29th ECCMID Amsterdam, Netherlands 13–16 April 2019 | ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

Oral session PK/PD to guide dosing in special populations – presentation O1160 – 16 Apr 2019

Determination of optimal loading and maintenance doses for continuous infusion of vancomycin in critically ill patients: population pharmacokinetic modelling and simulation

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Amsterdam - 2019

Conflict of interest disclosure

☑ I have no Conflict of Interest to report.

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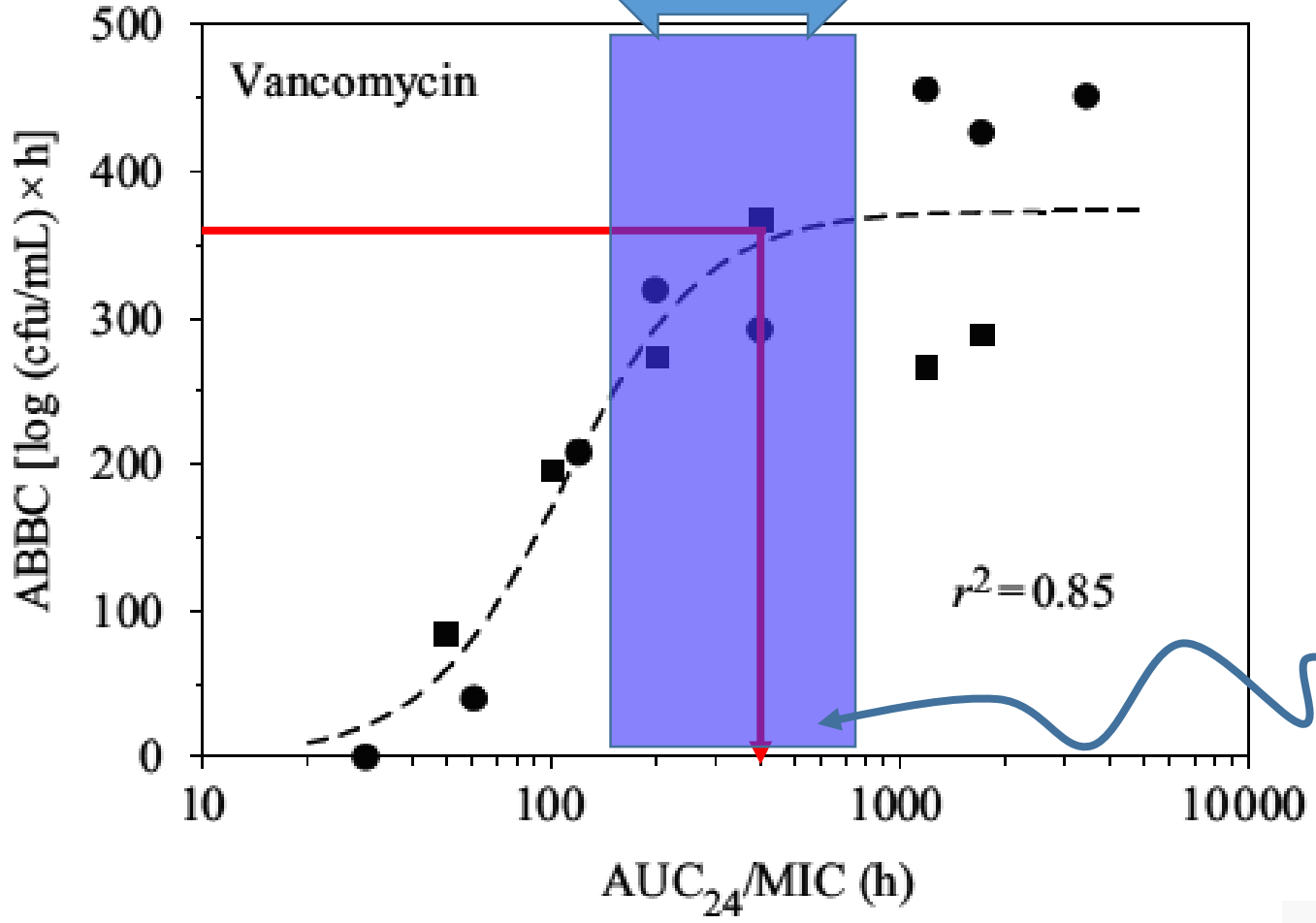
PK/PD of vancomycin

