Supplementary digital content 1

Definition of pharmacokinetic parameters

Pharmacokinetic parameters derived from measured serum vancomycin parameters

Bioavailability was calculated using the vancomycin dose that entered the trachea at the distal tip of the endotracheal tube (dose deposited in the nebulizer's chamber minus extrapulmonary deposition in inspiratory circuit and nebulizer). The bioavailability was calculated as:

$$F = AUC_{\text{serum infinity}} \text{ (nebulized)} / AUC_{\text{serum infinity}} \text{ (IV)} \times \text{Dose IV/Dose neb} \times 100$$

where $AUC_{\text{serum infinity}}$ is the area under the drug concentration-time curve to infinite.

Standard kinetic parameters like volume of distribution, serum clearance and elimination rate constant were calculated with PK Solutions 2.0 software program (Summit Research Services, Montrose, CO), using a mono-compartment pharmacokinetic open model.

Elimination clearance was calculated as:

$$CL \text{ (elimination clearance)} = S.F.D/ AUC$$

where S = Salt fraction (S=1), F = bioavailability, D = administered dose and AUC = area under the curve 0 to infinity.

Volume of distribution (Vd) was calculated as:

$$Vd = C.F/k\ AUC_{0\text{-infinity}}$$

In population pharmacokinetic model, F is estimated as an additional model parameter based on integrated information from volumes and clearances estimates in piglets receiving intravenous

vancomycin, where F=100%, and volumes and clearance estimates from piglets receiving inhaled vancomycin, where volume and clearances represent Vol/F and CL/F. This method is more robust, and shows F values different from F relative bioavailability calculated in the pharmacokinetic analysis.

Quality of fit of the vancomycin pharmacokinetic model

Traditional measured versus predicted plots, residual plots and a visual predictive check (VPC) plot were used to test for model misspecification. Predicted concentrations are all based on the final two-compartment model. Figure suppl 1 shows measured versus predicted vancomycin concentrations plots. Left plots show population predictions. This means that the concentrations predictions for a typical piglet are compared with measured concentrations. These left plots show high variability that precludes prediction from the estimated parameters (volumes clearances F and Tabs). Right plots use individual concentration predictions based on individual estimated parameters (volumes clearances F and Tabs). That is why the fit looks much better. This confirms the adequacy of our structural two compartment model. Future studies should be performed to clarify this high unexplained variability, exploring biologically plausible covariates in model parameters.

