Population Pharmacokinetic Modeling and Simulation for Optimizing the Loading and Maintenance Doses of Teicoplanin in Korean Pediatric Patients

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ABSTRACT

Population Pharmacokinetic Modeling and Simulation for Optimizing the Loading and Maintenance Doses of Teicoplanin in Korean Pediatric Patients

Background

Teicoplanin is commonly used to treat Gram-positive infections, including methicillin-resistant Staphylococcus aureus (MRSA), particularly in pediatric patients. Recent therapeutic drug monitoring (TDM) guidelines recommend a trough concentration (C_{min}) of 15–30 μg/mL; however, many pediatric patients remain subtherapeutic, highlighting the need for optimized dosing. Previous studies have focused on short-term exposure (e.g. Day 3 or 5) and assessed only the probability of exceeding specific trough thresholds, without evaluating sustained target attainment. Therefore, this study aimed to evaluate current teicoplanin dosing in Korean pediatric patients and develop a population pharmacokinetic (popPK) model to optimize both loading and maintenance regimens through simulation, targeting both early and sustained therapeutic exposure

Methods

This retrospective study included pediatric patients (0–18 years) treated with teicoplanin at Severance Hospital between November 1, 2005, and January 1, 2025. Clinical, demographic, and laboratory data were extracted from electronic medical records for population pharmacokinetic (popPK) analysis. Structural models were evaluated using the SAEM algorithm in Monolix, and covariate selection followed a stepwise approach based on statistical significance and physiological relevance. Using the final model, dosing simulations were conducted in Simulx with 100 virtual patients and 1,000 replicates per regimen. Two strategies were evaluated: (1) early target attainment (within 48–72 hours) and (2) sustained maintenance over 21 days. The first strategy optimized loading doses (every 12 hours for three to five doses) followed by once-daily maintenance. The second strategy optimized maintenance dose first, then selected appropriate loading regimens. Probability of target attainment (PTA) was evaluated at 47–71 hours after the initial dosing to assess early therapeutic exposure in the early target attainment strategy. In contrast, in the sustained maintenance strategy, the optimal maintenance dose was first determined based on the trough concentration on Day 21, followed by the selection of a corresponding loading dose. The combined regimens were then evaluated for their ability to maintain target concentrations on Days 4, 7, 14, and 21.

Results

A total of 108 teicoplanin serum concentrations from 34 pediatric patients were analyzed. Only 32.4% of initial and 36.1% of total TDM samples were within the target range, with subtherapeutic levels common in children under three years. A one-compartment popPK model identified body weight as the only significant covariate (Vd: 11.98 L; CL: 0.22 L/h), with OFV reduced from 805.9 to 746. In the early target attainment strategy, optimal loading doses were 12 mg/kg q12h ×4 for <4 kg and 10, 8, and 6 mg/kg q12h ×5 for 4–10, 10–50, and >50 kg, respectively. Combined with appropriate once-daily maintenance doses (12, 10, 8, and 6 mg/kg for <4, 4–10, 10–50, and >50 kg, respectively), PTA remained >50% across all groups and time points. In the sustained target attainment strategy, optimal once-daily doses were 14, 10, 8, and 6 mg/kg for <4, 4–10, 10–50, and >50 kg, respectively. Supporting loading regimens (14, 12, and 10 mg/kg q12h ×3 for <4, 4–10, and ≥10 kg) also achieved PTA >50% through Day 21, supporting their feasibility for both early and sustained target attainment.

Discussion

This study highlights the need to enhance current pediatric teicoplanin dosing regimens, which frequently result in subtherapeutic concentrations, particularly in younger or lower-weight children. By applying a popPK model and two simulation strategies, we identified weight-based dosing combinations that improved the PTA while balancing the risks of subtherapeutic and supratherapeutic exposures. Notably, the proposed regimens-maintained PTA within the 15–30 μg/mL range at >50% across all weight groups and over 21 days. However, assumptions regarding sampling times, infusion durations, sparse and inaccurate timed TDM data may have introduced bias in trough concentrations and limited the detection of covariates such as renal function.

Conclusion

This study proposes alternative teicoplanin loading and maintenance regimens tailored to pediatric body weight, demonstrating consistent target attainment with PTA exceeding 50% over 21 days. These model-informed dosing strategies may improve treatment efficacy and safety in pediatric populations. Future studies should incorporate pharmacodynamic markers (e.g., $AUC_{0–24}$/MIC), precisely timed and increased number of TDM data, and clinical outcome. Such evidence will be necessary for advancing precision dosing approaches and optimizing teicoplanin therapy in real-world pediatric settings.

Key words : Teicoplanin, Pediatric, Population pharmacokinetic, Therapeutic drug monitoring, Methicillin-resistant Staphylococcus aureus, Loading dose, Maintenance dose, Dosing optimization

1. Introduction

1.1 Background

Teicoplanin, a glycopeptide antibiotic, is widely used to treat Gram-positive infections, particularly those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) (Yamada et al., 2021). It exerts its antimicrobial effect by binding to the D-alanyl-D-alanine terminus of peptidoglycan precursors, thereby inhibiting the transglycosylation step in bacterial cell wall synthesis (Sosio et al., 2003; Wood, 1996). Clinically, teicoplanin is indicated for use in both adults and children from birth for the treatment of a broad range of Gram-positive infections, including complicated skin and soft tissue infections, bone and joint infections, hospital and community acquired pneumonia, urinary tract infections, infective endocarditis, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), and bacteremia related to these conditions (European Medicines Agency [EMA], 2022).

Pharmacokinetically, teicoplanin differs from other glycopeptides, such as vancomycin, in several key aspects. It exhibits high protein binding (~90%, primarily to albumin) and is mainly eliminated via glomerular filtration (Yamada et al., 2021; Wilson, 2000). One of its most distinctive characteristics is a prolonged elimination half-life of 88 to 182 hours, allowing for once-daily dosing, in contrast to vancomycin's shorter half-life of 4 to 6 hours (U.S. Food and Drug Administration [FDA], 2022; Wilson, 2000). Comparative studies have shown similar clinical efficacy between teicoplanin and vancomycin, with teicoplanin demonstrating a more favorable safety profile, particularly with respect to nephrotoxicity and infusion-related reactions (Cavalcanti et al., 2010; Wood, 1996). Therefore, these characteristics have made teicoplanin a preferred treatment option for MRSA infections in pediatric patients, especially in Europe and Asia (Hanai et al., 2024).

MRSA can cause a wide spectrum of organ-specific infections, with skin and subcutaneous tissue infections being the most common, followed by more invasive infections such as osteomyelitis, meningitis, pneumonia, lung abscess, and empyema (Siddiqui & Koirala, 2023). It remains a leading cause of hospital-acquired infections, contributing to significant increase in morbidity, mortality, and extended hospital stays, healthcare costs. Delayed initiation of appropriate antimicrobial therapy has been associated with nearly a two-fold increase in mortality among patients with MRSA infections, emphasizing the need for early and effective treatment in the management of MRSA infections (Kaasch et al., 2013).

