

# Pediatric Assessment of Vancomycin Empiric Dosing 2 (PAVED2)

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## Background

- Vancomycin is commonly used as part of British Columbia Children's Hospital (BCCH)'s empiric regimen to treat severe infections caused by resistant organisms
- Trough concentrations of 10-20 mg/L are targeted to achieve an AUC:MIC  $\geq 400$  which has been associated with a higher likelihood of successful clinical outcomes
- Previous study, PAVED, found therapeutic concentrations of vancomycin are not achieved using BCCH's empiric dosing regimen (60 mg/kg/day divided q6h or q8h), and recommended an alternative dosing regimen<sup>1</sup>
- PAVED dosing regimen required validation to evaluate whether it would more reliably achieve target serum drug concentrations compared with BCCH's current regimen

## Objectives

- Primary:**
  - Describe the proportion of patients who would have reached initial trough concentrations of 10-15 or 15-20 mg/L using the new empiric dosing guidelines recommended by PAVED
- Secondary:**
  - Describe the pharmacokinetic parameters of each age group
  - Compare AUC:MIC calculated using patient-specific parameters with the Pai et al<sup>2</sup> method
  - Describe the concordance between trough concentrations and AUC:MICs

## Methods

- Design:** Retrospective chart review
- Institutional ethics board approval
- Population:** Patients who received vancomycin at BCCH between August 2012 - August 2014
- Inclusion:** >1 month post-natal age, two interpretable vancomycin serum concentrations
- Exclusion:** Extracorporeal life support, dialysis, cystic fibrosis
- Statistics:** Fisher's exact; Wilcoxon rank sum and signed rank;  $p < 0.05$  deemed statistically significant
- Sample size:** Based on 50% achieving target trough concentrations, absolute precision of 7%, 95% confidence interval, N = 196 patients

## Results

Table 1: Subject Demographics

	1 m.o.-1 y.o.	1-6 y.o.	6-13 y.o.	13-18 y.o.	Total
n	50	50	50	50	200
Age†, years	0.3 (0.3)	2.3 (2.2)	9.4 (4.4)	15.4 (2.3)	6.0 (11.9)
% male	66	46	52	64	57
Weight†, kg	6.4 (2.7)	13.0 (5.2)	41.0 (18.5)	54.1 (19.5)	19.8 (31.4)
SrCr†, umol/L	23 (9)	30 (14)	41 (19)	59 (19)	35 (29)
Dose†, mg/kg/day	59.8 (3.3)	60.0 (2.6)	60.0 (14.6)	59.2 (10.8)	60 (3.2)
<b>Dosing interval</b>					
q6h n (%)	33 (69)	32 (67)	34 (68)	27 (54)	126 (64)
q8h n (%)	15 (31)	16 (33)	16 (32)	23 (46)	70 (36)

† Median (IQR)

