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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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Synopsis

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.

Introduction

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

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

Methods

Identification of individual patient data

Published PK or PK/PD studies were identified through databases (PubMed, Embase) in 2014. The investigator responsible for the publication was contacted, invited to participate in the present study and provided individual vancomycin dose and concentration data and associated covariates. Additional, non-published, routine Therapeutic Drug Monitoring (TDM) data were also used. All data were anonymised before transfer with a pre-defined data sharing agreement, according to Good Clinical and Laboratory Practices.

Requested covariates and individual information

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

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

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

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

Biological covariates: serum creatinine concentrations

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

153 **Data analysis**

154 PK data were made available on a standard Microsoft Office Excel spreadsheet (CIC,
155 1426, Hôpital Robert Debré) and formatted for subsequent modelling using NONMEM V
156 7.2 (Icon Development Solutions, USA).

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

166 Covariate analysis followed a forward and backward selection process. The likelihood
167 ratio test was used to test the effect of each variable on model parameters. The effects
168 of current weight, gestational age, postnatal age, postmenstrual age, serum creatinine
169 concentration, analytical methods of vancomycin and creatinine, and ethnicity were
170 investigated as potential covariates affecting PK parameters. During the first step of
171 covariate model building, a covariate was included if a significant ($p<0.05$, $\chi 2$ distribution
172 with one degree of freedom) decrease (reduction>3.84) in the objective function value
173 (OFV) from the basic model was obtained. All the significant covariates were then added
174 simultaneously into a 'full' model. Subsequently, each covariate was independently
175 removed from the full model. If the increase in the OFV was higher than 6.635 ($p<0.01$,
176 χ^2 distribution), the covariate was retained in the final model.

Model validation was based on graphical and statistical criteria. Goodness-of-fit plots, including observed (DV) *versus* population prediction (PRED); DV *versus* individual prediction (IPRED); conditional weighted residuals (CWRES) *versus* time and CWRES versus PRED were initially used for diagnostic purposes. The stability and performance of the final model was also assessed by means of a nonparametric bootstrap with re-sampling and replacement. Re-sampling was repeated 200 times and the values of estimated parameters from the bootstrap procedure were compared with those estimated from the original data set. The entire procedure was performed in an automated fashion, using Perl-speaks-Nonmem (PsN v2.30). The final model was also evaluated graphically and statistically by normalised prediction distribution errors (NPDE). One thousand datasets were simulated using the final population model parameters. NPDE results were summarized graphically by default as provided by the NPDE R package (v1.2): (i) QQ-plot of the NPDE; (ii) histogram of the NPDE. The NPDE is expected to follow the N (0, 1) distribution.[12]

Monte Carlo simulations for dosage optimisation were performed to evaluate different weight adjusted (mg/kg) dosing regimens for three predefined neonatal groups: postmenstrual age (PMA) <29, 29-35 and >35 weeks. Drug exposure was simulated 100 times for each set of patients including only the Caucasian patients. Area under the curve between 0 and 24h on the first treatment day (AUC_{0-24}) and AUC_{0-24} at steady state (AUC_{SS0-24}) were calculated for each simulated patient. The parameter estimates obtained from the final model were used to estimate the target attainment rate for an AUC_{0-24} of ≥400 mg*h/L with the standard dosage regimen recommended in the "Blue Book" [13] and 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. Patients' characteristics and vancomycin administration details are 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. Ethnicity (Malaysian patients) was identified as a sixth covariate (ΔOFV 302.1 units) on CL. The final model had the following structure:

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

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

Model evaluation

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

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

Dosing optimisation.

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

With the standard vancomycin dosing regimen at steady-state, the percentage of neonates reaching the target $AUC_{ss0\text{-}24}$ of ≥400 mg*h/ was 74.0% and the percentage exposed to an $AUC_{ss0\text{-}24}$ above 700 mg*h/L was 23.0% when considering all age groups. When considering only neonates <29 weeks PMA, the corresponding values fell to 27.7% and 1.1% respectively (Table 4).

With a loading dose of 25 mg/kg followed by the optimal maintenance dose of 15 mg/kg, either twice daily (BID) if ≤35 weeks PMA or three times daily (TID) if >35 weeks PMA, the percentage of neonates reaching the target AUC_{ss0-24} of 400 mg*h/L was 89.3% while the percentage exposed to an AUC_{ss0-24} over 700 mg*h/L was 33.3% when considering all age groups. When considering only neonates <29 weeks PMA, the corresponding values increased to 95.0% and 45.5% respectively (Table 5).

The target attainment rate on the first day of treatment increased from 42.6% with the standard regimen to 88.9% with the loading dose strategy.