The antimicrobial efficacy of teicoplanin is best described by its pharmacokinetic/pharmacodynamic (PK/PD) index—specifically, the ratio of the area under the concentration-time curve to the minimum inhibitory concentration (AUC/MIC) (Craig, 2003). However, due to the practical challenges of AUC monitoring, which requires multiple serum concentrations, trough concentration (C_{min}) is commonly used as a surrogate marker. Studies have

demonstrated a strong linear correlation between AUC and C_{min}, supporting the use of therapeutic drug monitoring (TDM) of C_{min} to guide dosing (Byrne et al., 2017; Wang et al., 2018).

Recent TDM guidelines recommend a target C_{min} of 15–30 µg/mL for non-complicated MRSA infections and 20–40 µg/mL for severe or deep-seated infections such as endocarditis or osteomyelitis (Hanai et al., 2024). TDM is generally advised between Day 3 to Day 5 of treatment to ensure early attainment of therapeutic concentrations. According to the EMA (2022), the recommended pediatric dosing regimen for teicoplanin includes a loading dose of 10 mg/kg every 12 hours for three doses for children aged 2 months to 12 years, followed by a maintenance dose of 6–10 mg/kg once daily. For adolescents over 12 years, adult dosing guidelines apply.

Despite these recommendations, several studies have reported subtherapeutic teicoplanin levels in pediatric patients receiving guideline-based dosing. Zhao et al. (2015) found that 48% of pediatric patients aged 0.5 to 16.9 years had trough concentrations below the target range. Similarly, Sun et al. (2020) reported a subtherapeutic rate of 52.7%, while Yamada et al. (2016) found that 46.2% of patients aged 2–16 years were also below 15 µg/mL. These findings highlight the need for optimized dosing strategies in pediatric populations to ensure therapeutic efficacy. However, there remains limited information and data on the optimal loading and maintenance regimens required to consistently achieve the recommended target range of 15 – 30 µg/mL in the pediatric population (Kato et al., 2016; Nakamura et al., 2015; Ueda et al., 2013; Zhang et al., 2023).

Pediatric pharmacokinetics is highly variable due to age-related changes in body composition and organ maturation. For example, total body water (TBW) and extracellular fluid (ECF), which influence the volume of distribution (Vd) of hydrophilic drugs such as teicoplanin, decrease with age—from 85% TBW and 50% ECF in preterm neonates to approximately 60% TBW and 20% ECF in adolescents, respectively (Shi & Derendorf, 2010). Consequently, younger children may require higher per-kilogram loading doses to achieve therapeutic concentrations due to their larger Vd (Matalová et al., 2016). Also, renal clearance undergoes rapid maturation during the first two years of life, further influencing drug elimination (Holford, 2013). These developmental factors necessitate age-appropriate dosing strategies for teicoplanin in pediatric patients (Matalová et al., 2016).

Population pharmacokinetic (popPK) modeling offers a powerful approach for optimizing dosing, particularly in pediatric populations where sparse sampling and developmental changes significantly affect both pharmacokinetics and pharmacodynamics (De Cock et al., 2010). By incorporating covariates such as age, weight, and renal function, popPK models enable individualized dosing recommendations and improve the probability of achieving therapeutic targets. In addition, they support the analysis of sparse data due to ethical and practical limitations on the number and volume of blood sampling in pediatric populations (De Cock et al., 2010).

While previous studies have provided valuable insights into the pharmacokinetics of teicoplanin in pediatric patients, there remains a need for dosing strategies that better reflect real-world clinical scenarios. Many prior simulation-based studies have assessed trough concentrations at Day 3 or Day 5 (Yamada et al., 2022; Zhang et al., 2023), which aligns with the recommended timing for TDM in clinical guidelines (Hanai et al., 2022). However, these studies did not assess whether therapeutic concentrations are sustained throughout longer treatment durations, which is an essential consideration for managing prolonged infections such as infective endocarditis. In addition, evaluating whether therapeutic concentrations are achieved after the loading dose is also important, as early attainment of target concentrations may influence clinical outcomes. Although some studies optimized dosing using AUC/MIC-based targets (Zhao et al., 2015; Zhang et al., 2023), other study evaluated the probability of exceeding trough thresholds (e.g., >10, >15, >20, or >30 μg/mL) (Kim et al., 2024). However, these approaches did not directly evaluate whether drug concentrations consistently remain within the recommended therapeutic target of 15–30 μg/mL. As highlighted by Byrne et al. (2017), TDM is most effective when a defined target range is applied, to ensure adequate exposure for efficacy while avoiding toxicity. Therefore, evaluating the probability of achieving and maintaining concentration within this specific range may provide a more clinically relevant framework for optimizing teicoplanin dosing in pediatric patients.

1.2 Objectives

In this regard, the objectives of this study was to 1) retrospectively evaluate current teicoplanin dosing practices in Korean pediatric patients at Severance Hospital in Seoul, 2) develop a popPK model tailored to this population, 3) perform simulation-based dose optimization using two distinct strategies: one focusing on early target attainment and the other on sustained target attainment, and 4) assess the probability of target attainment (PTA) for various simulated teicoplanin dosing strategies.

The goal was to identify dosing regimens that maximize PTA within the target trough concentration range of 15–30 μg/mL for both loading and maintenance doses, while minimizing the proportion of subtherapeutic (<15 μg/mL) and supratherapeutic (>30 μg/mL) concentrations.

2. Materials and Methods

2.1 Study Design and Patient Population

This study was conducted retrospectively utilizing medical records of patients who were treated at Severance Hospital in Seoul, Republic of Korea, in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the Institutional Review Board of Severance Hospital (IRB No. 4-2024-0857).

Clinical and laboratory data of patients aged 0 to 18 years who received teicoplanin treatment and had at least two serum teicoplanin concentrations for TDM at Severance Hospital between November 1, 2005, and January 1, 2025, were extracted from electronic medical records through the Data Center. Patients were excluded if they met any of the following criteria: 1) incomplete records of teicoplanin administration, such as missing dose information and infusion start times, 2) missing key demographic or laboratory data relevant to pharmacokinetic analysis. If any of the laboratory measurements were not available within ±48 hours of teicoplanin administration, the closest available measurement relative to the dosing time was used.

2.2 Data Collection

Relevant clinical data were retrospectively collected from electronic medical records for use in popPK modeling. The collected data included patient demographics, laboratory measurements, teicoplanin dosing information, and TDM data. All variables were recorded using standardized definitions and appropriate units.

Extensive data processing was performed to compile a dataset suitable for popPK modeling. Data were extracted from six difference sources within the electronic medical records in Excel format: 1) a list of patients who were prescribed for teicoplanin, 2) teicoplanin administration records, 3) measured teicoplanin concentrations, 4) a filtered list of patient IDs for study inclusion, 5) laboratory variables, and 6) demographic variables.