In vitro simulation for bactericidal effect of different AUC_{24}/MIC



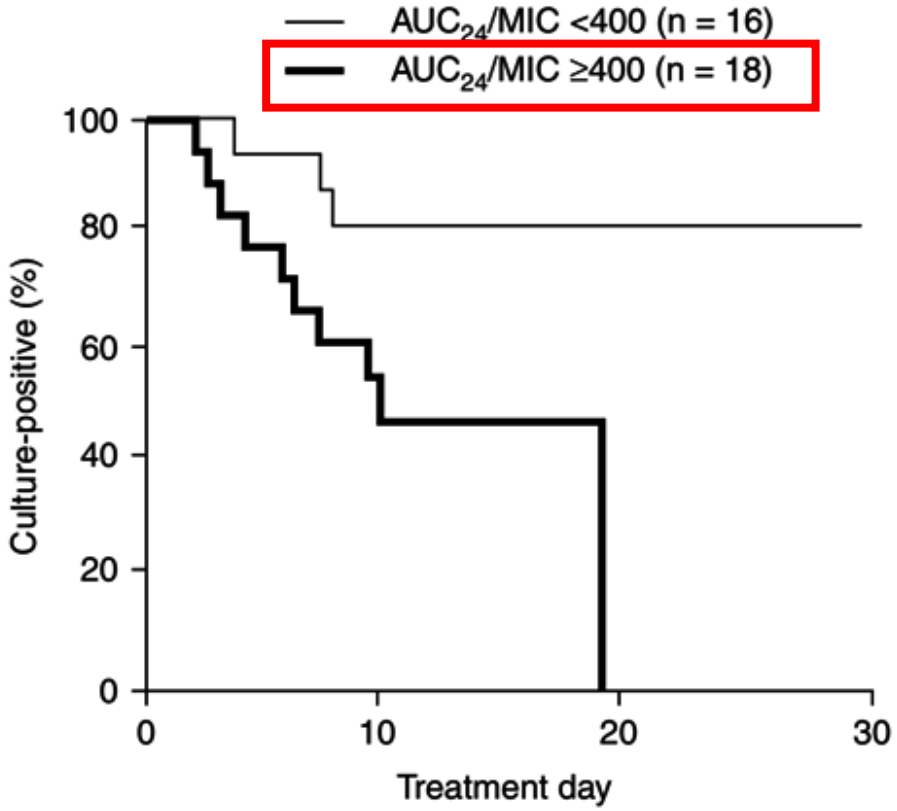
Patient variability:
160 - 783

Targeted $AUC_{0\text{-}24}$
400 for **MIC = 1**

Lubenko *et al.* J Antimicrob Chemother. 2008; 62:1065-9.

PK/PD of vancomycin

Bactericidal effect



Moise-Broder *et al.* Clin Pharmacokinet 2004; 43:925-942

Prevention of emergence of resistance

Table 3 Variables associated with emergence of hVISA in the multivariate analyses

	Variable	Relative Risk	95% confidence interval	*P-value*
Day 1	$AUC_{0\text{-}24h}/MIC_{BMD} \geq 521$	0.14	0.03–0.60	0.008
	CL_{CR}	0.93	0.88–0.98	0.004
	Presence of IE	4.94	1.67–14.68	0.004
	Skin and soft tissue source	4.89	1.43–16.71	0.01
Day 2	$AUC_{24\text{-}48h}/MIC_{BMD} \geq 650$	0.16	0.02–1.28	0.08
	CL_{CR}	0.95	0.91–0.98	0.007
	Presence of IE	4.62	1.67–12.77	0.003

Martirosov *et al.* BMC Infect Dis 2017; 17:554

- AUC/MIC > 400: microbiological response
- AUC/MIC of 500-600: prevent the emergence of resistance.
- Targeted AUC of 400 – 600 for *S. aureus* of MIC≤1.

Vancomycin continuous infusion in critically-ill patients

VAN continuous infusion (1 compartment modeling)

1. a loading dose of 35 mg/kg was suggested

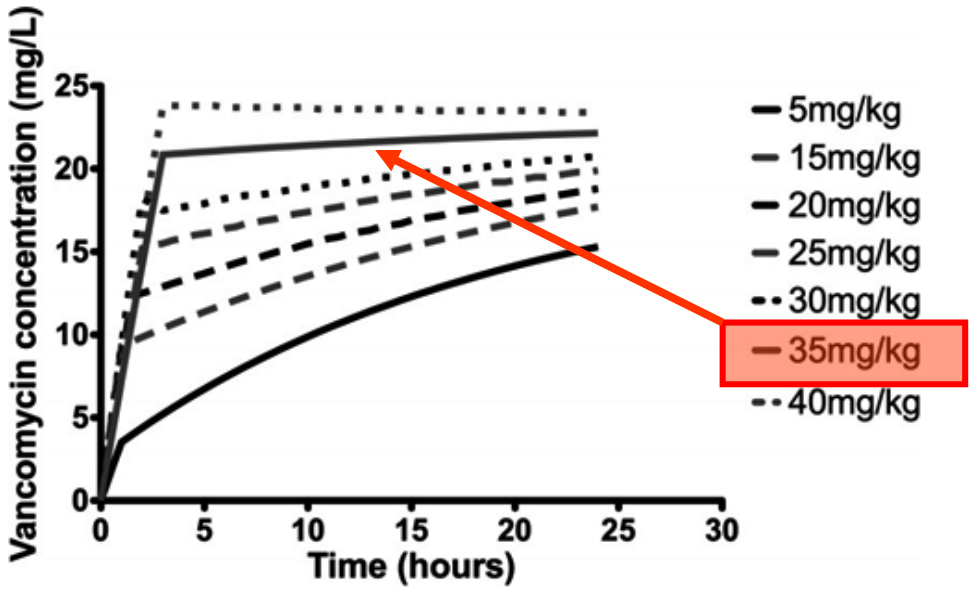


FIG. 2. The effect of loading dose on rapid attainment of target vancomycin concentrations. Different weight-based doses are simulated for a critically ill patient with a creatinine clearance of 100 ml/min/1.73 m^2, followed by administration as a 35-mg/kg/day continuous infusion.

