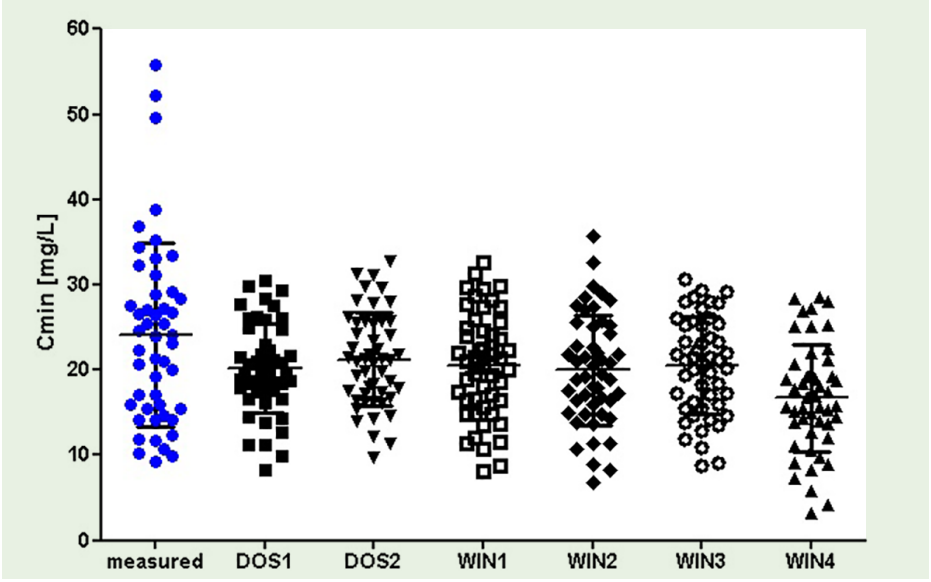
Fig. 1. *Vancomycin concentration measured and predicted by models*



Tab. 2. *Pharmacokinetic parameters of vancomycin. k_{12}, k_{21} – rate constants, k_{elm} – elimination rate constant non-renal, k_{elr} – elimination rate constant renal, V1 – volume of distribution related to lean body mass, fr – renal fraction. Individualized data presented as mean ± standard deviation. ‡ P < 0.0001, ‖ P < 0.01, § P < 0.05 compared to population data; † P < 0.0001, * P < 0.05 compared to DOS1*

	V1	k_{12}	k_{21}	k_{elr}	fr	Cl_m	k_{elm}
population							
DOS1	0.17	0.92	0.46	0.0037			
DOS2	0.21	1.12	0.48		0.75	0.21	
WIN1	0.21	1.12	0.48	0.00327			0.0143
WIN2	0.21				0.75	0.21	
WIN3	0.21	1.12	0.48		0.75	0.21	
WIN4	0.39				0.79		
fitted							
DOS1	0.20 ± 0.03‡	0.99 ± 0.08‡	0.39 ± 0.14‖	0.004 ± 0.0007			
DOS2	0.31 ± 0.40	1.18 ± 0.17§,†	0.40 ± 0.11‡		0.84 ± 0.31		
WIN1	0.24 ± 0.03‡,†	1.27 ± 0.22‡,†	0.43 ± 0.06*,†	0.004 ± 0.001‖			
WIN2	0.22 ± 0.02‡,†				0.69 ± 0.47		
WIN3	0.23 ± 0.03‡,†	1.25 ± 0.18‡,†	0.44 ± 0.06‖,†		0.85 ± 0.33*		
WIN4	0.46 ± 0.20‡,*				0.72 ± 0.40		

Tab. 3. *Vancomycin serum levels (VCM), % prediction error (%PE), RMSE, Bland-Altman bias – comparison to measured values. Data presented as mean ± SD. ‡P < 0.0001, **P < 0.005, *P < 0.05 compared to measured; †P < 0.0001 compared to DOS1*