For the patient list, individuals prescribed 'Teicoplanin' between '2005-11-01 to 2025-01-01' were identified and filtered by age '≤18 years' at the time of prescription, resulting in a total of 4,289 pediatric patients.

For the teicoplanin administration data, the patient list was used to identify those who had received teicoplanin administration, narrowing down to 4,253 patients. The dosing history, including the start of infusion date and time and administered dose was considered essential for the dataset. Although the end of infusion time was recorded for some patients, it was missing for most of the patients. Among patients with available infusion duration data, the duration was consistently approximately 30 minutes. Therefore, a fixed infusion duration of 30 minutes was assumed for all patients.

For concentration data, patients who underwent TDM were identified from the administration dataset. Teicoplanin concentrations were identified as 'Teicoplanin [Serum]' and extracted into an Excel file, resulting in an initial dataset of 123 patients. To ensure sufficient data for popPK modeling, only patients with at least two recorded teicoplanin serum concentrations were retained, resulting in a final cohort of 34 patients. The sampling date was considered essential for inclusion. A filtered list of patient IDs meeting these criteria was compiled for study inclusion and subsequently used to facilitate data merging and the extraction of relevant variables.

Laboratory variables included blood urea nitrogen (BUN), serum creatinine (SCr), aspartate aminotransferase (AST), albumin (ALB), direct bilirubin (DBIL), alanine aminotransferase (ALT), total protein (TP), total bilirubin (TBIL), white blood cell count (WBC), cystatin C (CysC), and estimated glomerular filtration rate (eGFR) derived from cystatin C. Demographic variables included sex, weight, height, body surface area, gestational age. These were extracted based on the filtered list of patient IDs. The recording of the sampling date and time for these laboratory and demographic variables was considered essential for inclusion in the dataset. Instead of using time-matched values for each dose, the single closest measurement to the first teicoplanin dosing time was selected for each variable.

2.3 Monolix Dataset Preparation

After data processing, the concentration, administration, laboratory, and demographic datasets were merged to prepare the Monolix-compatible dataset. In the EMR, serum concentration sampling time was uniformly recorded as 12:00, and the exact time of sampling was not available. Therefore, for samples drawn on the same day as teicoplanin administration, the concentration was assumed to represent a trough value obtained 30 minutes prior to the next dose. For serum concentrations measured on days without a recorded teicoplanin dose, the sampling time was retained as recorded in the EMR, which was uniformly recorded as 12:00. The time of the first teicoplanin administration was defined as time zero, and all subsequent time points were calculated in hours relative to this initial dose.

To account for developmental changes in drug clearance across different pediatric age groups, postnatal age (PNA), postmenstrual age (PMA), and corrected age (CA) were calculated when preparing the Monolix dataset (Holford et al., 2013). These variables were particularly important given that the dataset included infants and young children, in whom drug clearance is known to increase rapidly and non-linearly before two years of age due to physiological maturation and growth in body size (Holford et al., 2013). Therefore, PNA, PMA, and CA were incorporated as potential covariates in the popPK model to explore their influence on clearance. The following equations were used to compute these age variables (Committee on Fetus and Newborn, 2004):

$$PNA\ \ (weeks) = Current\ \ date - Birth\ \ date \tag{1}$$

$$PMA\ \ (weeks) = GA + PNA \tag{2}$$

$$CA\ \ (weeks) = PNA - (40\ \ weeks - GA) \tag{3}$$

Among the three, PMA is considered the most physiologically appropriate covariate for modeling clearance in children under two years of age, as maturation is expected to be complete by this time (Anderson & Holford, 2007; Holford et al., 2013). To account for maturation, PMA was categorized into two developmental groups: infants and young children (0–2 years, assigned a value of 1), and older children and adolescents (3–18 years, assigned a value of 2). This categorization was applied exclusively to PMA during covariate exploration, as PMA is widely recognized as a key variable for describing the time course of clearance changes (Anderson & Holford, 2007).

Also, because of the known challenges in accurately assessing renal function in pediatric populations, eGFR was calculated using both the Schwartz equation and a cystatin C–based formula (Alford et al., 2014; Anderson & Holford, 2007; Schwartz et al., 2012). However, eGFR values

calculated by the Schwartz equation were consistently overestimated in our dataset; therefore, only values derived from the cystatin C–based formula were used in subsequent analyses. eGFR values were then categorized into three groups following chronic kidney disease (CKD) staging criteria proposed by KDOQI and endorsed by KDIGO guidelines (Eckardt et al., 2009): eGFR $\geq$ 60 mL/min/1.73 m^2 as 1, eGFR < 60 mL/min/1.73 m^2 as 2, eGFR < 15 mL/min/1.73 m^2 to 3.

2.4 Population Pharmacokinetic Analysis

PopPK modeling was conducted using a non-linear mixed-effects modeling approach. Parameter estimation was performed using the stochastic approximation expectation-maximization (SAEM) algorithm, as implemented in Monolix (version 2024R1, Lixoft SAS, a Simulations Plus company), to estimate the pharmacokinetic parameters and their interindividual variability.

2.4.1 Base Model Selection

Given the sparsity of sampling and the predominance of pre-dose (trough) concentrations in the dataset, both one- and two-compartment models with first-order elimination were evaluated as candidate structural models. Each model included clearance (CL) and volume of distribution (Vd) as pharmacokinetic parameters. The selection of the basic structural model was based on the objective function values (OFVs; −2 log-likelihood), the relative standard errors (RSE) of estimated parameters, and visual diagnostic plots. Residual unexplained variability (RUV) was assessed using both proportional and combined error models. Interindividual variability (IIV) for model parameters was assumed to follow a log-normal distribution to characterize variability among individuals in PK parameters. The following equation was used to describe the relationship between individual parameters and covariates:

$$\log(\theta_i) = \log(\theta) + \beta \cdot Cov_i + \eta_i \quad (4)$$

θ_i is the individual parameter estimate, θ is the typical population PK parameter, β is the covariate coefficient, Cov_i is the covariate value for individual i^{th}, and η_i is the random effect for the i^{th} individual following a normal distribution $\eta_i \sim N(0,\omega^2)$ where ω represents the standard deviation of inter-individual variability.

2.4.2 Covariate Selection

Following the finalization of the structural model, potential covariate effects were evaluated to explain interindividual variability in pharmacokinetic parameters. Continuous covariates examined included age, weight, height, body surface area, BUN, AST, ALT, ALB, WBC, SCr, TBIL, DBIL, TP, CysC, GA, PNA, PMA, and eGFR calculated using both the Schwartz equation and a cystatin C–based equation. Categorical covariates included sex, PMA category, and eGFR category as previously defined.

