Pre-registered derivation of a held-out drug's dosing behaviour from class-analogy anchors: a dual-arm validation with a split outcome

Youssef Ghaly
GATMEDI
Correspondence: yg@gatmedi.org
Preprint — version 1 July 2026.

Abstract

Population pharmacokinetic models do not exist for every drug, dose, and population, and prescribers extrapolate by analogy to related drugs — a routine practice that is seldom validated against held-out truth. We report a pre-registered, dual-arm validation of a derivation capability that composes a target drug's pharmacokinetics from published models of related drugs, without access to the target drug's own fitted parameters, and evaluates the result directionally against independent reference data the derivation could not read. The two arms, the pass criteria, and a physiology-standard size-scaling correction were fixed and cryptographically committed before any result was generated; the derivation was leak-checked against both reference sources and its outputs are deterministic and content-hashed. In the adult arm, an out-of-set cephalosporin (cefepime) derived from penicillin and carbapenem anchors reproduced the reference dosing direction under augmented renal clearance: standard 2 g every 8 h reached a median 42.5% of the interval above the MIC, below the 65% target, whereas more-frequent and continuous regimens met it, and standard dosing at typical renal function was adequate. In the paediatric arm, an adult-to-child derivation (amoxicillin) returned an honest negative: after the pre-committed size-scaling correction the engine no longer reproduced the reference's under-dosing, because the available anchors do not span amoxicillin's clearance (derived 2.32 L/h against a size-scaled reference of approximately 5.4 L/h). The contrast — a directional pass where the analogy is clean, a diagnosed negative where the cross-population gap is widest — is the result. Every derived estimate carried a derived uncertainty band or was refused, and drugs outside the anchor class were refused without a number. The estimates are declared predictions, directional rather than parameter-level, and not externally validated.

1. Introduction

A population pharmacokinetic model is available for only a fraction of the drugs, doses, and patient groups a prescriber encounters; newly approved agents, rarely studied drugs, and paediatric populations are frequently without a fitted model. In such cases dosing is extrapolated by analogy to pharmacologically related drugs, adjusted for body size and organ function. This is standard practice, yet it is rarely tested by deriving a drug's behaviour without its own data and then checking the derivation against independent evidence the derivation did not use. The question addressed here is whether a system can derive a held-out drug's dosing behaviour from related drugs alone, be correct where the analogy is sound, and reveal — rather than conceal — where it is not.

The components the derivation relies on are standard and public: analogy within a pharmacological class, allometric size scaling, Monte-Carlo simulation of target attainment, and the

pharmacokinetic/pharmacodynamic index used for beta-lactams (the fraction of the dosing interval with free concentration above the MIC). This study claims none of these as novel. The object under test is a derivation capability, and the claim assessed is directional: that, given only published models of related drugs, the system reproduces the reference dosing direction for a held-out drug where the analogy holds, and fails safely and diagnosably where it does not. The derived estimates are declared predictions — mechanism-composed quantities that carry their own derived uncertainty and are explicitly labelled as not externally validated — and are directional rather than parameter-level. The composition method and the compiled substrate it draws on are proprietary; only observable inputs, outputs, and behaviour are described here.

The work was performed at an early stage of compilation, well below the intended scale of the underlying substrate; the claims are bounded accordingly. What follows sets out the pre-registration discipline, the two arms and their held-out references, the pass criteria, and the results — one directional pass, one honest negative with its mechanism diagnosed — together with the shared safety conditions.

2. Methods

2.1 Scope of disclosure

The published population pharmacokinetic models used as analogy anchors, and the two held-out reference studies, are cited so that the validation is independently checkable. How the target drug's pharmacokinetics are composed from the anchors, and the substrate the composition draws on, are proprietary and out of scope; the derivation is described only at the level of publicly standard pharmacometric practice (class analogy, allometric size scaling, and a derived uncertainty band), without the composition procedure.

2.2 Pre-registration and reproducibility

The two arms, the pass criterion for each, the anchor set, and the held-out references were written down and cryptographically committed before any result was generated, with an explicit commitment to report whatever each arm produced. A physiology-standard size-scaling correction was documented in the committed record before the run rather than introduced afterwards. Both reference sources were quarantined and a value-based check confirmed that no quantity was read from either into the derivation. Outputs are deterministic and reproduce with an identical content hash across clean-environment runs. A prior single-arm record is superseded by this dual-arm result. Provenance identifiers are listed in the Appendix.