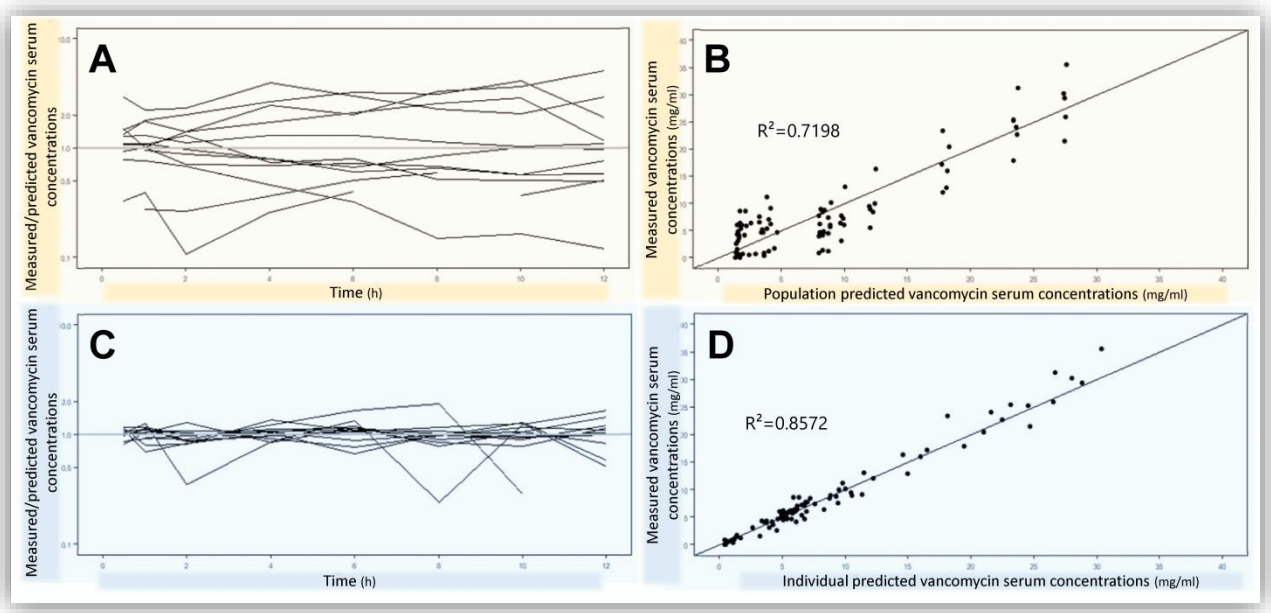

Figure suppl 1. Measured vs predicted plots of the final two-compartment weight scaled allometric vancomycin pharmacokinetic model. **A** Measured vancomycin serum concentrations/population predicted serum vancomycin concentrations vs time. **B** Measured vancomycin serum concentrations/individual predicted vancomycin serum concentrations vs time. **C** Measured vancomycin serum concentrations vs population predicted vancomycin serum

concentrations. **D** Measured vancomycin serum concentrations vs individual predicted vancomycin serum concentrations - Horizontal lines (top plots) and diagonal lines (bottom plots) represent perfect fit of measured and predicted data

Figure suppl 2 shows conditional weighted residual (CWRES) plots. CWRES are calculated as the approximated difference between an individual's data and the model prediction of that data divided by the root of the covariance of the data given the model. No apparent deviations between model vancomycin concentrations predictions and data are observed, confirming the adequacy of our structural two compartment model.

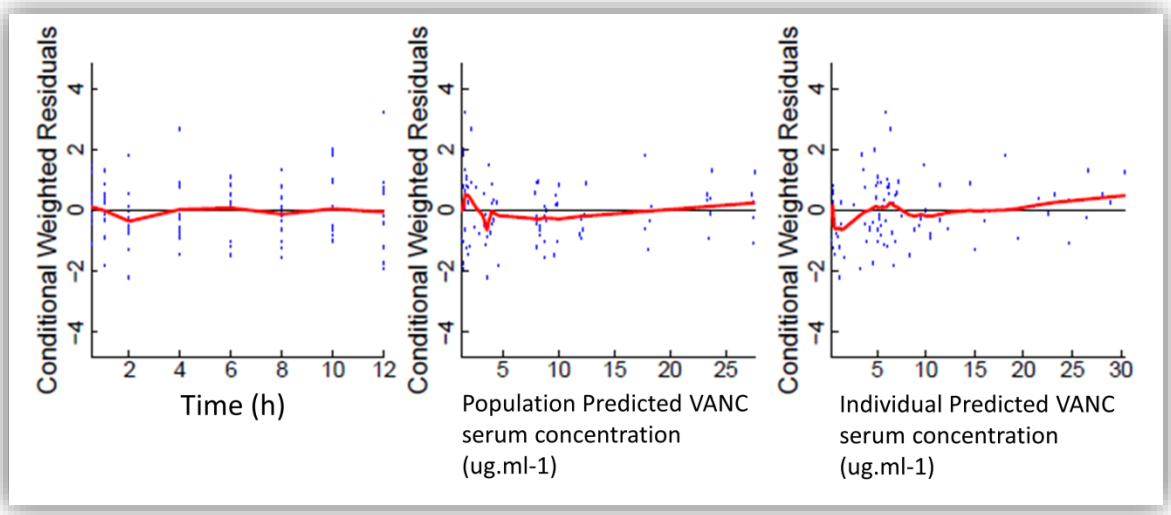

Figure suppl 2. Conditional Weighted Residual (CWRES) goodness of fit plots of the final two-compartment weight scaled allometric vancomycin pharmacokinetic model. Conditional Weighted Residual (CWRES) vs Time (left panel), Population predictions (middle panel) and Individual predictions (right panel) plots. Blue points represent the CWRES distribution. The red line is a super smoother. The horizontal black line at y=0 represents a perfect fit. In the 3 plots the CWRES are homogeneously distributed above and below the horizontal line at y=0.