All continuous covariates were normalized relative to their median values and incorporated into the model using the following equation:

$$for\ \ continuous\ \ covariates, CL_i = CL_{pop}\ \times \left(\frac{COV_i}{COV_{median}}\right)^{\beta} \times\ \ e^{\eta CL,i} \qquad (5)$$

where CL_i is the individual clearance, CL_{pop} is the typical population value, COV_i is the individual covariate value, COV_{median} is the population median, β is the estimated covariate effect, and $\eta_{CL,i}$ represents interindividual variability. For categorical covariates, the relationship were modeled as:

$$for\ \ categorical\ \ covariates, CL_i = \ \ CL_{pop}\ \ \times\ \ e^{\beta \cdot COVi} \times e^{\eta CL,i} \qquad (6)$$

Where COV_i is an indicator variable coded as 0 or 1. Given that body weight is a physiologically relevant and readily measurable surrogate of body size, an allometric scaling model with fixed coefficient of 0.75 for clearance and 1 for volume was compared against models in which these coefficients were estimated, to determine the most appropriate final model (Anderson & Holford, 2007; Holford et al., 2013).

Covariates were initially screened using univariate statistical tests—Pearson's test for continuous covariates and analysis of variance (ANOVA) for categorical covariates. The covariate with the lowest p-value was added first. Covariate selection was guided by both statistical significance and physiological relevance. A combined stepwise forward selection and backward elimination approach was also applied. Covariates were retained in the model if forward inclusion resulted in a decrease in the objective function (−2 log-likelihood, −2LL) of ≥3.84 ($p < 0.05$), and backward elimination retained covariates that increased −2LL by ≥7.88 ($p < 0.005$) upon removal.

2.4.3 Model Evaluation

Model evaluation was conducted using a combination of statistical criteria and visual diagnostic tools to assess model suitability and predictive performance. Statistical indicators included the Akaike Information Criterion (AIC), objective function value (OFV), and Bayesian Information Criterion (BIC), with lower values suggesting an improved model fit. The precision and reliability of the estimated parameters were assessed based on relative standard error (RSE), where values ≤30–50% were considered acceptable for model stability.

Visual diagnostic plots were also used to support model evaluation. The goodness-of-fit (GOF) assessments included plots such as observed data (DV) against individual prediction (IPRED), DV versus population prediction (PRED), population weighted residuals (PWRES), and individual weighted residuals (IWRES). Visual predictive checks (VPC) were also inspected for model suitability. The VPC plot will be constructed using 500 Monte Carlo simulations from the model. For each simulation, the 10^{th}, 50^{th}, and 90^{th} percentiles of the simulated data were calculated to assess the model's predictive performance.

2.5 Simulation for Optimal Dosage Regimen

PopPK simulations were performed using the final model to determine optimal teicoplanin dosing regimens in pediatric patients. All simulations were conducted in Simulx (version 2024) with 100 virtual patients and 1,000 replicates per dosing scenario. The primary endpoint was the PTA, defined as the proportion of individuals with trough concentrations within the therapeutic range of 15–30 μg/mL, as well as <15 μg/mL and >30 μg/mL. Since simulation outcomes were expressed as percentages per individual, the mean PTA was calculated by averaging results across all replicates for each individual within each dosing regimen. All figures of PTA plots were generated using R (version 4.4.2) and the ggplot2 package.

Two simulation strategies were applied: (1) early target attainment and (2) sustained target attainment. The first strategy aimed to maximize early target attainment within the initial 48–72 hours, which is considered as critical for severe infections such as Staphylococcus aureus bacteremia. Clinical studies have shown that persistent bacteremia beyond one day is associated with a heightened risk of metastatic complications and mortality, particularly within the first four days (Shah & Baltas, 2024). To enhance early exposure while maintaining a standard 12-hour dosing interval (q12h), 6, 8, 10, 12, 14, 16, 18 mg/kg of loading dose regimens comprising 3, 4, or 5 doses were simulated based on prior modeling studies (Byrne et al., 2017; Cazaubon et al., 2017; Ueda et al., 2020). Then the regimen yielding the highest PTA at 47, 59, or 71 hours was selected and fixed. Using this fixed loading dose, 6, 8, 10, 12, 14, 16, 18 mg/kg of once-daily maintenance doses was simulated to identify the maintenance dose with the highest PTA on Day 21. The final loading dose and maintenance dose combination was then used to simulate PTA at Day 4, 7, 14, and 21 to evaluate consistency of target attainment over the treatment period.

The second strategy prioritized maintaining therapeutic levels throughout prolonged treatment courses (e.g., infective endocarditis), typically requiring ≥21 days of therapy (EMA, 2022). To reflect this need for sustained drug exposure, the optimal maintenance dose was first selected based on the highest PTA at Day 21. The maintenance dose was then fixed, and loading dose regimens consisting of three doses administered at 12-hour intervals were simulated to assess early exposure at 47 hours. This reverse strategy was designed to balance initial drug exposure with long-term pharmacokinetic stability and aligns with treatment objectives in prolonged infections requiring consistent therapeutic levels over extended periods.

Trough sampling for PTA evaluation was performed at D4, D7, D14, and D21 for both strategies. Day 4 was chosen as a surrogate marker for assessing the adequacy of the loading dose, given teicoplanin's long half-life and delayed achievement of steady state (Hanai et al., 2022). Day 7 was selected as a follow-up time point to evaluate the effects of the maintenance dose within the first week after the loading phase (Hanai et al., 2022). Day 14 was included as this corresponds to the time when approximately 93% of steady-state concentration is achieved (Wilson, 2000). Finally, Day 21 was selected to assess long-term exposure, particularly in serious infections such as infective

endocarditis, which requires a minimum of 21 days of treatment (EMA, 2022). In addition, sampling at 47, 59, or 71 hours (depending on LD schedule) was included to determine the optimal loading doses.

3. Results

3.1 Characteristics of Patients

After data processing and the application of sequential inclusion and exclusion criteria, a total of 108 teicoplanin serum concentrations from 34 pediatric patients (19 males and 15 females) were included in the popPK analysis. The inclusion and exclusion process is illustrated in Figure 1.

The overall demographic and laboratory characteristics of the study population are summarized in Table 1. The median (range) age and weight were 4.50 years (0–18) and 12.83 kg (0.60–74.50), respectively. The median estimated glomerular filtration rate (eGFR) was 57.86 mL/min/1.73 m^2 (25.26–169.85). In terms of age distribution, 24 patients (70.6%) were between 2 months and 12 years of age, and 10 patients (29.4%) were aged 12 years or older. A detailed age distribution across the 0 to 18 years is provided in Table 2.