Roberts *et al.* Antimicrob Agents Chemother 2011; 55:2704-9

2. the maintenance dose was adjusted based on CrCl

TABLE 1 Initial daily doses of vancomycin according to estimated creatinine clearance

CG-CrCL[a] (ml/min)	Daily dose (mg/kg)
>150	45
120–150	40
80–119	30
50–69	25
25–50	14
<25 (anuria)	7

[a] Creatinine clearance, estimated using the Cockcroft-Gault formula.

Cristallini *et al.* Antimicrob Agents Chemother 2016;60:4750-6.

Vancomycin continuous infusion in critically-ill patients

High loading dose (35mg/kg/3h): Enough maintenance dose?

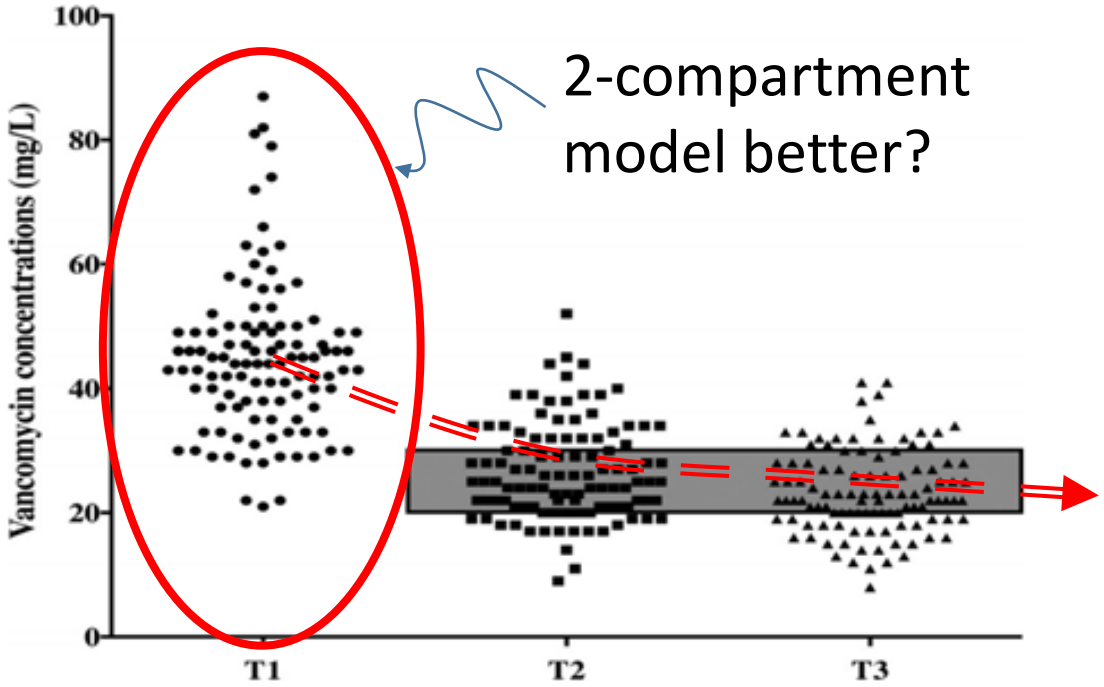
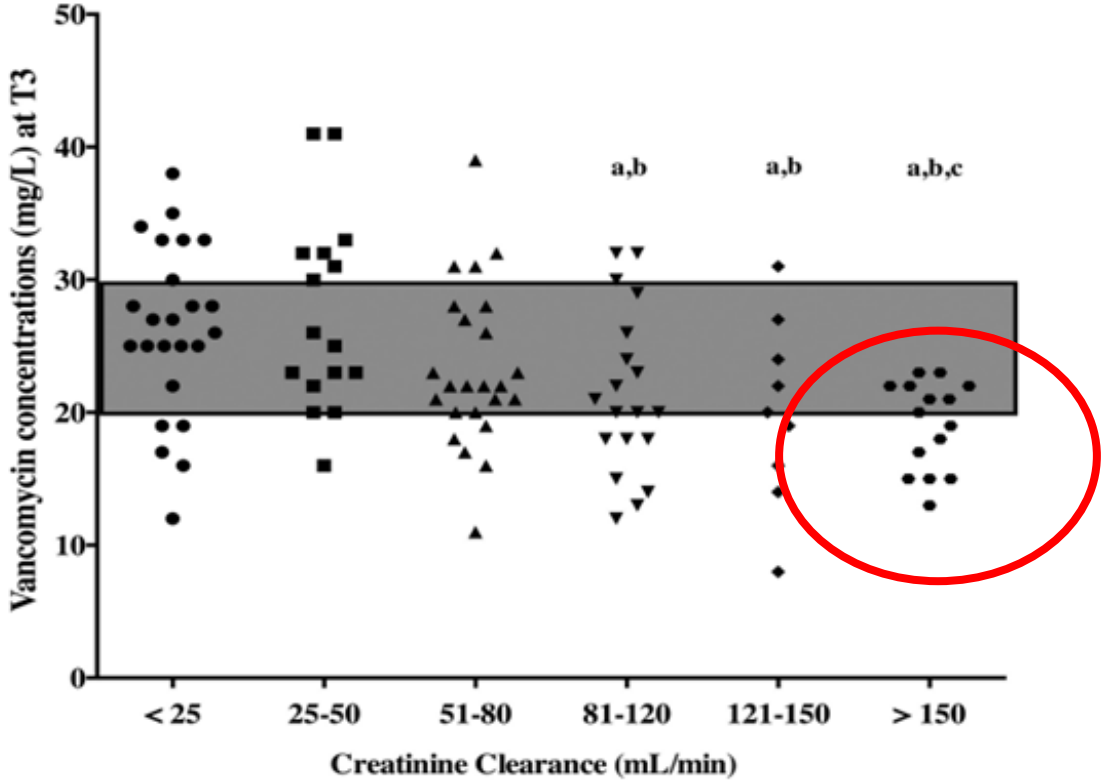