Discussion

To the best of our knowledge, this is the largest meta-analysis that has assessed the population PK of vancomycin in neonates and young infants aged less than 3 months. The analysis has combined vancomycin concentrations linked to key demographic and biological covariates from 15 pharmacokinetic studies conducted in 7 different countries. Monte-Carlo simulations showed that the current dosage regimen was not suitable for the treatment of staphylococcal infection and that the optimal vancomycin dosing regimen should include a loading dose of 25 mg/kg for all neonates, irrespective of their PMA, followed by a maintenance dose adapted to their PMA.

Although widely used for many years, important questions remain on how to optimise vancomycin dosing in neonates.[2,8,9] In the absence of prospective evaluation, most neonatal units have developed local dosing recommendations, resulting in variable exposures that may lead to poor efficacy, induction of resistance or toxicity[3] Consequently, vancomycin dosage regimens adapted to neonates require harmonisation, taking into account the impact of developmental pharmacology on disposition and PK parameters from very preterm neonates through term neonates to older children.[27] This

issue is central and initiatives from both the FDA and EMA are currently being undertaken to revise vancomycin dosing.[28,29]

Drug pharmacokinetics and dynamics need to be linked to explicative individual characteristics either constitutional (age, weight, genetics, etc.) or environmental (pathology, drug interactions, etc.). In this context, population modelling allows assessment and quantification of sources of variability in drug exposure and response in the target population, even under sparse sampling conditions [30-32] The present study has confirmed the impact of serum creatinine and vancomycin assay methods as predictors of vancomycin concentrations in neonates.[33,34] Additional covariates, such as ventilation,[35] co-administered drugs (e.g. aminoglycosides or ibuprofen), ECMO,[37] whole body cooling,[38] as well as centre or country dependent effects linked to ethnic, environmental and nutritional differences, were not explored in the current study, as they were not available in all data sets. However, it is recognised that they may also contribute to PK variability in neonates.

Model-based approaches to characterise drug PK/PD have been recommended as powerful tools for overcoming the practical and ethical challenges associated with dose selection for neonatal indications.[39,40] For vancomycin, a model tailored dose had already been demonstrated to increase substantially the target attainment rate of vancomycin in treated neonates.[10] However, there were few neonates less than 29 weeks gestational age in that study and centre-effects could not be eliminated. These limitations were addressed in the present PK meta-analysis, which was conducted by pooling 4894 vancomycin concentrations from 1631 neonates. Although robust parameter estimates were obtained with this strategy, different strategies may be necessary when data are heterogenous.[41]

For vancomycin, exposure, measured by AUC_{0-24}, is the PK/PD parameter influencing efficacy and emergence of resistance,[42-44] but also influencing toxicity. Nephrotoxicity is a multifactorial, well-identified risk of high vancomycin exposure and high trough concentrations.[45] AUC_{0-24} or trough levels can vary widely and independently, since the trough depends on both the daily dose and the frequency of administration, whereas AUC_{0-24} only depends on the daily dose. Consequently, in the present study, simulations were performed to evaluate the current dosage regimen[13] and to optimize efficacy by determining the target attainment rate and exposure to vancomycin measured by the AUC_{0-24}. A target AUC_{0-24} of at least 400 mg*h/L was selected as an AUC_{0-24}/MIC ratio of 400 has been associated with favourable treatment outcomes in adults, assuming that bacterial strains have a vancomycin MIC ≤1 mg/L.[43,46] Simulations of the current dosage recommendation (see table 5) were performed after the first dose and at steady-state. Our results showed that the current daily dose was too low for all neonatal age groups but particularly for neonates <29 weeks, as less than 30% of neonates reached the steady-state target. As a loading dose strategy is recommended in adult settings in order to reduce the time needed to reach the target AUC_{0-24} [47,48] simulations were then performed with a loading dose and optimal maintenance doses in all age groups, based on weight and PMA. Increasing the maintenance dose to 15 mg/kg BID instead of OD was also tested in the group <29 PMA weeks to optimise dosage. These modifications led to an increase in the target attainment rate after the first dose and at steady-state in all age groups.

Nephrotoxicity is a recognised side-effect of vancomycin treatment, although its safety profile is considered favorable. The risk of nephrotoxicity primarily increases with high vancomycin exposure and duration of administration.[45,49] In studies in adults and children,[45] reported incidence varied widely, from 5% to 43%, occurrence increased with

longer durations of administration with a range of 4.3 to 17 days and nephrotoxicity was reversible in the majority of cases. In neonates, most studies were not sufficiently powered to detect nephrotoxicity and, when reported, renal impairment was frequently associated with concomitant administration of nephrotoxic drugs.[50]

Therefore, optimising exposure while reducing duration of administration would maximisze clinical efficacy while minimising toxicity and selection of resistance.