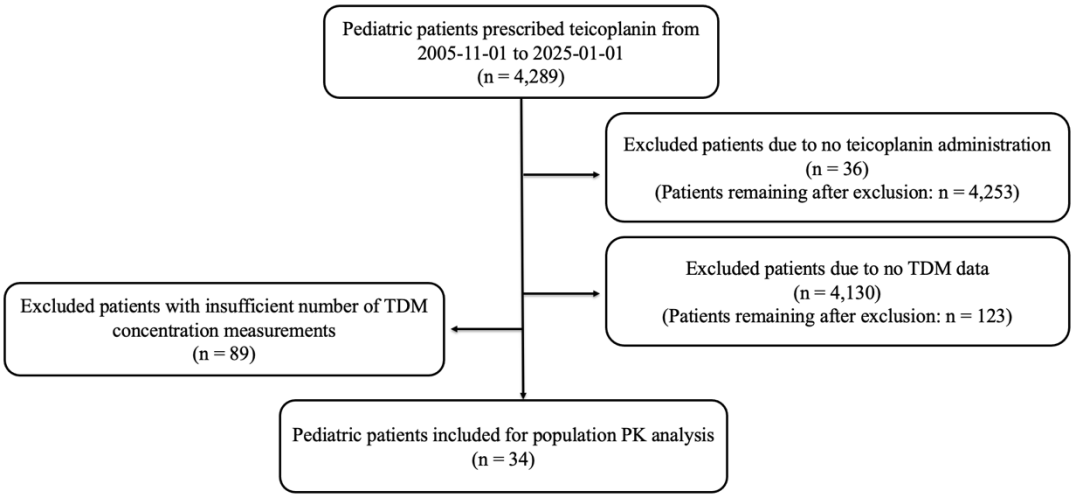

Figure 1. Flow diagram of patient selection of population pharmacokinetic analysis.
TDM, therapeutic drug monitoring; PK, pharmacokinetics

Table 1. Demographic and clinical characteristics of pediatric patients included in the population pharmacokinetic analysis

Demographic or clinical characteristics	Median value (range)
Demographic characteristics	
Number of patients	34
Sex (M:F)	19:15
Age (yrs)	4.50 (0-18)
Weight (kg)	12.83 (0.60-74.50)
Height (cm)	95.60 (27.00-180.00)
BSA (m^2)	0.59 (0.10-1.86)
GA (wks)	40.00 (23.14-40.00)
PNA (wks)	244.64 (0.00-963.29)
PMA (wks)	284.64 (24.71-1003.29)
Laboratory parameter	
BUN (mg/dL)	14.20 (5.10-52.90)
SCr (mg/dL)	0.39 (0.16-2.07)
AST (IU/L)	46.00 (12.00-2599)
ALT (IU/L)	28.50 (2.00-1467.00)
ALB (g/dL)	3.50 (1.90-4.80)
TBIL (mg/dL)	0.85 (0.20-14.20)
DBIL (mg/dL)	0.85 (0.10-6.30)
TP (g/dL)	5.60 (3.60-9.20)
WBC ($10^3/\mu L$)	7.24 (0.05-34.35)
Cys C (mg/L)	1.24 (0.39-3.65)
eGFR (mL/min/1.73 m^2)	57.86 (25.26-169.85)

M, male; F, female; BSA, body surface area; GA, gestational age; PNA, postnatal age; PMA, postmenstrual age; BUN, blood urea nitrogen; SCr, serum creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; TBIL, total bilirubin; DBIL, direct bilirubin; TP, total protein; WBC, white blood cell count; CysC, cystatin C; eGFR, estimated glomerular filtration rate

Table 2. Distribution of pediatric patients by age included in the population pharmacokinetic analysis

Age (yrs)	Number of Patients (n)
0	13
1	2
2	1
3	0
4	1
5	2
6	0
7	0
8	1
9	0
10	2
11	2
12	0
13	2
14	2
15	2
16	2
17	0
18	2

yrs, years; n, number of patients

3.2 Evaluation of Standard Dosage Regimens of Teicoplanin at Severance Hospital

To evaluate the appropriateness of standard teicoplanin dosage regimens, patients were stratified into six finer age groups as presented in Table 3. This stratification was performed to allow a more detailed evaluation of dosing adequacy, as current dosing guidelines group pediatric patients into broad age categories that may overlook pharmacokinetic variability within each group. Three key components were evaluated for each age group: 1) the median time from first teicoplanin administration to initial TDM sampling; 2) the number of patients whose initial teicoplanin concentration fell within the target therapeutic range (15–30 μg/mL); and 3) the number of TDM samples within the target range across all sampling time points.

The age distribution of the included patients was uneven, with nearly half (47.1%, n = 16) classified into the $0 \leq \text{Age} < 3$ group, as shown in Table 3. This uneven distribution of included patients should be considered when evaluating the standard dosing regimens of teicoplanin at Severance Hospital.

Table 3. Age group categorization for analysis

Categorization	Age (yrs)	Total Number of Patients
1	$0 \leq \text{Age} < 3$	16
2	$3 \leq \text{Age} < 6$	3
3	$6 \leq \text{Age} < 9$	1
4	$9 \leq \text{Age} < 12$	4
5	$12 \leq \text{Age} < 15$	4
6	$15 \leq \text{Age} \leq 18$	6

yrs, years

3.2.1 Median Time to Initial TDM

The median time to initial TDM varied by age group, with median values ranging from 4.00 to 8.90 days, as summarized in Table 4.

In the youngest age group ($0 \leq \text{Age} < 3$), the median (range) time to initial TDM was 5.96 days (1.98–14.98). A shorter median of 4.93 days (1.98–7.06) was observed in the $3 \leq \text{Age} < 6$ group, suggesting earlier TDM in this subgroup. The $6 \leq \text{Age} < 9$ group had the longest median time of 8.90 days; however, this result was based on a single patient and thus may not be generalizable.

The shortest median time was observed in the $9 \leq \text{Age} < 12$ group at 4.00 days (2.77–4.98), after excluding one patient whose initial TDM sampling occurred at 89.01 days. Among adolescents, the median times were 6.12 days (4.98–9.60) in the $12 \leq \text{Age} < 15$ group and 6.76 days (2.71–26.13) in the $15 \leq \text{Age} \leq 18$ group.

These findings highlight variation in the timing of TDM initiation across age groups, which may impact the interpretation of early drug exposure and target attainment.

Table 4. Median time to initial sampling day after first teicoplanin administration.

Age Groups	Median Time [hours (range)]	Median Time [days (range)]
0 ≤ Age < 3	142.92 (47.50–359.50)	5.96 (1.98–14.98)
3 ≤ Age < 6	118.25 (47.50–169.50)	4.93 (1.98–7.06)
6 ≤ Age < 9[a]	213.50	8.90
9 ≤ Age < 12[b]	96.00 (66.50–119.50)	4.00 (2.77–4.98)
12 ≤ Age < 15	146.75 (119.50–230.50)	6.12 (4.98–9.60)
15 ≤ Age ≤ 18	162.25 (65.02–627)	6.76 (2.71–26.13)

[a] Since there was only one individual in this age group, the value is reported instead of the median

[b] The first sampling for ID 27 was excluded from the median calculation due to an excessively delayed sampling time (ID 27 = 2136.33 hours, 89.01 days)

3.2.2 Number of Patients within Optimal Concentration Range on Initial Sampling Day

The distribution of teicoplanin concentrations on the initial TDM day varied across age groups, with the majority of patients failing to achieve the target therapeutic range of 15–30 μg/mL, as summarized in Table 5. Overall, only 32.4% (n = 11) of the 34 patients were within the optimal concentration range, while 55.9% (n = 19) had subtherapeutic levels (<15 μg/mL) and 11.8% (n = 4) showed supratherapeutic levels (>30 μg/mL).