	VCM concentration [mg/L]	%PE [%]	RMSE [%]	Bland-Altman bias ± SD (95% limits of agreement)
measured	24.1 ± 10.8			
DOS1	20.2 ± 5.3**	–5.7 ± 34.5	35	3.96 ± 9.15 (–14.0–21.9)
DOS2	21.2 ± 5.5*	–3.2 ± 33.0	33	3.29 ± 8.74 (–13,8–20.4)
WIN1	20.6 ± 6.2*	–4.4 ± 36.4	36	3.55 ± 9.17 (–15.0–22.1)
WIN2	20.0 ± 6.4**	–7.4 ± 36.7	37	4.09 ± 9.10 (–13.7–21.9)
WIN3	20.5 ± 5.7*	–4.5 ± 36.2	36	3.64 ± 9.22 (–14.4–21.7)
WIN4	16.7 ± 6.3‡†	–20.8 ± 39.4†	44	7.41 ± 11.44 (–15.0–29.8)

Tab. 4. *Vancomycin serum levels (VCM), % prediction error (%PE), RMSE, Bland-Altman bias – comparison to DOS1 model. Data presented as mean ± SD*

	%PE [%]	RMSE [%]	Bland-Altman bias ± SD (95% limits of agreement)
DOS2	4.1 ± 13.9	14	–0.66 ± 2.48 (–5.5–4.2)
WIN	–16.8 ± 24.9	30	3.44 ± 5.06 (–6.5–13.4)
WIN1	1.7 ± 15.2	15	–0.42 ± 2.75 (–5.8–5.0)
WIN2	–1.4 ± 15.8	16	0.13 ± 3.03 (–5.8–6.1)
WIN3	1.7 ± 12.7	13	–0.33 ± 2.31 (–4.8–4.2)

The best outcomes in terms of %PE, RMSE, Bland-Altman bias as well as Pearson's R were obtained with the DOS2 model. WIN1 produced the lowest %PE and Bland-Altman bias (Table 3, Fig. 2) among the WIN models, but the correlation (Pearson's R) between the predicted and measured vancomycin values was less tight (Fig. 3). RMSE was the same while %PE and Bland-Altman bias were almost the same in the WIN3 model, with a slightly better correlation than the WIN1 model.

Comparison of pharmacokinetics parameters

The DOS2 and WIN1–3 models use the same population-based pharmacokinetics parameters (Table 2). The DOS1 model uses lower V1 and both rate constants, whereas the one-compartment WIN4 model uses higher V1 and renal fraction.

When compared to population-based data, all two-compartment models used higher V1, rate constant k_{12}, and fr, with the exception of fr in WIN2, while k_{21} was slightly lower. WIN4 used higher V1 and lower fr. WIN1–3 models used slightly higher V1 than DOS1, 0.22–0.24 vs. 0.20 L/kg LBMc, P < 0.0001. k_{12} was higher in WIN1 and WIN3 –1.27 and 1.25, respectively vs. 0.99, P < 0.0001. DOS2 used higher V1 and k_{12}, whereas its k_{21} was similar to DOS1 (Table 2).

Comparison to DOS1 model

All three two-compartment WIN models (WIN1-WIN3) produced similar %PE and RMSE when compared with the DOS1 model (Table 4). %PE and Bland-Altman bias were the lowest in the WIN2 model, whereas RMSE was the lowest and Pearson's R was the highest in the WIN3 model. %PE, Bland-Altman bias, and Pearson's R were higher, but RMSE was similar in the DOS2 model, compared to the WIN models. The one-compartment WIN4 model differed most from the DOS2 model. Bland-Altman plots for all model comparisons are shown in Fig. 4.

The Pearson's R between vancomycin concentrations predicted by the WIN and DOS models varied from 0.631 to 0.941, P < 0.0001 (Fig. 5).

The Pearson's R between %PE produced by DOS1 and those produced by other models varied from 0.830 to 0.930 (Fig. 6), P < 0.0001.