2.3 Design

Two arms were derived under one lock. In the adult arm, the pharmacokinetics of cefepime, a cephalosporin absent from the anchor set, were composed from six published beta-lactam models (piperacillin-tazobactam and meropenem populations) and evaluated against Bilal et al. 2023 at an augmented-renal-clearance scenario (creatinine clearance ≥ 130 mL/min), MIC 8 mg/L, and a 65% fT>MIC target. In the paediatric arm, the pharmacokinetics of amoxicillin were composed from the same class anchors, scaled to a 14 kg child, and evaluated against De Cock et al. 2015 at an augmented-renal-clearance scenario, MIC 8 mg/L, and a 40% fT>MIC target. Nothing was read from either reference into

the corresponding derivation. Each arm was scored on whether the derived dosing direction agreed with the reference, not on parameter-level reproduction. The derived models are summarised in Table 1.

Arm (target drug)	CL typical (L/h)	CL, ARC (L/h)	V_1 (L)	ω_CL	fu
Adult (cefepime)	5.34	16.19	29.6	0.86	0.80
Paediatric (amoxicillin, 14 kg)	1.10	2.32	5.18	0.86	0.82

Table 1. Derived models (outputs of the derivation, not inputs). CL, clearance; ARC, augmented renal clearance; V_1, central volume; ω_CL, derived between-subject coefficient of variation for clearance; fu, unbound fraction from physicochemistry. The wide ω_CL reflects cross-class derivation.

2.4 Metrics and pre-registered bars

Each arm passed only if the derived dosing direction agreed with its reference. Four shared conditions were also required: uncertainty integrity, meaning every derived estimate carried a non-degenerate uncertainty band or was refused; safe failure of negative controls; reproducibility by identical content hash; and no leakage of any reference value into either derivation. A pre-specified infusion-duration sub-check in the adult arm was designated report-only and did not enter the verdict.

3. Results

3.1 Adult arm: cefepime (directional pass)

The derived model reproduced the reference dosing direction under augmented renal clearance (Table 2, Figure 1). Standard 2 g every 8 h reached a median 42.5% fT>MIC, below the 65% target, with a probability of target attainment of 31.7%; a more-frequent 2 g every 6 h regimen reached 66.6% (attainment 51.7%) and a 6 g/day continuous infusion reached 100% (attainment 73.3%), while standard 2 g every 8 h at typical renal function was adequate (100%, attainment 80.0%). Standard dosing therefore under-doses the augmented-clearance band and a more-frequent or continuous regimen is required, in agreement with the reference; the derivation drew nothing cefepime-specific from it. The derived clearance carried a wide uncertainty band (ω_CL 0.86), consistent with cross-class derivation.

Regimen (ARC unless noted)	Median %fT>MIC	PTA ≥ 65%
2 g q8h (standard)	42.5	31.7%
2 g q6h (more frequent)	66.6	51.7%
6 g/day continuous infusion	100.0	73.3%
2 g q8h at typical renal function	100.0	80.0%

Table 2. Adult arm (cefepime vs Bilal et al. 2023; MIC 8 mg/L, 65% fT>MIC target). Standard dosing under-doses the augmented-clearance band; more-frequent and continuous regimens meet the target — directionally consistent with the reference.