Among the youngest group (0 ≤ Age < 3), 68.8% (n = 11) of patients were subtherapeutic and 31.3% (n = 5) were within the target range. In the 3 ≤ Age < 6 group, 66.7% (n = 2) achieved the target concentration while one patient (33.3%) was subtherapeutic. The 6 ≤ Age < 9 group included only a single patient, who showed subtherapeutic concentration. In the 9 ≤ Age < 12 group, half of the patients (n = 2) reached the optimal range, whereas one patient (25.0%) was subtherapeutic and another (25.0%) was supratherapeutic. In the 12 ≤ Age < 15 group, two patients (50.0%) were subtherapeutic, while one patient each (25.0%) fell within the target or supratherapeutic range. Similarly, in the 15 ≤ Age ≤ 18 group, 50.0% (n = 3) were subtherapeutic, 16.7% (n = 1) within range, and 33.3% (n = 2) supratherapeutic.

These findings demonstrate variability in target attainment across age groups, with subtherapeutic exposure being most prevalent, particularly in younger children. Notably, 68.8% of patients in 0 ≤ Age < 3 group showed subtherapeutic concentrations, suggesting that the current dosing regimens may be insufficient for achieving therapeutic levels, highlighting the potential need for dose optimization especially in younger pediatric populations.

Table 5. Initial teicoplanin concentration by age group at first TDM

Age Groups	<15 μg/mL [n (%)]	15-30 μg/mL [n (%)]	>30 μg/mL [n (%)]	Total (n)
0 ≤ Age < 3	11 (68.75)	5 (31.25)	0	16
3 ≤ Age < 6	1 ((33.33)	2 (66.67)	0	3
6 ≤ Age < 9	1 (100)	0	0	1
9 ≤ Age < 12	1 (25.00)	2 (50.00)	1 (25.00)	4
12 ≤ Age < 15	2 (50.00)	1 (25.00)	1 (25.00)	4
15 ≤ Age ≤ 18	3 (50.00)	1 (16.67)	2 (33.33)	6
Total	19 (55.88)	11 (32.35)	4 (11.76)	34

n, number of patients

3.2.3 Number of Samples within Optimal Concentration Range Across All Sampling Days

The distribution of teicoplanin concentrations across all TDM samples, including the first measurement, is summarized in Table 6 and Figure 2. Overall, only 36.1% (n = 39) of the 108 total samples were within the target therapeutic range (15–30 μg/mL), whereas 52.8% (n = 57) were subtherapeutic (<15 μg/mL) and 11.1% (n = 12) were supratherapeutic (>30 μg/mL).

In the 0 ≤ Age < 3 group, the majority of samples (67.4%, n = 33) were subtherapeutic, while 28.6% (n = 14) fell within the optimal range and 4.1% (n = 2) were supratherapeutic. The 3 ≤ Age < 6 group had the highest proportion of optimal concentrations (53.9%, n = 7), with 38.5% (n = 5) subtherapeutic and 7.7% (n = 1) supratherapeutic. In the 6 ≤ Age < 9 group, all samples (100%, n = 3) were subtherapeutic, although this reflects data from a single patient.

Among the 9 ≤ Age < 12 group, 43.8% (n = 7) of samples were within the target range, with 31.3% (n = 5) subtherapeutic and 25.0% (n = 4) supratherapeutic. The 12 ≤ Age < 15 group showed 40.0% (n = 4) within range, 50.0% (n = 5) subtherapeutic, and 10.0% (n = 1) supratherapeutic. Similarly, in the 15 ≤ Age ≤ 18 group, 41.2% (n = 7) of samples achieved the target range, while 35.3% (n = 6) were subtherapeutic and 23.5% (n = 4) supratherapeutic.

These results demonstrate the overall limited attainment of therapeutic teicoplanin concentrations across pediatric age groups, with younger children showing particularly high rates of subtherapeutic exposure despite ongoing treatment. This finding further supports the need for age-specific dose optimization, especially in patients under 3 years of age.

Table 6. Teicoplanin concentrations by age group across all TDM samples.

Age Groups	<15 μg/mL [n (%)]	15-30 μg/mL [n (%)]	>30 μg/mL [n (%)]	Total (n)
0 ≤ Age < 3	33 (67.35)	14 (28.57)	2 (4.08)	49
3 ≤ Age < 6	5 (38.46)	7 (53.85)	1 (7.69)	13
6 ≤ Age < 9	3 (100)	0	0	3
9 ≤ Age < 12	5 (31.25)	7 (43.75)	4 (25.00)	16
12 ≤ Age < 15	5 (50.00)	4 (40.00)	1 (10.00)	10
15 ≤ Age ≤ 18	6 (35.29)	7 (41.18)	4 (23.53)	17
Total	57 (52.78)	39 (36.11)	12 (11.11)	108

