

Introduction

Local population pharmacokinetic (popPK) model development

- Ensures the model accurately reflects the target population ✓
- Often only small datasets are available in vulnerable populations ✗

External evaluation of published models

- More practical, even with as few as 12 patients¹ ✓
- Predictive performance can often be suboptimal² ✗

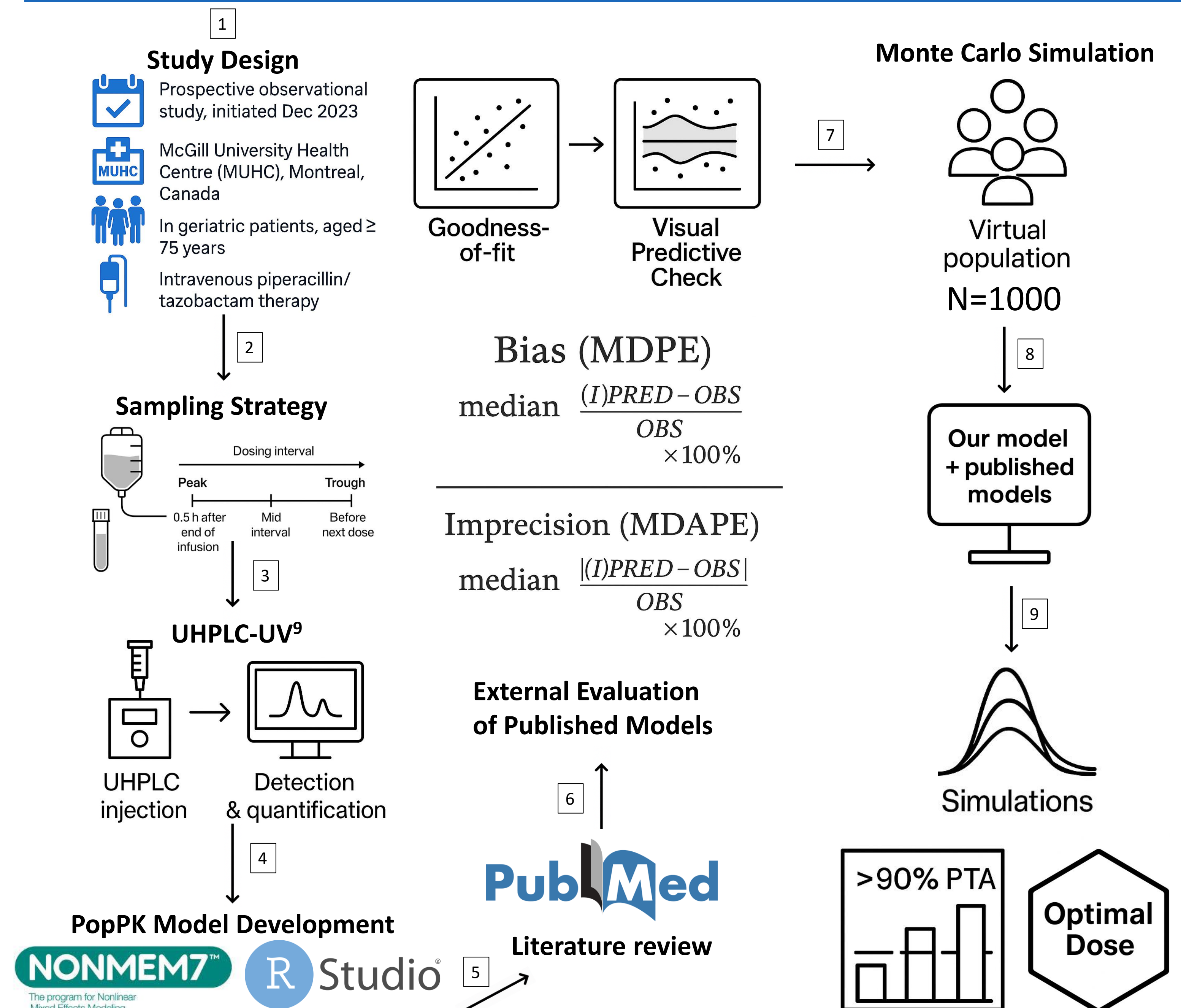
What Can You Do with a Small Dataset?