FIG 1 Distribution of vancomycin concentrations at the end of the loading dose (T1), at 12 h (T2), and at 24 h after the onset of therapy (T3). The shaded zone indicates target drug concentrations, assessed at T2 and T3.

Cristallini *et al.* Antimicrob Agents Chemother 2016;60:4750-6.

What about patients with Augmented Renal Clearance (ARC) ?



→ What should be the optimal loading dose and maintenance dose?

Methods

TDM protocol for VAN continuous infusion in Bach Mai hospital

Loading dose (weight based [20 mg/kg])

ABW (kg)	LD (g)	Infusion intruction:
< 40	0.75	LD ≤ 1g diluted in 250ml of solvent then infused over 60 mins.
40 – 65	1.0	
66 – 90	1.5	LD from 1 to 1.5g diluted in 250ml solven then infused over 90 mins.
> 90	2.0	LD > 1.5g diluted in 500ml solven then infused over 120 mins.

Maintenance dose (eGFR based)

eGFR (ml/min)	Infusion rate (mg/h)
<10	12
10 – 20	20
21 – 30	32
31 – 45	40
46 – 60	64
61 – 85	84
86 – 110	104
>110	124

Dose adjustment (concentration)

Vancomycin concentration (mg/L)	Dose adjustment
0 – 5	Add a loading dose (20 mg/kg) and increase infusion rate (+ 20 mL/h or + 60mg/h)
6 – 10	Add a loading dose (15 mg/kg) and increase infusion rate (+ 15 mL/h or + 45mg/h)
11 – 15	Add a loading dose (10 mg/kg) and increase infusion rate (+ 10 mL/h or + 30mg/h)
16 – 19	Increase infusion rate (+ 5 mL/h or + 15 mg/h)
20 – 30	No change
31 – 35	Reduce infusion rate (- 5 mL/h or -15mg/h)
> 35	Stop infusion for 6h and reduce infusion rate (- 10 mL/h or -30mg/h)

Retrospective data collection.

- Inclusion: VAN continuous infusion, ≥ 1 VAN measurement.
- Exclusion: < 18 y, used intermittent infusion within 48h, Renal Replacement Therapy.

Methods

Retrospective data

+ Patient medical records and TDM form
+ TDM data (loading and maintenance dose, VAN conc., dose adjustment…)

Pop PK Modelling

+ Nonlinear mixed effect model
+ NONMEM (Perl-speaks-NONMEM (PsN) tool kit and Xpose (Version 4)