The upper AUC_{0-24} limit remains a matter of debate. "Usual" AUC_{0-24} values of 700 or 800 mg*h/L have been used in both adults [46,51,52] and children,[48] however, more extreme values have also been reported, with breakpoints for nephrotoxicity of <600 or >1300 mg*h/L.[51,53] In the absence of specific neonatal data, a value of 700 mg*h/L was used in the present study. With our simulated dosage regimen, 89% of neonates reached the predetermined AUC_{ss0-24} target and 21.0% had an AUC_{ss0-24}, over 800 mg*h/L; this was slightly higher that the percentage expected with the dosing regimen that is currently used. Additional TDM is necessary to individualise therapy for patients at risk of high exposure rates.

Although the simulated dosage regimens increased the percentage of patients who would reach the target for efficacy, interpatient variability means that close monitoring is required with early analysis (ideally after the first dose) in patients for whom renal impairment is suspected. In the absence of pharmacokinetic interpretation software, it is easier to use trough concentrations than AUC_{0-24} to monitor vancomycin exposure but toxicity data in neonates remain sparse. A nephrotoxicity threshold of 15- 20 mg/L has been reported in both adult and paediatric studies,[24,54,55] although it is clear that a trough level is not a very good predictor of AUC_{0-24}.[56,57] Further data are also needed because additional factors specific to neonates may contribute to toxicity. These include hypovolemia, concurrent nephrotoxic drug use and duration of administration. This potential higher risk of

nephrotoxicity requires further evaluation. In our recent patient-tailored vancomycin dose study in 190 neonates, no patient developed nephrotoxicity after model-based TDM although the initial AUC_{0-24} reached 1200 mg·h/L in some patients.[10]

The drug regimen identified in the present, pre-clinical component of the NeoVanc programme is now being taken forward in a RCT of the optimised regimen in which the duration of vancomycin therapy is reduced to 5 days, compared to a standard dosing regimen and administration for 10 days. The aim of this change is to maximise clinical efficacy while minimising toxicity and selection of resistance. Due to multifactorial variability in vancomycin disposition, drug monitoring is being performed in the two arms to further guide dosing[58] and identify additional variability factors specific to neonates.

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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.

Transparency declarations section: the authors have no conflict of interest to declare

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References

1. de Hoog M, Mouton JW, van den Anker JN. Vancomycin: pharmacokinetics and administration regimens in neonates. *Clin Pharmacokinet* 2004; **43**: 417-40.
2. Jacqz-Aigrain E, Zhao W, Sharland M *et al*. Use of antibacterial agents in the neonate: 50 years of experience with vancomycin administration. *Semin Fetal Neonatal Med* 2013; **18**: 28-34.
3. Leroux S, Zhao W, Bétrémieux P *et al.* Therapeutic guidelines for prescribing antibiotics in neonates should be evidence-based: a French national survey. *Arc Dis Child* 2015; **100**: 394-8.
4. Gharbi M, Doerholt K, Vergnano S *et al*. Using a simple point-prevalence survey to define appropriate antibiotic prescribing in hospitalised children across the UK. *BMJ Open* 2016 **3**; 6:e012675.
5. Metsvaht T, Nellis G, Verandi H *et a*l. High variability in the dosing of commonly used antibiotics revealed by a Europe-wide point prevalence study: implications for research and dissemination. *BMC Pediatr* 2015; **15** :41-51.
6. Kadambari S, Heath PT, Sharland M *et al*. Variation in gentamicin and vancomycin dosage and monitoring in UK neonatal units. *J Antimicrob Chemother* 2011; **66**: 2647-50.
7. Osowicki J Gwee A, Noronha J et al. Australia-wide Point Prevalence Survey of Antimicrobial Prescribing in Neonatal Units: How Much and How Good? *Pediatr Inf Dis J* 2015; **34**:e185-90.
8. Jacqz-Aigrain E, Leroux S, Zhao W *et al*. *Expert Rev Clin Pharmacol* 2015; **8**: 635-48.
9. De Cock RF, Allegaert K, Brussee JM *et al*. Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to

adults: towards a semi-physiological function for maturation in glomerular filtration. *Pharm Res* 2014; **31**: 2643-54.