- Minimum sample sizes reported for model development:
 - As few as five patients with sparse TDM data for simple models³
 - Up to ~50 subjects for more complex models⁴.
- No study has compared local popPK model development with limited data vs external evaluation and assessed their impact on initial dosing.

Objectives

- Develop a popPK model for initial piperacillin/tazobactam dosing in elderly patients using a small, sparsely sampled dataset.
- Compare its initial dosing recommendations with those from externally evaluated published models.

Methods



Results

Table 1. Characteristics of patients admitted to the MUHC

Characteristics	Median (Range)
Sex (male/female)	4/9 (n=13)
Age (years)	89 (76-93)
Weight (kg)	63.2 (49.0-90.5)
Height (cm)	172 (148-178)
BMI (kg/cm ²)	22.8 (20.4-29.6)
Race	64.3% Caucasian
Serum creatinine (μmol/L)	72.0 (53.0-148)
Creatinine clearance* (mL/min)	44.0 (29.8-120)
Creatinine clearance** (mL/min/1.73 m ²)	75.0 (40.7-97.6)
Sample type	Peak: 7 (25%), Mid: 12 (43%) Trough: 9 (32%)

*Creatinine clearance estimated with Cockcroft-Gault equation

**Creatinine clearance estimated with CKD-EPI equation

Table 2. Parameter estimates of the final model

Parameter	Estimation		Bootstrap	
	Estimate (%RSE)	Shrinkage	Median	95% CI
θ_{CL} (L/h)	4.92 (6.00)		4.88	4.34 – 5.65
θ_{expCL}	0.624 (45.0)		0.605	0.0955 – 1.11
V (L)	13.3 (14.0)		13.1	10.3 – 16.8
ω_{CL}	0.0168 ^a (22.0)	31.0%	0.0156	0.000753 – 0.0777
$\sigma_{proportional}$	0.0994 ^b (6.00)	9.00%	0.0817	0.0130 – 0.162

^aCoefficient of variation = 13.0% calculated as $\sqrt{\exp(\omega_{CL}) - 1}$

^bCoefficient of variation = 32.3% calculated as $\sqrt{\exp(\sigma_{proportional}) - 1}$

Table 3. Parameter estimates of evaluated popPK models

Parameter	Ishihara et al. ⁷	Hemmersbach-Miller et al. ⁸
CL (L/h)	4.58	4.09
V _c (L)	5.39	31.8
Q (L/h)	20.7	-
V _p (L/h)	6.96	-
ω_{CL} (as %CV)	26.6	14.4
ω_{Vc} (as %CV)	69.0	25.0
$\sigma_{proportional}$ (as %CV)	3.04	35.8
$\sigma_{additive}$ (mg/L)	5.00	0.0488

Table 4. Predictive performance of evaluated popPK models

Model	Population		Individual	
	MDPE	MDAPE	MDPE	MDAPE
Ishihara et al. ⁷	2.4	23.8	0.5	3.2
Hemmersbach-Miller et al. ⁸	-37.8	43.2	-21.4	31.3

