Vancomycin IV – Pediatric (Smit) Model
Clinical Summary

Executive Summary

Dosing intravenous (IV) vancomycin in pediatric patients who are normal weight has been thoroughly investigated. However, there is limited data on how to adjust dosing in obese children and adolescents.[1,2]

As background, the published Vancomycin IV - Pediatric (Lamarre) model[3] has been available in DoseMeRx since 2014 and is still available for use. This new Vancomycin IV - Pediatric (Smit) model characterizes pharmacokinetics of vancomycin in a large, multicenter clinical population of normal weight, overweight and obese children, and adolescent with varying renal function.

To change your default model for pediatric dosing to the Vancomycin IV - Pediatric (Smit) model, contact our support team via live chat or send an email with your request to support@doseme-rx.com.

Key Points About the Vancomycin IV - Pediatric (Smit) Model

- This two-compartment model was developed and validated using a data set of 5,542 blood samples from 1,344 normal weight, 247 overweight and 301 obese pediatric patients with diverse ethnic backgrounds
- Patients admitted to ICU (35%) as well as patients with neutropenia (17%) were included in the model sample
- In this model, creatinine clearance as estimated using the bedside Schwartz equation as well as total body weight (TBW) best described vancomycin clearance. In addition, TBW was the most significant covariate for central and peripheral volume of distribution and intercompartmental clearance
- When compared to the commonly referenced Lamarre model, the Smit et al. model demonstrated considerably lower bias and higher overall precision and accuracy
- As part of external validation, predicted blood plasma concentrations as well as dosing recommendations produced by DoseMeRx have been validated using the FDA-recognized standard pharmacokinetics software package (NONMEM 7.4)

DoseMeRx Vancomycin IV - Pediatric (Smit) Model Overview

This two-compartment model was developed and validated using a data set of 5,542 blood samples from 1,344 normal weight, 247 overweight and 301 obese pediatric patients with diverse ethnic backgrounds from 21 hospitals of the Utah, USA-based HMO Intermountain Healthcare organization between 2006 and 2012.

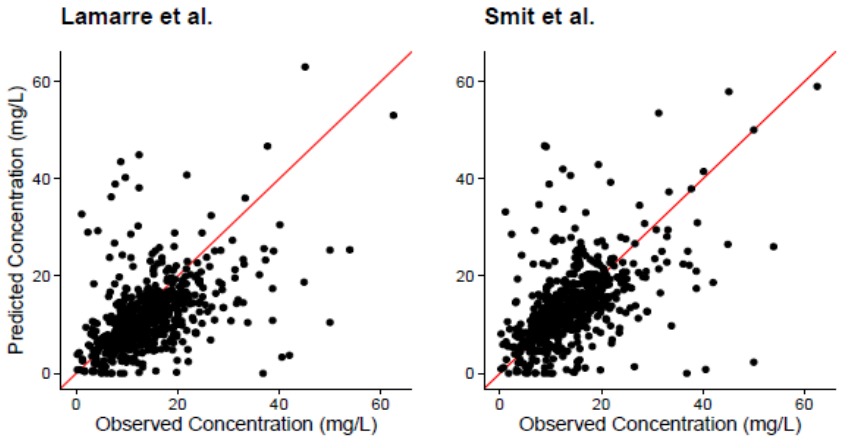
Individuals were categorized as begin normal weight, overweight, or obese according to the WHO and CDC growth charts, where overweight and obesity were defined as >85th percentile or >95th percentile of the BMI (corrected for age and sex) growth charts of the WHO for age 1–2 years, and CDC for 2–18 years. There was a broad range in ClCr (bedside Schwartz equation) with values as low as 8.6mL/min/1.73 m^2. [4,5]

Side by Side Comparison of the Smit and Lamarre Pediatric Models

	Smit et al.	Lamarre et al.
Year of publication	2021	2000
Vancomycin levels	N=5524	N= 256
Patients	N=1982	N=78
ICU	N=670	N.A.
Neutropenic	N=316	N.A.
Age	1 - 18 years	0.01 - 18 years
Weight	5.8 - 188 kg	0.96 – 74 kg
Overweight	N=247	N.A.
Obese	N=301	N.A.
ClCr Estimation Method	bedside Schwartz	Schwartz
Covariates	ClCr, Weight	ClCr, Weight
Number of random effects	2	4
Number of compartments	2	2

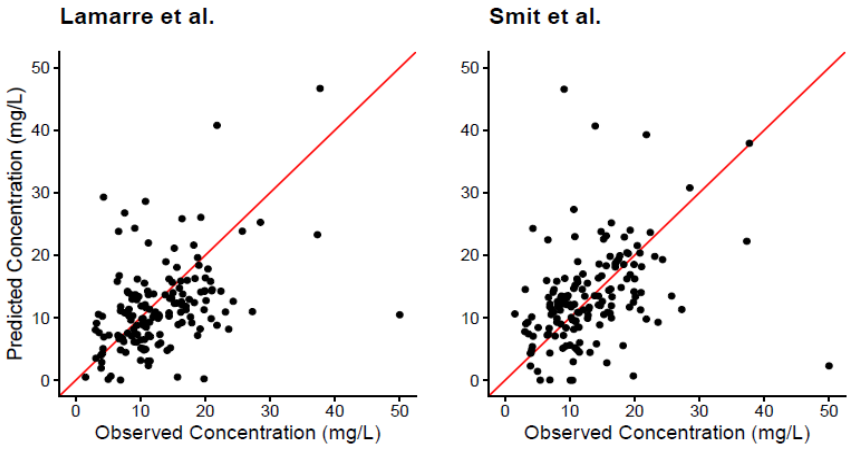
As part of our review, we further evaluated using a data set of routine clinical data from 308 pediatric patients, of which 73 were patients aged below one year. Bias, accuracy, and precision were numerically evaluated. Non-parametric bootstrap was used to calculate 95% confidence intervals. The two models exhibited similar precision and accuracy in all cohorts.