Figure 1: Targets Achieved Using Current Regimen

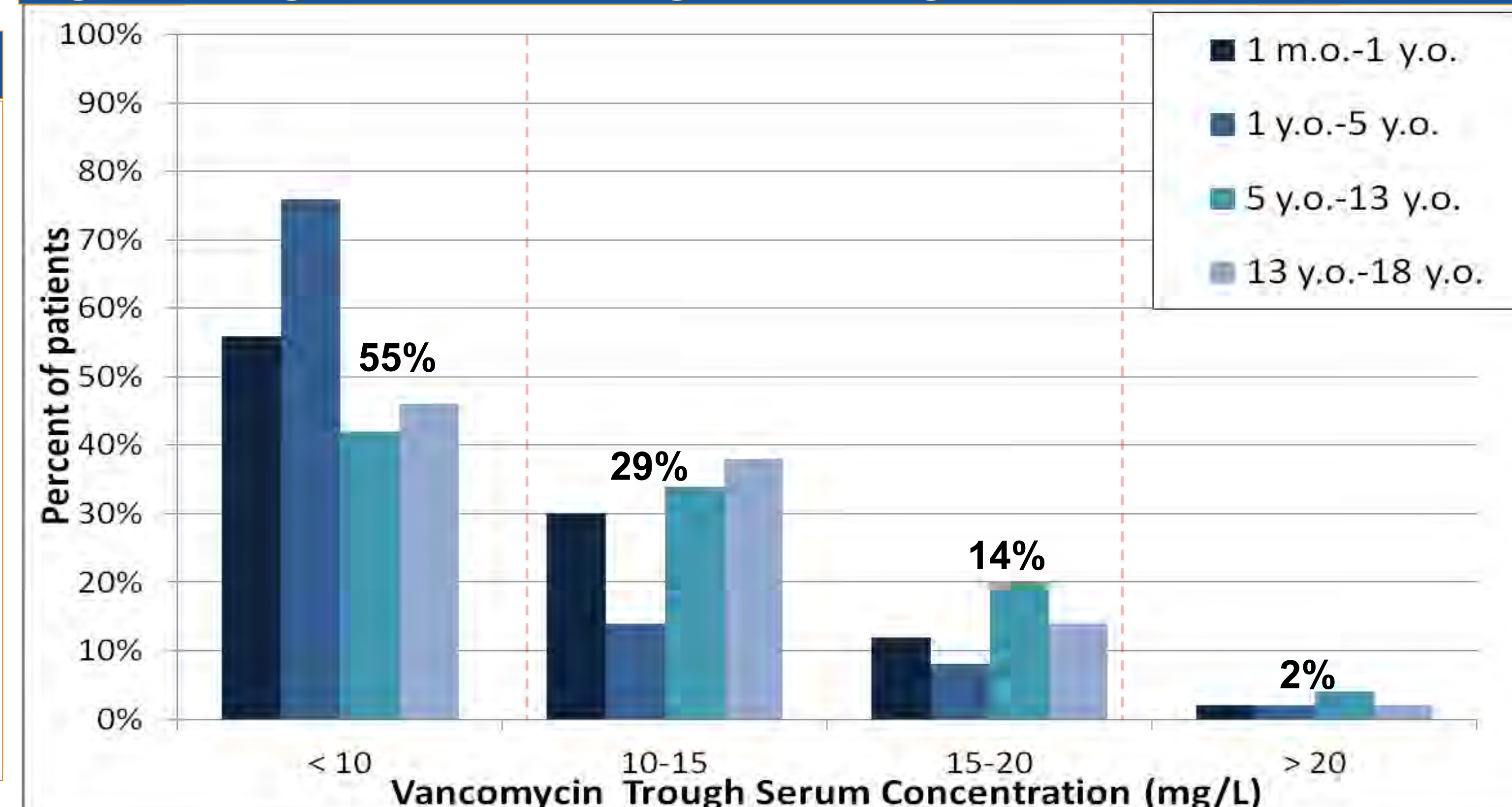


Figure 2: Targets Predicted Using PAVED Regimen

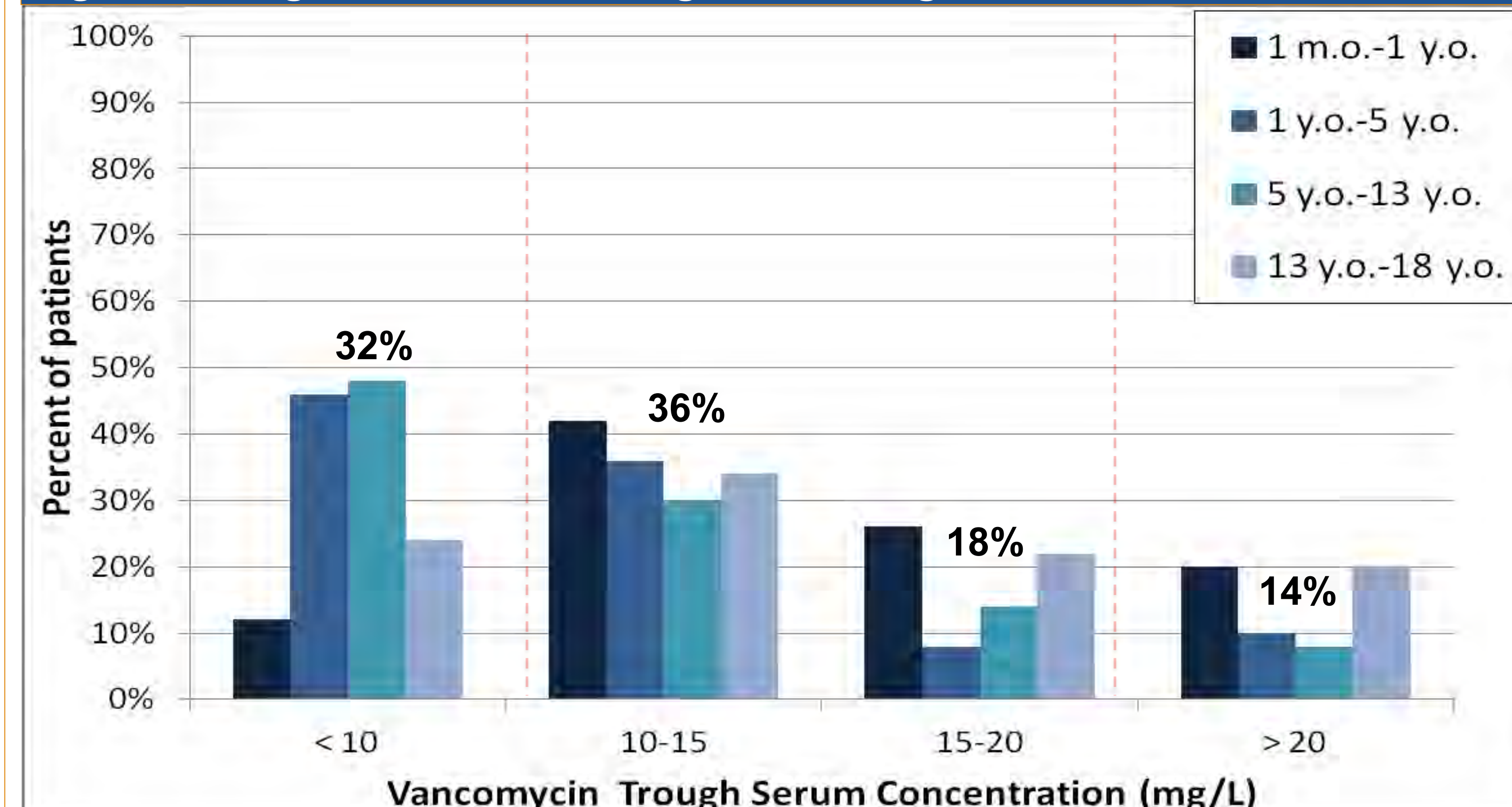


Table 2: Pharmacokinetic Parameters. (Median (IQR))

Age	1 m.o.-1 y.o.	1 y.o.-6 y.o.	6 y.o.-13 y.o.	13 y.o.-18 y.o.
$k_e$ (h <sup>-1</sup> )	0.24 (0.05)	0.26 (0.08)	0.26 (0.09)	0.23 (0.05)
$t_{1/2}$ (h)	2.9 (0.59)	2.7 (0.81)	2.7 (1.01)	2.98 (0.71)
Vd (L/kg)	0.57 (0.16)	0.64 (0.28)	0.49 (0.26)	0.45 (0.14)

Wilcoxon rank sum  $p < 0.05$  except  $t_{1/2}$  1<sup>st</sup> group vs. all, and 2<sup>nd</sup> vs. 3<sup>rd</sup> group

Table 3: Description of AUC and AUC:MIC Ratio

	1 m.o.-1 y.o.		1 y.o.-6 y.o.		6 y.o.-13 y.o.		13 y.o.-18 y.o.	
<b>AUC</b>								
	Patient	Pai	Patient	Pai	Patient	Pai	Patient	Pai
Median	453	418	369	343	540	496	502	459
IQR	173	154	170	157	307	282	223	208
<b>AUC:MIC Ratio</b>								
MIC 0.5	905	836	737	687	1081	992	1004	918
MIC 1	453	418	369	343	540	496	502	459
MIC 2	226	209	184	172	270	248	251	229

Wilcoxon signed rank  $p < 0.01$  for patient vs. Pai AUC in all groups

Table 4: Comparison of Trough Concentrations and AUC

Serum Concentration	Current Regimen		PAVED Regimen	