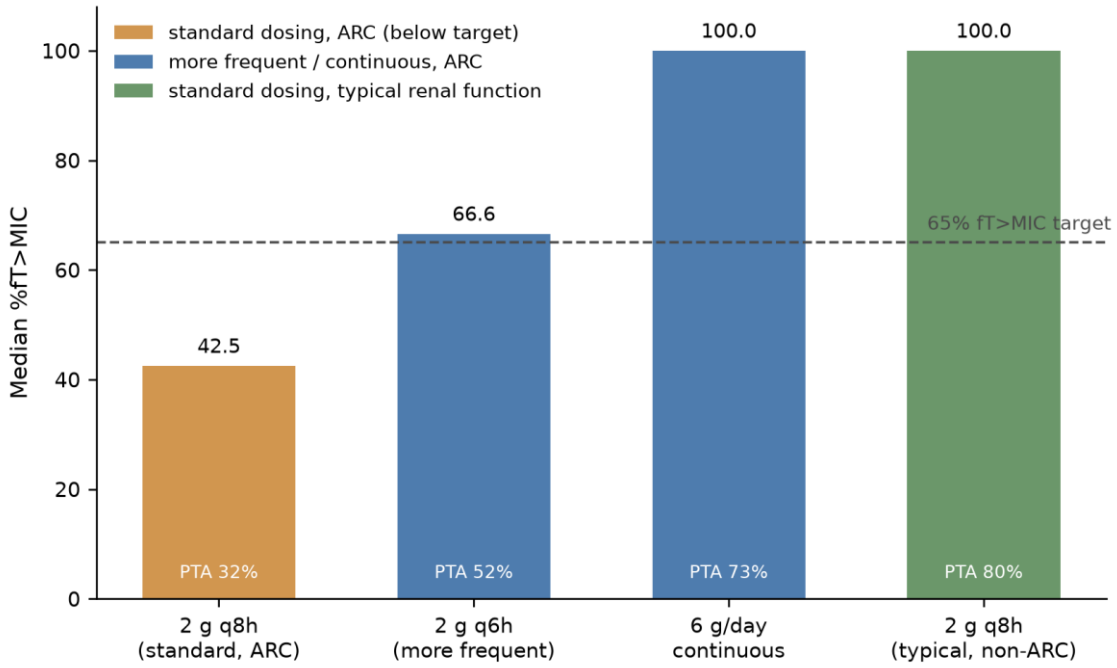

Figure 1. Adult arm (cefepime). Median attainment by regimen against the 65% target, with probability of target attainment annotated. Standard dosing falls below target under augmented renal clearance; more-frequent and continuous regimens, and standard dosing at typical renal function, meet it.

A pre-specified report-only sub-check compared infusion durations and did not enter the verdict. In the derived model a 3 h infusion outperformed a 0.5 h infusion (median 60.6 versus 43.7% fT>MIC), which does not match the reference finding that the two were comparable. This is attributable to the derived drug's high clearance and correspondingly short half-life, at which prolonging the infusion helps; it is recorded as a discrepancy rather than a verdict driver.

3.2 Paediatric arm: amoxicillin (honest negative)

The paediatric arm did not reproduce the reference direction and is reported as a negative (Table 3, Figure 2). The reference reports that standard dosing is sub-therapeutic and that a shorter dosing interval is required. After the pre-committed size-scaling correction the derived clearance was 2.32 L/h, at which standard 25 mg/kg every 6 h already attained the 40% target (median 86.6%, attainment 81.7%), so the derivation did not predict under-dosing. The full dose ladder from every 12 h to every 4 h attained median values of 45.5, 53.6, 86.6, and 100%.

Regimen (ARC child, 14 kg)	**Median %fT>MIC**	**PTA ≥ 40%**
25 mg/kg q12h	45.5	51.7%
25 mg/kg q8h	53.6	65.0%
25 mg/kg q6h (standard)	86.6	81.7%
25 mg/kg q4h	100.0	90.0%

Table 3. Paediatric arm (amoxicillin vs De Cock et al. 2015; MIC 8 mg/L, 40% fT>MIC target). Standard 25 mg/kg q6h already attains the target in the derived model, so the derivation does not reproduce the reference's under-dosing finding.

