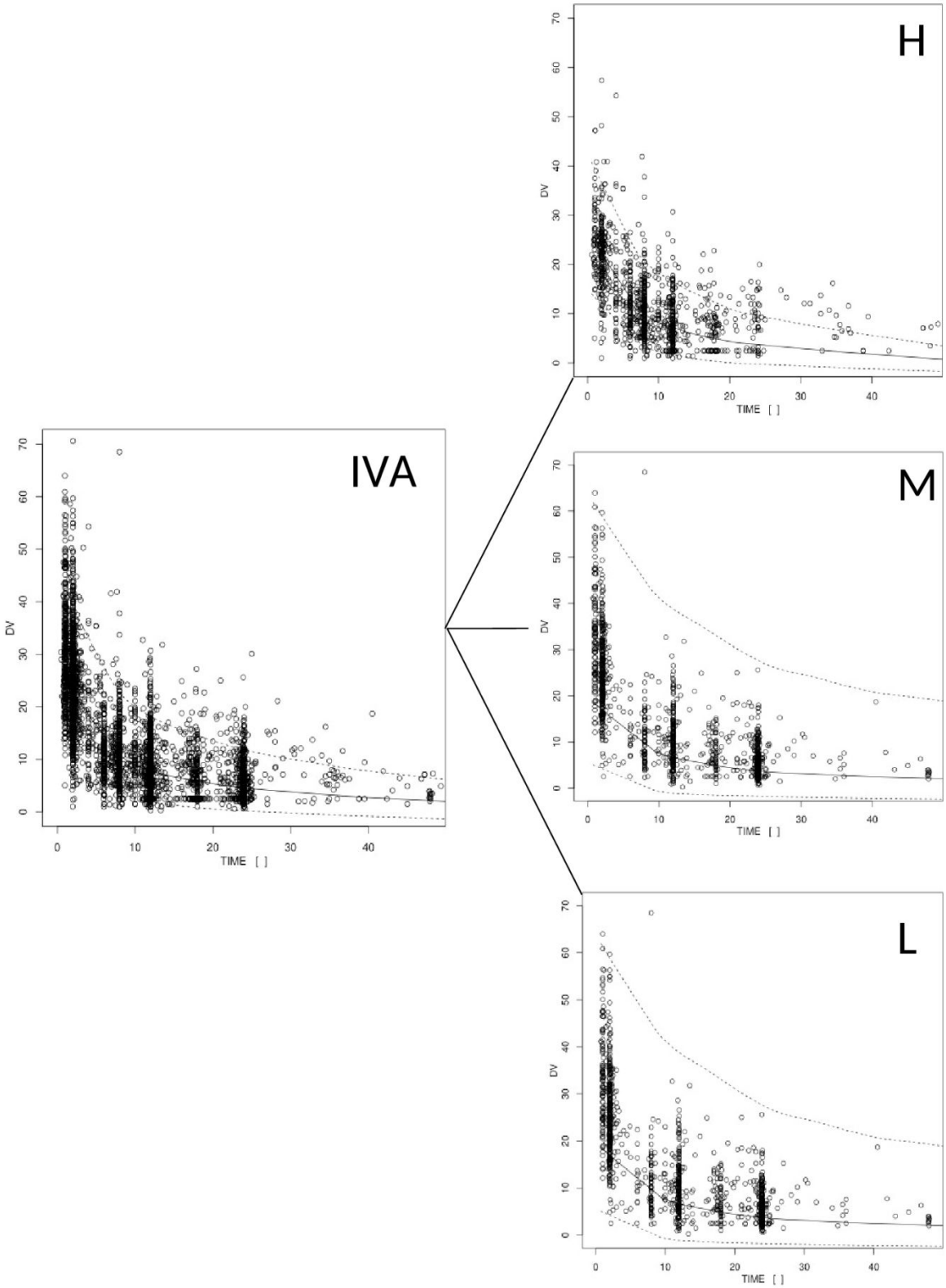
FIGURE 2





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