Simulation

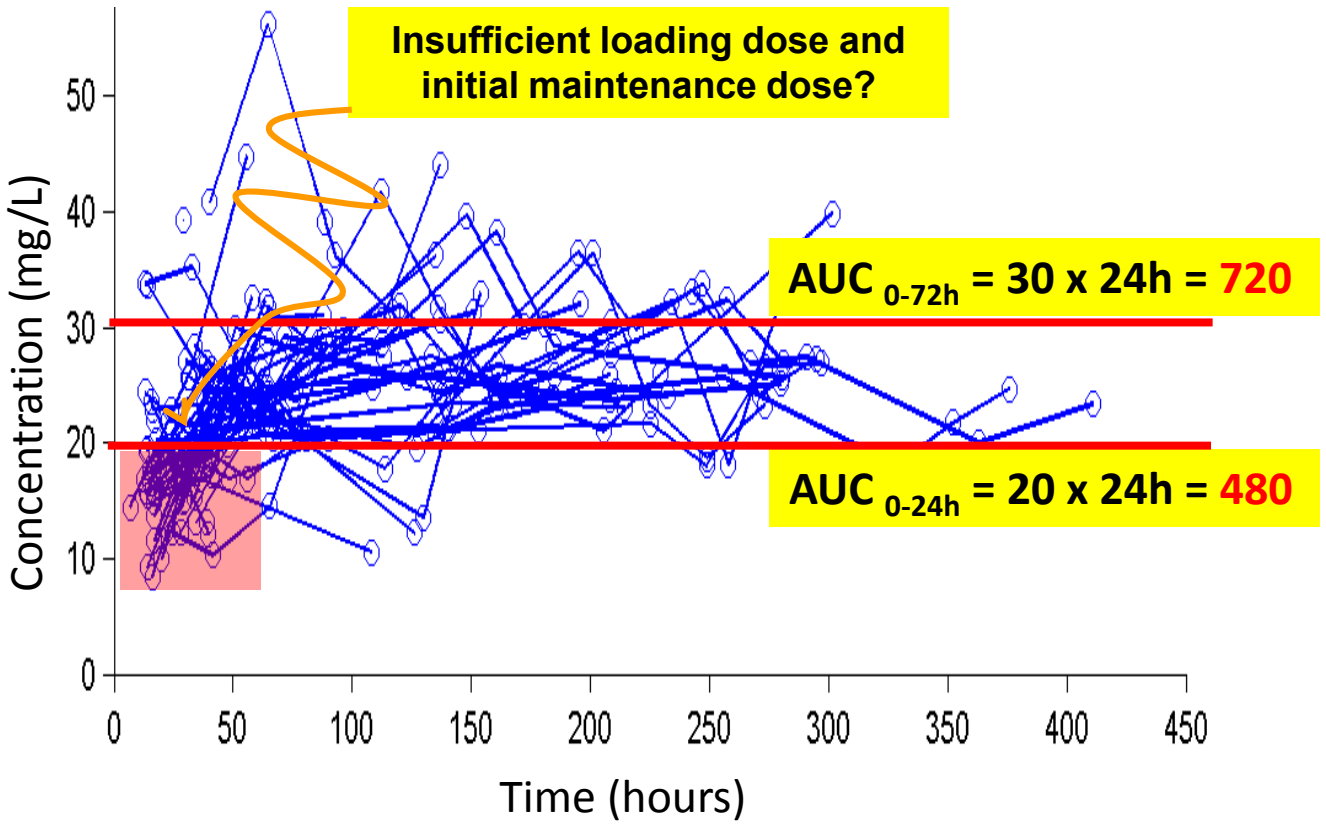
+ Target conc. 20-30 mg/L
+ Simulation 1: Loading dose: 10 mg/kg to 40 mg/kg.
  % Patients reaching target after loading dose.
+ Simulation 2: Maintenance dose: 0.3 to 4.5 g/24h; Clcr: 10 – 240 ml/min.
  % Patients reaching target at 24 hours after loading and maintenance dose.

Patient characteristics

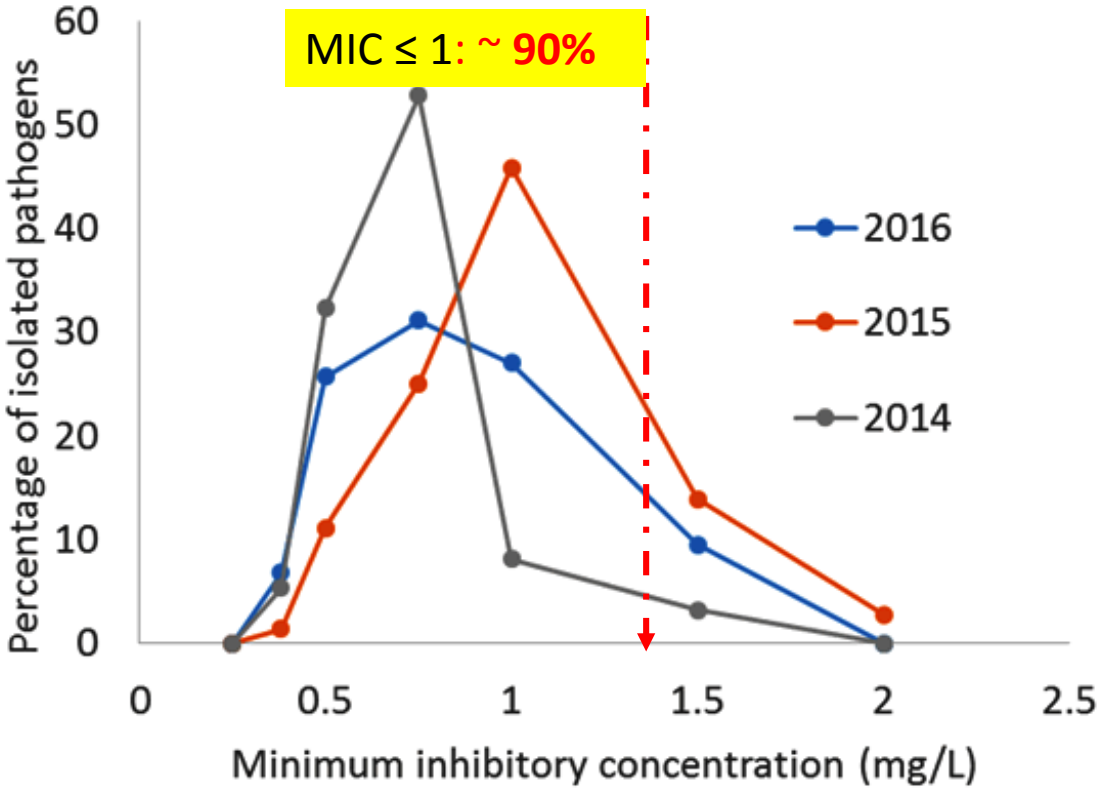
Information	Results (n = 55)
Demographic data	
Sex (male)	36 (65.5)
Age (years)	55 ± 18
Actual body weight (kg)	55.9 ± 11.1
Clinical characteristics (at start of VAN)	
APACHE II score	14 [8 – 19]
SOFA score	4 [3 – 6]
CHALSON comorbidity index	1 [1 – 3]
Mechanical ventilation	36 (65.5)
Vasopressor	6 (10.9)
Septic shock	4 (7.3)
Baseline Clcr (mL/min)	76.5 ± 36.4
Co-administered nephrotoxicity agents	
Furosemide	31 (56.4)
NSAIDs	9 (16.4)
ACEI/ARB	5 (9.1)