10. Leroux S, Jacqz-Aigrain E, Biran V *et al*. Clinical Utility and Safety of a Model-Based Patient-Tailored Dose of Vancomycin in Neonates. *Antimicrob Agents Chemother* 2016; **60**:2039-42.
11. FP7 Vancomycin trial NeoVanc, available at : www.neovanc.org
12. Comets E, Brendel K, Mentré F. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. 2008; **90**: 154–66.
13. Sharland M. *Manual of childhood infections. The Blue Book* - Oxford University Press, 2011.
14. Grimsley C, Thomson AH. Pharmacokinetics and dose requirements of vancomycin in neonates. *Arch Dis Child Fetal Neonatal Ed* 1999; **81**:F221-7.
15. Capparelli EV Lane JR, Romanowski G *et al*. *J. Clin. Pharmacol.* 2001; **41**: 927-34.
16. Thomson AH, Sie A. Prospective Evaluation of Neonatal Vancomycin Dosage Guidelines and Population Parameter Estimates. *Paediatr Perinat Drug Ther* 2003; **5**: 116-123.
17. Anderson BJ, Allegaert K, Van den Anker JN *et al*. Vancomycin pharmacokinetics in preterm neonates and the prediction of adult clearance. *Br J Clin Pharmacol* 2007; **63**:75-84.
18. Lo YL, van Hasselt JG, Heng SC *et al*. Population pharmacokinetics of vancomycin in premature Malaysian neonates: identification of predictors for dosing determination. *Antimicrob. Agents Chemother.* 2010; **54**: 2626-32.

19. Oudin C, Vialet R, Boulamery A, *et al*. Vancomycin prescription in neonates and young infants: toward a simplified dosage. *Arch Dis Child Fetal Neonatal Ed.* 2011; **96**: F365-70.

20. Marsot A, Vialet R, Boulamery A, *et al*. Vancomycin: Predictive Performance of a Population Pharmacokinetic Model and Optimal Dose in Neonates and Young Infants. *Clinical Pharmacol Drug Dev.* 2012; **1**: 144–151.

21. Mehrotra N, Tang L, Phelps SJ, *et al*. Evaluation of vancomycin dosing regimens in preterm and term neonates using Monte Carlo simulations. *Pharmacotherapy* 2012; **32**: 408-19.

22. Patel AD, Anand D, Lucas C, *et al*. Continuous infusion of vancomycin in neonates. *Arch Dis Child* 2013; **98**: 478-9.

23. Zhao W, Kaguelidou F, Biran V, *et al*. External Evaluation of Population Pharmacokinetic Models of Vancomycin in Neonates: the transferability of published models to different clinical settings. *Br J Clin Pharmacol* 2013; **75**: 1068–1080.

24. Zhao W, Lopez E, Biran V, et al. Vancomycin continuous infusion in neonates: dosing optimisation and therapeutic drug monitoring. *Arch Dis Child* 2013; **98**: 449-53.

25. Samardzic J, Smits A, Spriet I, *et al*. Different Vancomycin Immunoassays Contribute to the Variability in Vancomycin Trough Measurements in Neonates. *Biomed Res Int* 2016; 2016:1974972.

26. Padari H, Oselin K, Tasa T, *et al*. Coagulase negative staphylococcal sepsis in neonates: do we need to adapt vancomycin dose or target? *BMC. Pediatr* 2016; **16**: 206.

27. Kearns GL, Abdel-Rahman SM, Alander SW, *et al*. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; **349**: 1157-67.

28. EMA recommends changes to prescribing information for vancomycin antibiotics http://www.ema.europa.eu/ema – Last update 17/11/2017

29. Vancomycin Hydrochloride for Injection, USP. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/062911s035lbl.pdf

30. Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. *Clin Pharmacokinet* 2008; **47**: 231-43.

31. Vermeulen E, van den Anker JN, *et al*. Global Research in Paediatrics (GRiP). How to optimise drug study design: pharmacokinetics and pharmacodynamics studies introduced to paediatricians. *J Pharm Pharmacol* 2017; **69**: 439-447.

32. Leroux S, Turner MA, Guellec CB, *et al*. Pharmacokinetic Studies in Neonates: The Utility of an Opportunistic Sampling Design. *Clin Pharmacokinet* 2015; **54**: 1273-85.

33. Zhao W, Jacqz-Aigrain E. The importance of knowing how vancomycin is measured when interpreting its pharmacokinetic results. *Ther Drug Monit* 2013; **35**: 416.

34. Oyaert M, Peermans N, Kieffer D, *et a*l. Novel LC-MS/MS method for plasma vancomycin: comparison with immunoassays and clinical impact. *Clin Chim Acta* 2015; **441**: 63-70.

35. Medellín-Garibay SE, Romano-Moreno S, Tejedor-Prado P, et al. Influence of Mechanical Ventilation on the Pharmacokinetics of Vancomycin Administered by Continuous Infusion in Critically Ill Patients. *Antimicrob Agents Chemother* 2017; **61**. pii: e01249-17.