	AUC <400	AUC $\geq 400$	AUC <400	AUC $\geq 400$
<10 mg/L (n, %)	89 (73)	33 (27)	33 (50)	32 (49)
>10 mg/L (n, %)	1 (1)	77 (99)	1 (1)	134 (99)

Fisher's exact test  $p < 0.05$

## Conclusions

- PAVED regimen achieves higher trough concentrations and AUC:MIC values in a greater proportion of the population; however, there is a greater likelihood of reaching trough concentrations >20 mg/L
- A significant proportion of individuals who do not achieve therapeutic trough concentrations do achieve desired AUC  $\geq 400$
- In light of these data regarding this discordance between therapeutic trough concentrations and AUC values, pediatric target trough concentrations should be reassessed before implementing a new empiric regimen

## References

- Rainkie, D., Ensom, M. H. H., & Carr, R. Pediatric Assessment of Vancomycin Empiric Dosing (PAVED): a Retrospective Review. *Pediatric Drugs*, Mar 27, 2015 [Epub ahead of print] doi: 10.1007/s40272-015-0122-8
- Pai, M. P., Neely, M., Rodvold, K. A., & Lodise, T. P. Innovative Approaches to Optimizing the Delivery of Vancomycin in Individual Patients. *Advanced drug delivery reviews*, 2014; 77, 50-57.