Data presented as n (%), median [interquartile range] or mean ± standard deviation when applicable

Was VAN concentration reaching the PK/PD target ?



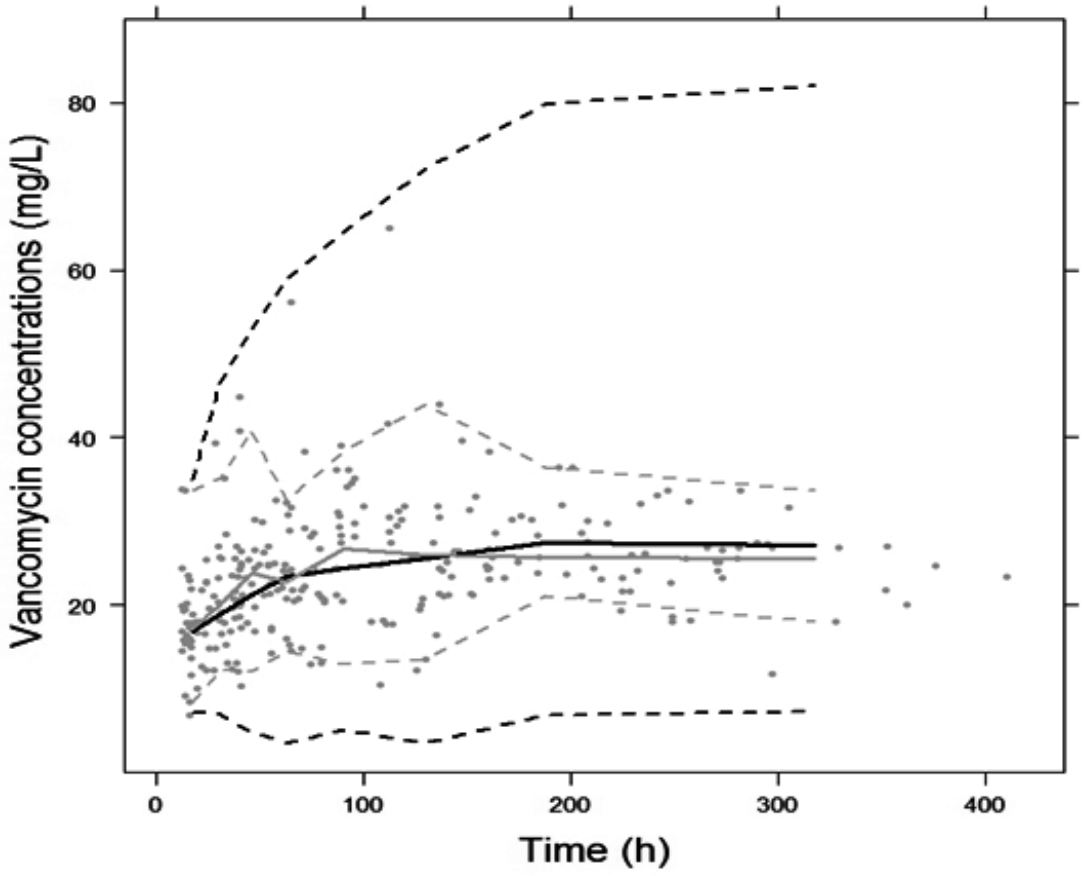
MICs of vancomycin on *S. aureus* in our hospital



- Loading AND/OR maintenance dose(s) seem too low (see left)
- High concentration variability ! (see left)
- Targeting 20-30 mg/L will cover a large proportion of *S.aureus* isolated *d*uring the three previous years (see right)