36. Constance JE, Balch AH, Stockmann C, *et al.* A propensity-matched cohort study of vancomycin-associated nephrotoxicity in neonates. *Arch Dis Child Fetal Neonatal Ed* 2016; **101**: F236-43.

37. Donatello K, Roberts JA, Cristallini S, *et al*. Vancomycin population pharmacokinetics during extracorporeal membrane oxygenation therapy: a matched cohort study. *Crit Care* 2014; **18**: 632.

38. de Haan TR, Bijleveld YA, van der Lee JH *et al*. Pharmacokinetics and pharmacodynamics of medication in asphyxiated newborns during controlled hypothermia. The PharmaCool multicenter study. *BMC Paediatr*. 2012; **12**: 45.

39. Rathi C, Lee RE, Meibohm B. Translational PK/PD of anti-infective therapeutics. *Drug Discov Today Technol* 2016; **21-22**: 41-49.

40. Admiraal R, van Kesteren C, Boelens JJ, *et al.* Towards evidence-based dosing regimens in children on the basis of population pharmacokinetic pharmacodynamic modelling. *Arch Dis Child* 2014; **99**: 267-72.

41. Svensson E, van der Walt JS, Barnes KI, *et al*. Integration of data from multiple sources for simultaneous modelling analysis: experience from nevirapine population pharmacokinetics. *Br J Clin Pharmacol.* 2012; **74**: 465-76.

42. Ruback M, Lomaestro B, Rotschafer JC, *et al*. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of Infectious Diseases Pharmacists *Am J Health Syst Pharm.* 2009; **66**: 82-98.

43. Sakoulas G, Moise-Broder PA, Schentag J, *et al*. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant staphylococcus aureus bacteremia. *J Clin Microbiol* 2004; **42**: 2398-402

44. Mouton JW, Brown DF, Apfalter P, *et al*. The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach *Clin Microbiol Infect* 2012; **18**: E37-45.

45. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrob Agents Chemother* 2013; **57**: 734-44.

46. Pappas PG, Kauffman CA, Anders DR, *et al*. *Clin Infect Dis* 2009; **48**: 503-35.

47. Álvarez O, Plaza-Plaza JC, Ramirez M, *et al*. *Antimicrob Agents Chemother* 2017; **61**. pii: e00280-17.

48. Le J, Ny P, Capparelli E, *et al*. *J Pediatric Infect Dis Soc.* 2015; **4**: e109-16.

49. Filippone EJ, Kraft WK, Farber JL. The Nephrotoxicity of Vancomycin. Clin Pharmacol Ther 2017; **102**: 459-469.

50. Lestner JM, Hill LF, Heath PT, Sharland M. Vancomycin toxicity in neonates: a review of the evidence Curr Opin Infect Dis. 2016; **29**: 237-47.

51. Suzuki Y, Kawasaki K, Sato Y, et al Is peak concentration needed in therapeutic drug monitoring of vancomycin? A pharmacokinetic-pharmacodynamic analysis in patients with methicillin-resistant staphylococcus aureus pneumonia. *Chemotherapy* 2012; **58**: 308-12.

52. Zasowski EJ, Murray KP, Trinh TD, *et al*. Identification of Vancomycin Exposure-Toxicity Thresholds in Hospitalized Patients Receiving Intravenous Vancomycin. https://www.ncbi.nlm.nih.gov/pubmed/29084753 *Antimicrob. Agents Chemother.* 2017; **62**. pii: e01684-17.

53. Lodise TP, Patel N, Lomaestro BM, *et al*. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. *Clin Infect Dis* 2009; **49**: 507-14.

54. Labreche MJ, Graber CJ, Nguyen HM. Recent Updates on the Role of Pharmacokinetics-pharmacodynamics in Antimicrobial Susceptibility Testing as Applied to Clinical Practice. *Clin Infect Dis.* 2015; **61**: 1446-52.

55. Zhao W, Leroux S, Jacqz-Aigrain E. Dosage individualization in children: integration of pharmacometrics in clinical practice. *World J Pediatr.* 2014; **10**: 197-203.

56. Neely MN, Youn G, Jones B, *et al*. Are vancomycin trough concentrations adequate for optimal dosing ? *Antimicrob Agents Chemother*. 2014; **58**: 309-16.

57. Hale CM, Seabury RW, Steele JM, *et al*. Are Vancomycin Trough Concentrations of 15 to 20 mg/L Associated With Increased Attainment of an AUC/MIC ≥ 400 in Patients With Presumed MRSA Infection? *J Pharm Pract*. 2017; **30**: 329-335.