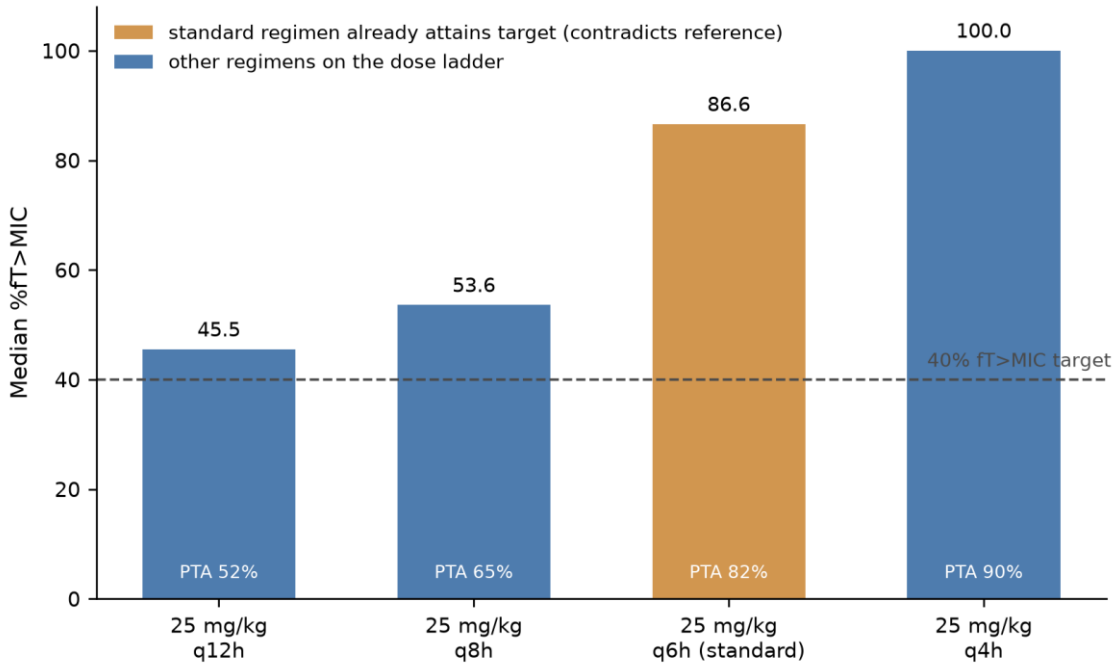

Figure 2. Paediatric arm (amoxicillin). Median attainment by regimen against the 40% target. The standard regimen already attains the target in the derived model, which is why the derivation does not reproduce the reference's under-dosing finding.

The miss is diagnosable and is a property of the anchor set rather than of the derivation method (Figure 3). The size-scaling correction lowered the derived clearance because the available anchors — piperacillin-tazobactam and meropenem models — carry a lower weight-normalised clearance than amoxicillin; the reference's own amoxicillin clearance, size-scaled to a 14 kg child, is approximately 5.4 L/h, against the derived 2.32 L/h. An earlier estimate had coincidentally matched the reference clearance through an un-scaled coefficient; the pre-committed correction removed that coincidence, which is why the honest negative surfaced. The anchor set does not span amoxicillin's true clearance, and the derivation under-shoots accordingly.

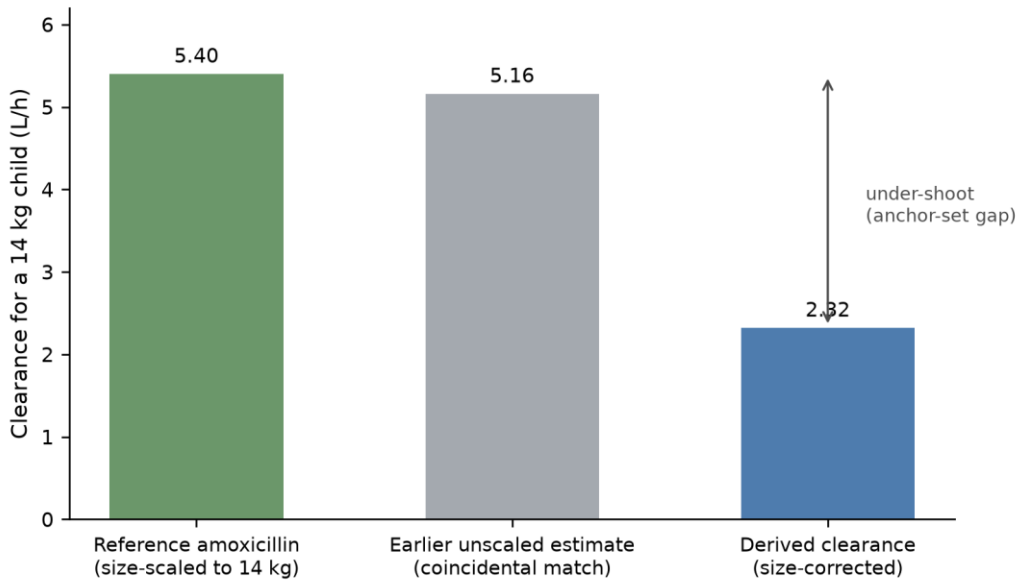

Figure 3. Diagnosed mechanism of the paediatric negative. The size-corrected derived clearance under-shoots the reference amoxicillin clearance scaled to a 14 kg child; an earlier un-scaled estimate matched the reference only coincidentally.