Observed versus Individualized Predicted Concentrations *(All Patients)*



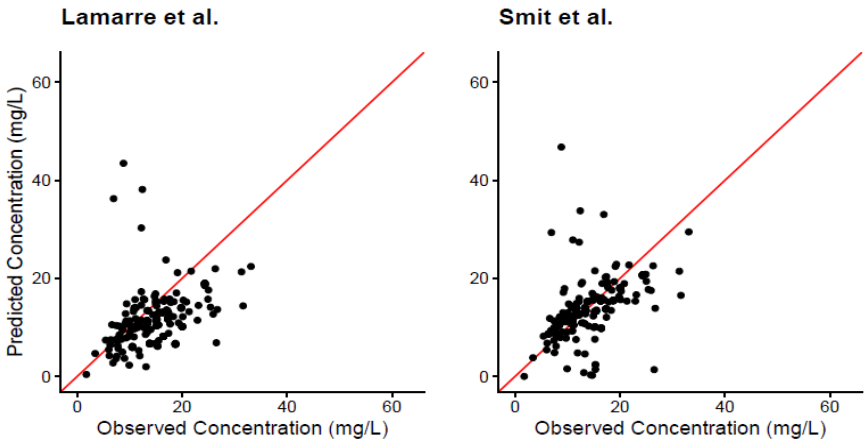
Predicted concentrations by the Lamarre et al. model exhibited a negative bias. No bias was observed for the Smit et al. model. The Smit et al. model has better overall predictive ability and exhibited better performance (lower mean absolute error, MAE) for 155 patients, while the Lamarre et al. had better performance for 137 patients. The two models performed equally well (within MAE tolerance of 0.1 mg/L) in 16 patients.

Observed versus Individualized Predicted Concentrations *(Infants)*



Bias, accuracy, and precision of the Lamarre at al. and the Smit et al. models in infant cohort were numerically evaluated. In infants, a negative bias in predicted concentrations by the Lamarre et al. model was also evident. No bias was observed for the Smit et al. model. The Smit et al. model had about the same predictive ability as the Lamarre et al. model. In infants, the Lamarre et al. model exhibited better performance (lower mean absolute error) for 43 patients, while the Smit at al. had better performance for 29 patients. The two models performed equally well (within MAE tolerance of 0.1 mg/L) in one patient.

Observed versus Individualized Predicted Concentrations *(Overweight and Obese)*



Predicted concentrations by the Lamarre et al. model were negatively biased, while no such bias was observed for the Smit et al. model. Moreover, the Smit et al. model demonstrated a considerably better predictive ability in this cohort. In overweight and obese pediatric patients, the Smit et al. model exhibited better performance (lower mean absolute error) for 82 patients, while the Lamarre et al. model performed better in 55 patients. The two models performed equally well (within MAE tolerance of 0.1 mg/L) in 11 patients.

In conclusion, the two models perform equally well overall. Both exhibited similar precision and accuracy in all cohorts. The Smit et. al model performed better overall in 53% of *all* patients as well as 54% of overweight and obese patients, while the Lamarre et al. model performed better in 60% of infants.

Frequently Asked Questions

How was the DoseMeRx Vancomycin IV - Pediatric (Smit) Model validated for use?

This model has been independently reviewed by an external firm comprised of experts in drug development, clinical pharmacology, and pharmacometrics. The validation process utilized for this model follows the same rigorous scientific process that we have used to validate every drug model in DoseMeRx. Blood plasma concentration and dosing recommendations are simulated in DoseMeRx, and the results are validated in NONMEM, the FDA-recognized standard pharmacometrics software package.

Are the patient limits for the Smit et al. model different from the Lamarre et al. model in DoseMeRx?

Yes. Lamarre et al. weight range is 1-100kg and Smit et al. weight range is 1-340kg. Both models are applicable for the same age range of 0-18 years and height of 40-220 cm.

How do I determine which pediatric model to utilize for my patient?

It is up to the clinician to use their clinical judgement to make that assessment. The clinician should take into consideration their patient characteristics, similarities to the population model and clinical status to determine which model is most appropriate for their patients.

Where can I review a full copy of the model?

A full description of the model can be found within DoseMeRx in the Drug Information section or by contacting support@doseme-rx.com.

References:

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4. Smit, Cornelis, Sebastiaan C. Goulooze, Roger J. M. Brüggemann, Catherine M. Sherwin, and Catherijne A. J. Knibbe. 2021. "Dosing Recommendations for Vancomycin in Children and Adolescents with Varying Levels of Obesity and Renal Dysfunction: A Population Pharmacokinetic Study in 1892 Children Aged 1 Years." *The AAPS Journal* 23 (3): 53. https://doi.org/10.1208/s12248-021-00577-x
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