58. Finch NA, Zasowski EJ, Murray KP. A Quasi-Experiment To Study the Impact of Vancomycin Area under the Concentration-Time Curve-Guided Dosing on Vancomycin-Associated Nephrotoxicity. *Antimicrob Agents Chemother* 2017; **22** :61- e01293-17.

Figure Legend

	Number	Mean (SD)	Median (Range)
Patients	1631		

Figure 1: Goodness-of-fit plots: **A)** Population predicted (PRED) versus observed concentrations (DV); **B)** Individual predicted (IPRED) versus DV; **C)** Conditional weighted residuals (CWRES) versus time; **D)** CWRES) versus PRED, Normalised prediction distribution errors: **E)** QQ-plot of the distribution of the Normalised Prediction Distribution Errors (NPDE) versus the theoretical N (0,1) distribution; **F)** Histogram of the distribution of the NPDE, with the density of the standard Gaussian distribution overlaid.

Figure 2: Validation of the model by use of a visual predictive check (VPC) Visual predictive check after continuous (CVA: 2A) and intermittent (IVA) vancomycin administration. Comparison of the 5th (bottom dashed line), 50th (solid line), and 95th (top dashed line) percentiles obtained from 1,000 simulations and the observed data (circles) for vancomycin concentrations in premature neonates <29 weeks (L), 29-35 weeks (M) and >35 weeks (H). Open circles represents individual observed concentrations.

Ethnicity	1463 Caucasian 116 Malaysian 52 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		
Intermittent infusion	1336		

Table 1

Demographic characteristics of the 1631 neonates and infants included

Table 2

Presentation of the studies included in the vancomycin meta-analysis

608

609

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

611 **NP**: not published; **CVA**: Continuous intravenous Vancomycin Infusion; **IVA**: Intermittent

612 intravenous Vancomycin infusion; **PETINIA**: particle enhanced turbidimetric inhibition

Study	N of patients N=1631	PK study	Adminis-tration	Location	Creatinine method	Vancomycin method	Ref
1	59	Single center	IVA	Glasgow, UK	Jaffe	FPIA	14
2	294	Multi centers (4)*	IVA	San Diego, US	Jaffe	EMIT and FPIA	15
3	35	Single center	IVA	Glasgow, UK	Jaffe	FPIA	16
4	210	Single center	IVA	Leuven, Belgium	Jaffe	PETINIA	17
5	116	Single center	IVA	Kuala Lumpur, Malaysia	Jaffe	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

613 immunoassay **FPIA**: fluorescence polarization immunoassay method; **EMIT**: enzyme-

614 multiplied immunoassay method; **CMIA**: chemiluminescent microparticle immunoassay;

615 **CLIA**: chemiluminescent immunoassay; **CREA:** serum creatinine concentration in

616 µmol/L; **PMA:** postmenstrual age in weeks.

617 In our population, 1350 gram, 32 weeks and 52 µmol/L are the median current weight

618 (day of the study), postmenstrual age, and serum creatinine concentration values,

619 respectively.

620 **Table 3: Population pharmacokinetic parameters of vancomycin and Bootstrap results**

621 **(n=500)**

Parameters	Full dataset		Bootstrap	
	Final	RSE(%)	Median	2.5th – 97.5th
Central volume of distribution V_1 (L)				
$V_1=\theta1 \times (CW/1350)^{\theta2}$				
θ1	0.728	1.5	0.714	0.414 – 0.742
θ2	1.13	3.0	1.12	0.596 – 1.200
Peripheral volume of distribution V_2 (L)				
$V_2=\theta3 \times (CW/1350)^{\theta4}$				
θ3	0.358	11.1	0.335	0.185 – 0.474
θ4	1.15	14.9	1.25	0.75 – 1.93
Inter-compartment clearance Q (L/h)				
$Q=\theta5 \times (CW/1350)$				
θ5	0.0301	12.5	0.0361	0.0248 – 1.190
Clearance CL (L/h)				
$CL=\theta6\times(CW/1350)^{\theta7}\times RM\times RF\times F_{Jaffé\text{-}Enzymatic}\times$				
θ6	0.0680	1.3	0.0686	0.0664 – 0.0717
θ7	0.863	5.3	0.895	0.787 – 0.968
$RM= (PMA/32)^{\theta8}$				
θ8	0.544	30.3	0.544	0.143 – 0.816
$RF= 1/(F_{Jaffé\text{-}Enzymatic} \times CREA/54)^{\theta9}$				
θ9	0.666	3.6	0.655	0.598 – 0.718
$F_{Jaffé\text{-}Enzymatic}$				
θ10	0.720	2.8	0.716	0.682 – 0.756
F_{race}				
θ11	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	25.0	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	0.73 – 4.97