3.3 Shared conditions

All four shared conditions were met. Uncertainty integrity held at 100%: every derived estimate carried a non-degenerate band or was refused. The negative controls failed safely (Table 4): gentamicin and ciprofloxacin, which have no anchor in the class, were refused with no numeric result; teicoplanin was derived with an honestly wide band (ω_CL 0.92); and a degenerate single-anchor input was refused for want of derivable uncertainty. Outputs reproduced with an identical content hash, and the value-based leak check was clean for both arms.

Control	Class	Outcome
Gentamicin	no class anchor	refused — no numeric result
Ciprofloxacin	no class anchor	refused — no numeric result
Teicoplanin	glycopeptide	derived with honestly wide band (ω_CL 0.92)
Single-anchor input	degenerate	refused — no derivable uncertainty

Table 4. Negative controls. Drugs outside the anchor class are refused without a number; a class-adjacent drug is derived with an honestly wide band; a degenerate input is refused for want of derivable uncertainty.

4. Discussion

The two arms establish that the derivation reaches into territory for which the target drug's own parameters were withheld, and that it does so soundly where the analogy is clean and transparently where it is not. In the adult arm, a cephalosporin was dosed correctly in direction from penicillin and carbapenem anchors, under augmented renal clearance, without any cephalosporin-specific input. In the paediatric arm, an adult-to-child derivation produced a negative, and the negative was traced to a specific, measurable cause: the anchor set does not span the target drug's clearance. The contrast is more informative than two isolated passes would have been, because it shows the derivation exposes the boundary of its own reach rather than returning a confident answer beyond it.

The behaviour that distinguishes the capability is observable from the outside: it composes a prediction where a class analogy supports one, attaches a derived uncertainty band to it, and refuses when no analogy or no derivable uncertainty exists. What it produces is a declared prediction, not a validated measurement; the result is directional, the uncertainty bands are wide, and the outcome is a pharmacokinetic/pharmacodynamic surrogate rather than a clinical endpoint. The paediatric negative bounds the claim precisely: derivation across a wide cross-population gap is limited by anchor coverage, and additional anchors spanning the target's clearance would be required before such a case could be expected to reproduce.

5. Limitations

1. The derived estimates are declared predictions that carry derived uncertainty and are explicitly not externally validated; they are not fitted parameters or measured values.
2. Both arms were scored on directional, outcome-level agreement with the reference, not on parameter-level reproduction.
3. The derived uncertainty bands are wide, reflecting cross-class derivation, and are not offered as calibrated intervals.
4. The attainment metric is a pharmacokinetic/pharmacodynamic surrogate (percentage of the interval above the MIC), not mortality or any clinical outcome.
5. The paediatric negative is caused by the anchor set not spanning the target drug's clearance; it is a limitation of anchor coverage at the current stage, and additional anchors would be required to test the case fairly.
6. A residual cross-population approximation remains in the paediatric arm, where a covariate centre was retained in the anchor (adult) frame after the coefficient was size-scaled.
7. The adult reference's parameter table was extraction-uncertain, so that arm was scored on the reference's prose-stated outcome rather than on its tabulated parameters.
8. The validation is directional derivation against independent reference data, not prospective validation against newly measured patient concentrations.

6. Conclusion

Under a pre-registered, leak-checked, reproducible dual-arm protocol, a derivation capability reproduced the reference dosing direction for a held-out cephalosporin composed from unrelated beta-lactam anchors, and returned an honest, mechanistically diagnosed negative for an adult-to-child derivation whose anchor set did not span the target drug's clearance. The capability derives soundly where the class analogy is clean and reveals its own limits where the cross-population gap is widest; the estimates remain declared, directional predictions, and prospective validation against measured patient data is a separate, later step.