MDAPE, Median absolute prediction error; MDPE, Median prediction error

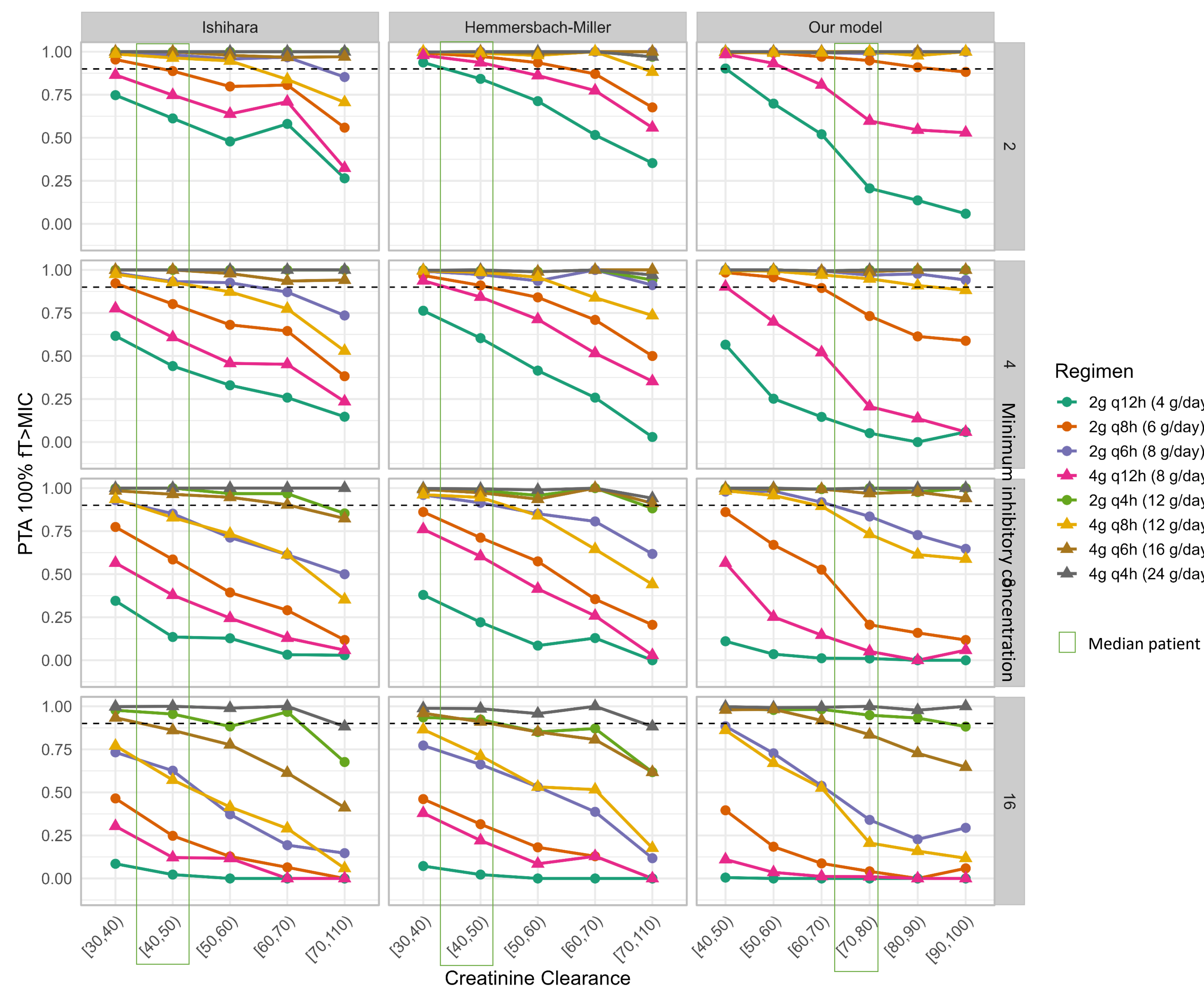


Figure 1. Probability of target attainment across different dosing regimens and creatinine clearance categories

Simulations were only performed for piperacillin. Creatinine clearance (x-axis) was calculated using the Cockcroft–Gault equation (mL/min) for the Ishihara and Hemmersbach-Miller models, and CKD-EPI (mL/min/1.73 m²) for our model. 30% unbound fraction was assumed in the simulations.

PTA: Probability of target attainment

References

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Acknowledgments

Conclusion

- Our model matched the dosing recommendations of the best-performing model (Ishihara et al.⁷) for a median patient across all MICs.
- Both local model development or external evaluation are appropriate to guide initial piperacillin/tazobactam dosing when data are limited.