n, number of samples

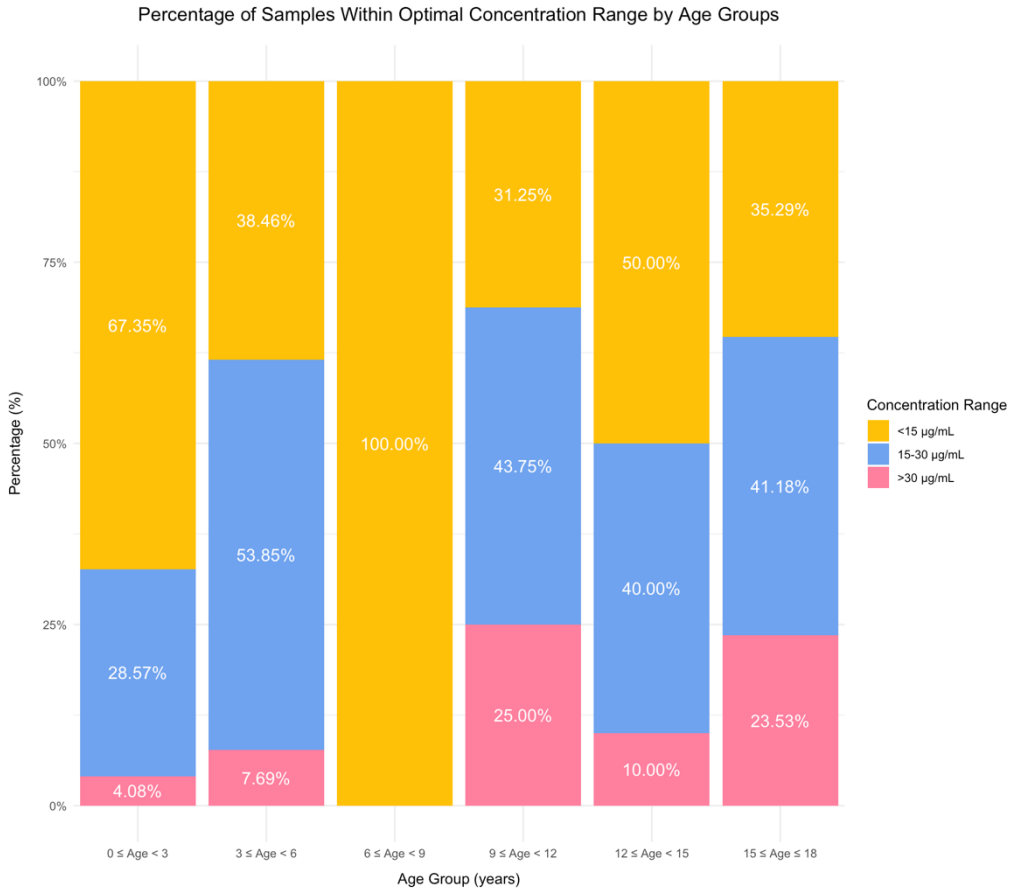

Figure 2. Percentage of samples within optimal concentration range by age groups.

3.3 Population PK Model

Various model structures were explored to determine the most appropriate base model. These included combinations of infusion administration with one- or two-compartment models, absorption with or without lag time, and linear or nonlinear elimination kinetics. However, models incorporating lag time or nonlinear elimination produced inappropriate parameter estimates with excessively large RSE values, as summarized in Tables 7–10.

During the error model evaluation, the proportional error model was determined to best fit the data, based on model fit statistics and parameter precision (Table 11). As a result, the teicoplanin concentration data were best described by a one-compartment structure with infusion administration, no absorption delay, and first-order (linear) elimination. The estimated pharmacokinetic parameters were clearance (CL) and volume of distribution (Vd), while residual variability was modeled using a proportional error model with a coefficient of b = 0.359.

Covariate analysis was performed using a combination of forward inclusion and backward elimination procedures (Table 12). Among the tested covariates (e.g., age, albumin, eGFR) only body weight resulted in a statistically significant reduction in the OFV. While other covariates were evaluated exploratorily, they did not meet criteria for inclusion. Consequently, body weight was retained as a covariate on both CL and Vd in the final model.

A comparison between the full covariate model and a fixed-exponent allometric scaling model (using exponents of 0.75 for CL and 1.0 for Vd) showed only a minor increase in OFV (743.69 vs. 746.00), which was not statistically significant ($p > 0.05$), as presented in Table 13. Given its enhanced interpretability and generalizability for pediatric populations, the allometric scaling model was ultimately chosen as the final model.

The final parameter estimates for both the base and final models are summarized in Table 14. In the final model, the estimated CL was 0.22 L/h and the Vd was 11.98 L, with acceptable precision and shrinkage. This model was subsequently used to perform simulations for identifying optimal teicoplanin dosing regimens in pediatric patients.

Table 7. Parameters estimates for one-compartment with infusion administration and no lag time.

Parameter	Infusion and non-linear elimination		Infusion and linear elimination	
	Value	RSE %	Value	RSE %
-2LL	806.18	-	805.93	-
AIC	820.18	-	815.93	-
BIC	830.87	-	823.56	-
V	8.61	54.6	10.615	53.989
CL	-	-	0.185	30.348
Vm	27765867.17	55.6	-	-
Km	142952991.9	55.1	-	-
ωV	1.4	25.0	1.417	23.253
ωCL	-	-	1.161	17.841
ωVm	0.69	34.1	-	-
ωKm	0.89	23.5	-	-
b	0.36	9.36	0.359	9.6

V, volume of distribution; CL, clearance; Vm, maximum elimination rate; Km, Michaelis constant; ω^2, between-subject variance for the corresponding parameter; b, proportional residual error; RSE, relative standard error; −2LL, negative twice the log-likelihood; AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 8. Parameters estimates for one-compartment with infusion administration and lag time.

Parameter	Infusion and non-linear elimination		Infusion and linear elimination	
	Value	RSE %	Value	RSE %
-2LL	805.95	-	806	-
AIC	823.95	-	820	-
BIC	837.69	-	830.68	-
Tlag	0.0017	1.47e+4	0.15	440
V	12.56	46.4	10.83	47.8
CL	-	-	0.19	24.7
Vm	59319567.36	115	-	-
Km	340061676.01	124	-	-
ωTlag	2.01	56.1	0.7	55.9
ωV	1.41	27.2	1.37	24.3
ωCL	-	-	1.13	14.8
ωVm	0.7	85.4	-	-
ωKm	0.93	56.7	-	-
b	0.36	9.17	0.36	9.14

V, volume of distribution; CL, clearance; Vm, maximum elimination rate; Km, Michaelis constant; Tlag, lag time; ω^2, between-subject variance for the corresponding parameter; b, proportional residual error; RSE, relative standard error; −2LL, minus twice the log-likelihood; AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 9. Parameter estimates for two compartments with infusion administration and no lag time.

Parameter	Infusion and non-linear elimination		Infusion and linear elimination	
	Value	RSE %	Value	RSE %
-2LL	799.82	-	804	-
AIC	821.82	-	822	-
BIC	838.61	-	835.74	-
V1	5.35	1.54e+12	7.1	112
Q	0.24	1.89e+3	235.9	5.26e+120
V2	1145.89	8.11e+27	0.14	7.19e+3
CL	-	-	0.19	32.3
Vm	0.00027	Infinity	-	-
Km	8729.32	NaN	-	-
ωV1	1.69	126	1.37	45.5
ωQ	1.26	68.0	4.37	167
ωV2	0.87	282	3.45	30.0
ωCL	-	-	1.14	15.7
ωVm	3.27	127	-	-
ωKm	1.97	493	-	-
b	0.33	34.1	0.33	10.3

V1, central volume of distribution; V2, peripheral volume of distribution; Q, intercompartmental clearance; CL, clearance; Vm, maximum elimination rate; Km, Michaelis constant; ω^2, between-subject variance for the corresponding parameter; b, proportional residual error; RSE, relative standard error; −2LL, minus twice the log-likelihood; AIC, Akaike information criterion; BIC, Bayesian information criterion; NaN, not a number, indicating unreliable or non-estimable parameter; Infinity, indicating an unreasonably large or undefined estimate due to model overparameterization or convergence failure.

Table 10. Parameters estimates for two compartments with infusion administration and lag time absorption.