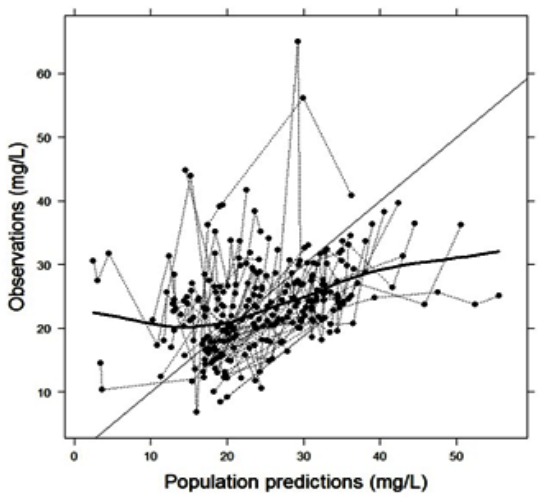
PopPK modelling

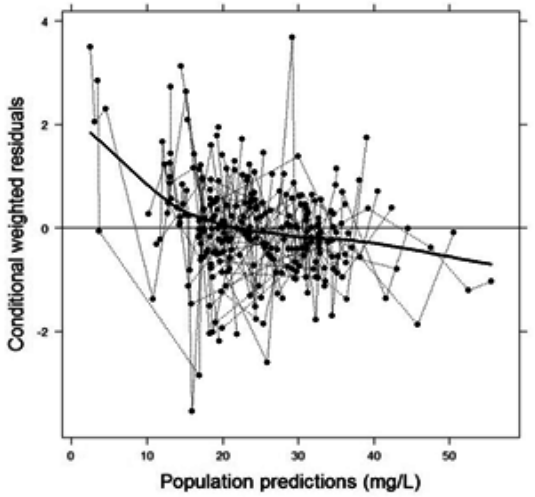
Visual predictive check plot

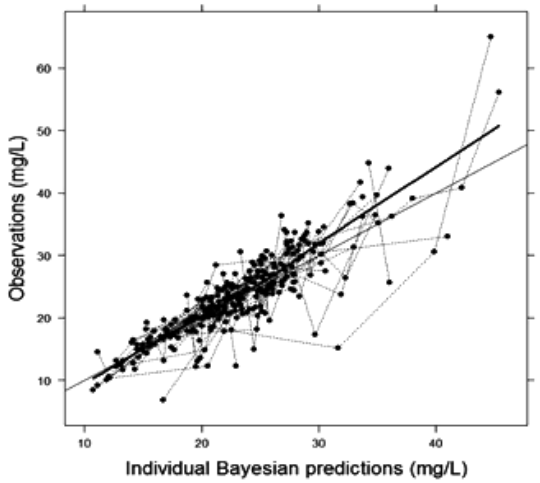


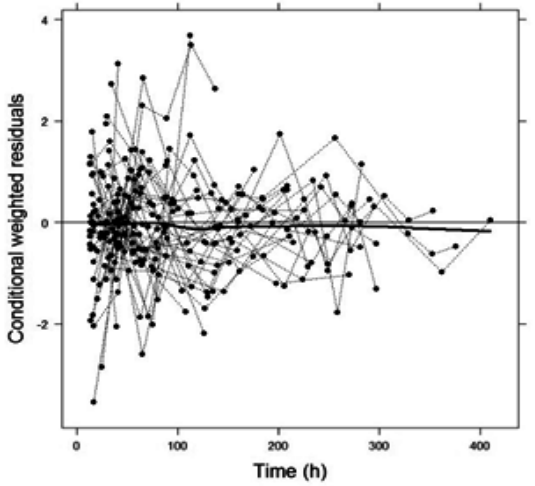
Modelling: **Two compartments** structure model and **proportional error** model fits data best