Competing interests

The author is the founder of GATMEDI, the company developing the engine evaluated in this study.

Funding

This work was funded internally by GATMEDI. It received no external funding.

Data and code availability

The engine, its source code, and the underlying compiled substrate are proprietary and are not available. The study used the published population-pharmacokinetic models cited in the References as class-analogy anchors and held-out reference data, which are publicly available; the engine and the evaluation harness are not.

Ethics

This study used only computational derivation and checking against published reference data. It involved no human subjects and no patient data, and did not require ethics approval.

References

1. Bilal M, Zoller M, Fuhr U, et al. Cefepime population pharmacokinetics, antibacterial target attainment, and estimated probability of neurotoxicity in critically ill patients. Antimicrob Agents Chemother. 2023;67(7):e00309-23. doi:10.1128/aac.00309-23.
2. De Cock PAJG, Standing JF, Barker CIS, et al. Augmented renal clearance implies a need for increased amoxicillin-clavulanic acid dosing in critically ill children. Antimicrob Agents Chemother. 2015;59(11):7027-7035. doi:10.1128/AAC.01368-15.
3. Hahn J, Min KL, Kang S, Yang S, Park MS, Wi J, Chang MJ. Population pharmacokinetics and dosing optimization of piperacillin-tazobactam in critically ill patients on extracorporeal membrane oxygenation and the influence of concomitant renal replacement therapy. Microbiol Spectr. 2021;9(3):e00633-21. doi:10.1128/Spectrum.00633-21.
4. Thy M, Urien S, Foissac F, et al. Piperacillin population pharmacokinetics and dosing regimen optimization in critically ill children receiving continuous renal replacement therapy. Antimicrob Agents Chemother. 2022;66(12):e0113522. doi:10.1128/aac.01135-22.
5. Selig DJ, DeLuca JP, Chung KK, et al. Pharmacokinetics of piperacillin and tazobactam in critically ill patients treated with continuous kidney replacement therapy: a mini-review and population pharmacokinetic analysis. J Clin Pharm Ther. 2022;47(8):1091-1102. doi:10.1111/jcpt.13657.
6. Klastrup V, Thorsted A, Storgaard M, Christensen S, Friberg LE, Öbrink-Hansen K. Population pharmacokinetics of piperacillin following continuous infusion in critically ill patients and impact of renal function on target attainment. Antimicrob Agents Chemother. 2020;64(7):e02556-19. doi:10.1128/AAC.02556-19.
7. Martínez-Casanova J, et al. Predictive factors of piperacillin exposure and the impact on target attainment after continuous infusion administration to critically ill patients. Antibiotics (Basel). 2023;12(3):531. doi:10.3390/antibiotics12030531.
8. Peng Y, Liu Y, Cheng Z, Zhang Q, Xie F, Zhu S, Li S. Population pharmacokinetics of prolonged infusion for meropenem: tailoring dosing recommendations for Chinese critically ill patients on continuous renal replacement therapy with consideration for renal function. Drug Des Devel Ther. 2025;19:1105-1117. doi:10.2147/DDDT.S489603.
9. Anderson BJ, Holford NHG. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008;48:303-332. doi:10.1146/annurev.pharmtox.48.113006.094708.
10. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters, version 16, 2026. https://www.eucast.org/clinical_breakpoints.

Appendix. Provenance and reproducibility

The dual-arm run was banked from a frozen derivation under a pre-registered, SHA-locked dual-arm record; outputs reproduce across clean-environment runs.

Item	Value
Dual-arm pre-registration lock (commit)	12476d6
Size-scaling correction (commit, pre-result)	6ca4435
Result content hash (SHA-256)	00f47d87c1b7c7102da20844d1e6d4f7268bbb1512738b0e61ac635a4f26a50d
Superseded single-arm record (commit / lock)	db9c1a5 / ce76770
Anchor set	6 published β-lactam models (piperacillin-tazobactam, meropenem)
Conditions	MIC 8 mg/L; targets 65% fT>MIC (adult), 40% fT>MIC (paediatric)
Reproducibility	identical content hash across two clean-environment runs
Leak check	value-based; clean for both arms