622
623

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

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
$AUC_{0\text{-}24h}$ 5^{th}-95^{th} (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} 5^{th}-95^{th} (mg*h/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				
$AUC_{ss\text{-}24h}$ median (mg*h/L)	338	536	654	520
$AUC_{ss\text{-}24h}$ 5^{th}-95^{th} (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
$AUC_{ss\text{-}24h}$ > 700mg*h/L (%)	1.1	18.7	42.5	23.0
$AUC_{ss\text{-}24h}$ > 800mg*h/L (%)	0.5	10.0	29.6	14.7
$C_{minss\text{-}24h}$ median (mg/L)	6.0	12.3	17.2	11.9
$C_{minss\text{-}24h}$ 5^{th}-95^{th} (mg*h/L)	1.1-14.7	4.1-28.3	5.6-46.0	2.8-34.4
$C_{minss\text{-}24h}$ > 20mg/L (%)	12.8	17.6	40.0	21.7

* as indicated in the Blue Book (12),

number of Caucasian patients,

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

C_{min24h} : trough level at the first day

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

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

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

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
$AUC_{0\text{-}24h}$ 5^{th}-95^{th} (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} 5^{th}-95^{th} (mg*h/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				
$AUC_{ss\text{-}24h}$ median (mg*h/L)	677	529	656	600
$AUC_{ss\text{-}24h}$ 5^{th}-95^{th} (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
$AUC_{ss\text{-}24h}$ > 800mg*h/L (%)	28.9	9.0	30.3	21.0
$C_{minss\text{-}24h}$ median (mg/L)	17.5	12.2	17.5	15
$C_{minss\text{-}24h}$ 5^{th}-95^{th} (mg*h/L)	6.5-38.0	4.0-28.5	5.6-46.1	4.9-37.6
$C_{minss\text{-}24h}$ > 20mg/L (%)	39.3	17.6	41.5	30.9