Basic goodness-of-fit plots









Pop PK estimation

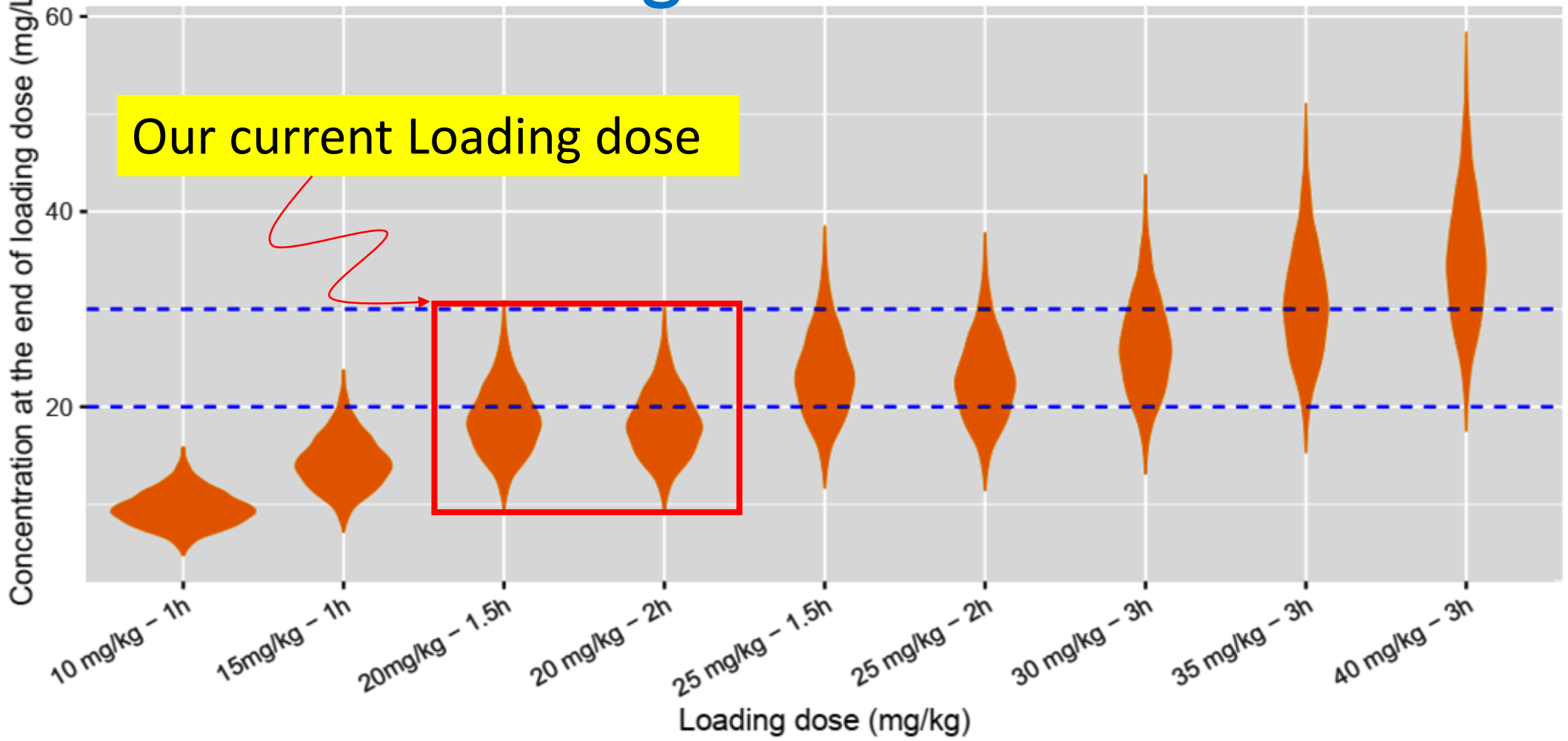
Current TDM protocol using Vd **40 L**

Parameter	Unit	Final model Estimate (RSE)	Bootstrap (n=1000) Median (2.5th–97.5th pc)
Pharmacokinetic parameter			
V1	L	71.8 (15.0%)	77.9 (55.9–97.9)
V2	L	167 (23.2%)	183 (88.3–949)
Q	L/h	1.92 (26.6%)	1.90 (0.96–3.41)
CL	L/h	3.63 (10.8%)	3.51 (2.14–4.33)
Covariate			
$P_{CLcr-CL}$		1.01 (18.3%)	1.06 (0.65–1.97)
Interindividual variability			
V1 (CV)	%	30.2 (41.2%)	27.6 (8.09–47.6)
V2 (CV)	%	62.0 (56.6%)	65.0 (17.8–203)
Q (CV)	%	107 (38.2%)	104 (36.3–153)
CL (CV)	%	53.1 (48.9%)	50.9 (28.7–80.8)
Residual variability			
ε_{prop} (CV)	%	41.4 (8.25%)	41.4 (38.3–45.3)
OFV		1250	1239

- **V1**, **V2**: central and peripheral compartment volume of distribution;
- **Q**: inter-compartment clearance;
- **CL**: total body clearance;
- **$P_{CLcr-CL}$**: fractional change on CL due to CLcr;
- **OFV**: objective function value

CL_{cr} is a significant covariate for CL

Simulation of the loading dose



Conc. (mg/L)	Percentage of patients								
>30	0	0	2	1	7.9	6.2	22.5	52.4	76.5
20-30	0	2.8	33.3	29.5	68.5	66.8	68.7	45.8	23.0
<20	100	97.2	66.5	70.4	23.6	27.0	8.8	1.8	5

Simulation of the maintenance dose for a given loading dose (*)

Percentage of simulated patient reaching target concentration range at 24h post dose

	Maintenance dose (mg/day)										
CLcr (mL/min)	**300**	**500**	**750**	**1000**	**1500**	**2000**	**2500**	**3000**	**3500**	**4000**	**4500**
<10	16.0%			74.1%	37.5%	11.3%					
10-20	4.7%	22.4%		74.8%	54.5%	19.4%	4.4%				
21-30		8.2%	34.5%		69.1%	31.3%	8.9%	2.5%			
31-45			13.3%	41.2%	77.4%	50.6%	19.4%	4.9%	1.3%		
46-60				17.0%	68.5%	71.5%	36.9%	13.2%	3.3%	0.9%	
61-85					38.4%	77.0%	65.6%	32.7%	13.2%	3.9%	
86-110						51.1%	79.0%	65.3%	35.1%	14.7%	5.0%
111-130							63.5%	81.2%	63.1%	35.1%	15.2%
131-180							21.8%	59.1%	77.4%	71.0%	48.1%
181-240							0.9%	9.7%			79.1%

CLcr, creatinine clearance

* loading dose: 25 mg/kg/2h

Current maintenance dose

Best simulated result

Conclusions

- A two-compartment model fit data better.
- Larger loading (of 25-30 mg/kg) is needed, but not necessarily larger than that.
- Higher maintenance doses should be considered, especially for patients with high CLcr
- High PK variability suggests that TDM is still required.

THANK YOU!

The discussion is open…