Figure suppl 3 is a visual predictive check (VPC) plot, a modelling tool that estimates the concentration prediction intervals and graphically superimposes these intervals on observed concentrations after a standardized dose. This method was used to evaluate how well the model predicted the distribution of observed vancomycin concentrations. Simulation was performed using 1000 subjects with characteristics taken from studied patients. The VPC plot confirms the adequacy of model predictions, showing no apparent deviations between model and data.

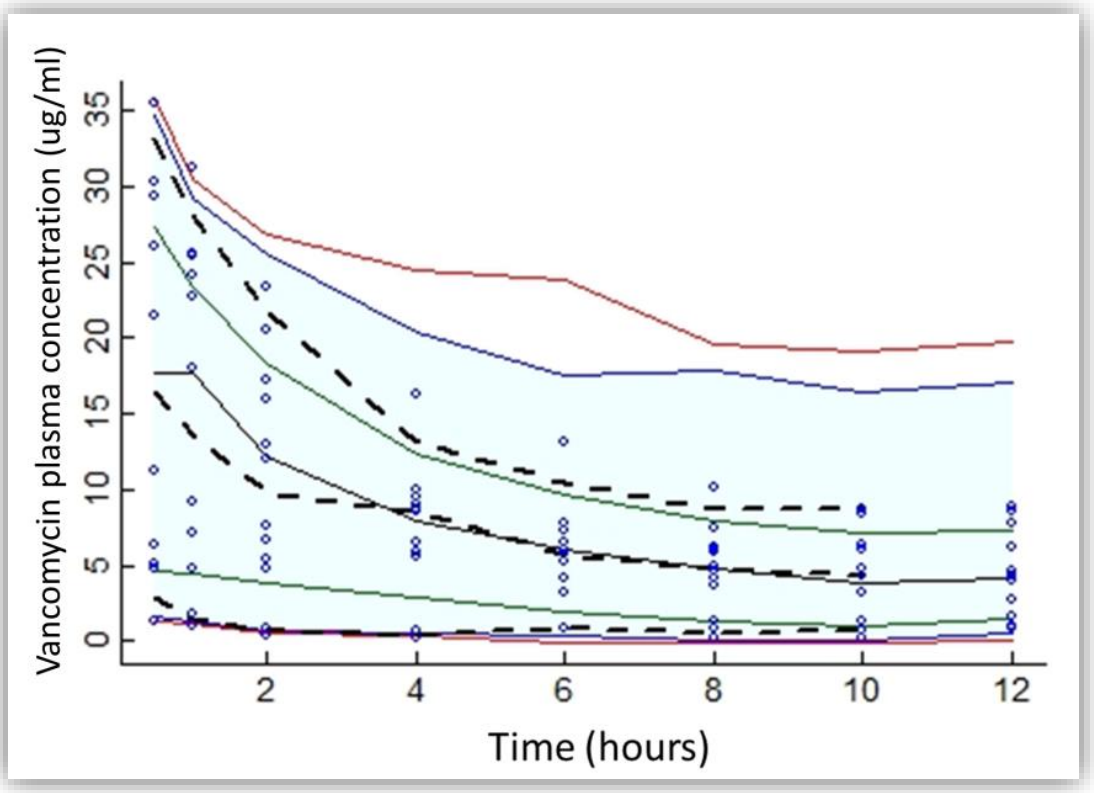

Figure suppl 3. Visual Predictive Check (VPC) plot. Solid lines indicate percentiles: 2.5, 97.5 (red); 5, 95 (blue); 25, 75 (green); 50 (black). Dashed lines indicate percentiles 5, 50, and 95 of observations. Shaded area indicates 90% prediction interval. Observed data lies within the model predicted intervals obtained by simulation.