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

C_{min24h} : trough level at the first day

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

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

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Figure 1

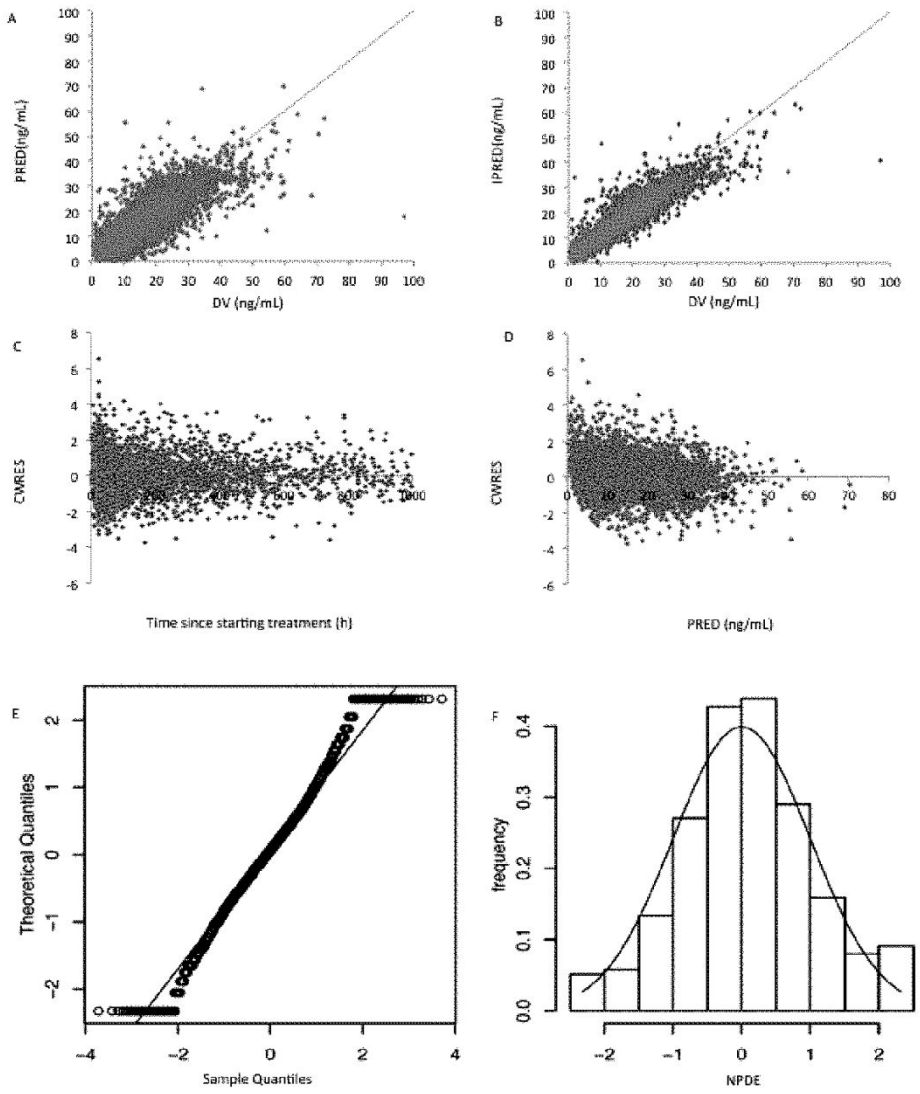

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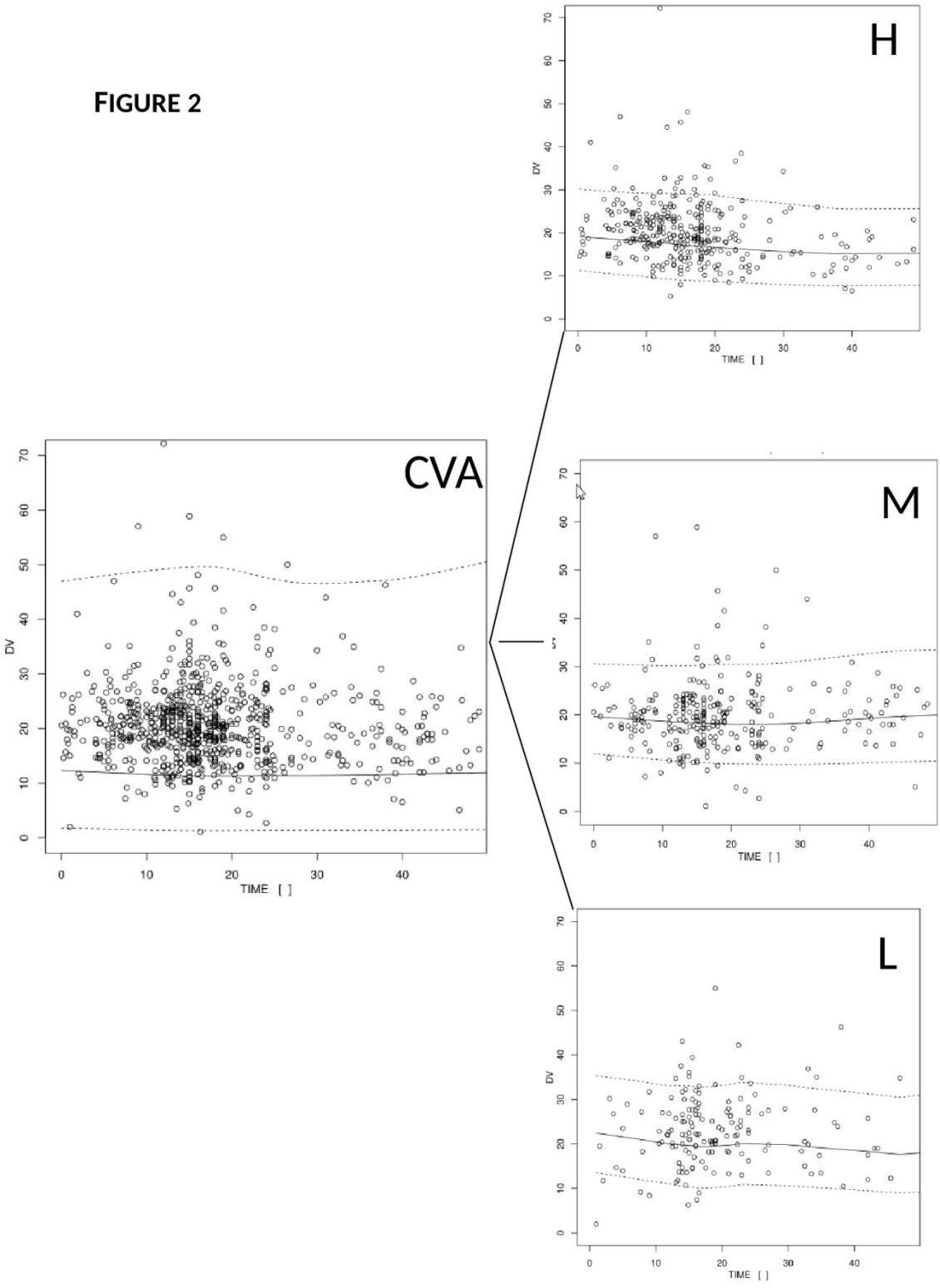
FIGURE 2



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