Parameter	Infusion and non-linear elimination		Infusion and linear elimination	
	Value	RSE %	Value	RSE %
-2LL	800.36	-	793.77	-
AIC	826.36	-	815.77	-
BIC	846.21	-	832.56	-
Tlag	0.0064	6.81e+5	0.017	NaN
V1	4.9	58.7	0.0019	Infinity
Q	0.26	30.4	66.62	1.36e+30
V2	1180.4	123	9.75	54.5
CL	-	-	0.19	29.9
Vm	0.00000058	1.21e+28	-	-
Km	15162.34	NaN	-	-
ωTlag	3.41	47.8	2.51	258
ωV1	1.33	31.5	3.54	80.1
ωQ	1.26	15.3	4.13	115
ωV2	1.06	44.3	1.41	29.5
ωCL	-	-	1.11	14.0
ωVm	5.68	85.5	-	-
ωKm	4.71	123	-	-
b	0.33	11.4	0.32	16.6

V1, central volume of distribution; V2, peripheral volume of distribution; Q, intercompartmental clearance; CL, clearance; Vm, maximum elimination rate; Km, Michaelis constant; Tlag, lag time; ω^2, between-subject variance for the corresponding parameter; b, proportional residual error; RSE, relative standard error; −2LL, minus twice the log-likelihood; AIC, Akaike information criterion; BIC, Bayesian information criterion; NaN, not a number, indicating unreliable or non-estimable parameter; Infinity, indicating an unreasonably large or undefined estimate due to model overparameterization or convergence failure.

Table 11. Comparison of parameter estimates across different error models using the selected base model.

Parameter	Infusion and linear elimination (proportional)		Infusion and linear elimination (combined 1)		Infusion and linear elimination (combined 2)		Infusion and linear elimination (constant)	
	Value	RSE %	Value	RSE %	Value	RSE %	Value	RSE %
-2LL	805.93	-	805.7	-	805.56	-	850.46	-
AIC	815.93	-	817.7	-	817.56	-	860.46	-
BIC	823.56	-	826.86	-	826.72	-	868.09	-
V	10.615	54.0	9.95	51.0	10.2	47.1	1.32	643
CL	0.185	30.3	0.19	27.0	0.19	25.3	0.34	23.0
ωV	1.417	23.3	1.36	23.4	1.35	21.5	2.85	34.6
ωCL	1.161	17.8	1.18	15.8	1.15	14.8	0.9	18.4
a	-		0.0096	8.15e+3	0.088	7.61e+3	9.65	8.58
b	0.359	9.6	0.36	13.4	0.35	9.13	-	-

V, volume of distribution; CL, clearance; ω^2, between-subject variance for the corresponding parameter; a, additive residual error; b, proportional residual error; RSE, relative standard error; –2LL, minus twice the log-likelihood; AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 12. Objective function values during covariate selection by stepwise forward inclusion and backward elimination.

Parameter	OFV	△OFV
Round 1: Forward inclusion	805.91	
logWT on V	789.49	-16.42
logWT on CL	**753.05**	**-52.86**
logALB on V	801.55	-4.36
Age on CL	778.09	-27.82
logeGFR on CL	805.32	-0.59
Round 2: Forward inclusion		
logWT on CL, logWT on V	**743.69**	**-9.36**
logWT on CL, logALB on V	752.94	-0.11
logWT on CL, Age on CL	751.84	-1.21
logWT on CL, logeGFR on CL	750.91	-2.14
Round 3: Forward inclusion		
logWT on CL, logWT on V, logALB on V	742.18	-1.51
logWT on CL, logWT on V, Age on CL	741.83	-1.86
logWT on CL, logWT on V, logeGFR on CL	742.23	-1.46
Round 5: Backward elimination		
logWT on CL	753.05	9.36
logWT on V	789.49	45.8

OFV, objective function value; ΔOFV, change in OFV relative to the base model; logWT, natural log-transformed body weight; logALB, natural log-transformed albumin; logeGFR, natural log-transformed estimated glomerular filtration rate; Bold text indicates statistically significant reduction in OFV ($p < 0.05$); Bold and underlined text indicates the covariate model selected as the final model during covariate selection.

Table 13. Comparison of objective function values between base, selected covariate, and allometric scaling model.

Parameter	Base Model	Covariate Model[1]	Allometric Scaling Model[2]
OFV	805.9	743.69	746

[1] Covariate model includes log-transformed body weight (logWT) as a covariate on clearance (CL) and volume of distribution (V).

[2] Allometric scaling model incorporates fixed exponents of 0.75 for CL and 1 for V based on body weight.
OFV, objective function value.

Table 14. Parameter estimates from the base and final population pharmacokinetic models.

Parameter	Base Model (OFV: 805.9)			Final Model (OFV: 746)		
	Population	RSE (%)	Shrinkage (%)	Population	RSE (%)	Shrinkage (%)
V (L)	10.615	53.989	39.333	11.982	30.847	47.644
CL (L/h)	0.185	30.348	7.747	0.22	9.758	9.04
Effect of weight on V	-	-	-	Fixed to 1	-	-
Effect of weight on CL	-	-	-	Fixed to 0.75	-	-
Between-subject variability (%CV)						
ωV	1.417 (253.863)	23.253	-	0.705 (80.21)	34.305	-
ωCL	1.161 (168.866)	17.841	-	0.448 (47.102)	15.748	-
Error model						
b	0.359	9.6	-	0.366	9.385	-

V, volume of distribution; CL, clearance; RSE, relative standard error; CV, coefficient of variation; %CV, percent coefficient of variation; ωV, between-subject variability (BSV) on volume of distribution (V); ωCL, between-subject variability (BSV) on clearance (CL); b, proportional residual error coefficient; OFV, objective function value.

3.4 Model Evaluation

The final model demonstrated improved parameter precision, with RSEs CL and V reduced compared to the base model. Specifically, the RSE for CL decreased from 30.35% to 9.76%, and the RSE for V from 53.99% to 30.85%, as summarized in Table 14. These values fell within the acceptable range (30–50%) defined in the methodology section, indicating that the final model provided reasonably precise parameter estimates.

GOF diagnostic plots for the final model are presented in Figures 3 to 6. In the observed versus predicted plots, the base model showed underprediction in the mid- to high-concentration range (~10–30 μg/mL), evidenced by the downward deviation of the spline curve from the identity line (Appendix 1, Figure 1). In contrast, the final model showed improved alignment, with the spline more closely following the y = x line across the concentration range, as shown in Figure 3.

Residual-based diagnostics further supported the improved performance. In the base model, population-weighted residuals (PWRES) showed extreme positive deviations exceeding +10 (Appendix 1, Figure 2). However, in the final model, PWRES were well constrained within approximately ±3 (Figure 4), indicating reduced variability and a better model fit.

Additionally, visual predictive check (VPC) plots (Figures 5 and 6) also confirmed enhanced predictive performance. The final model exhibited narrower 90% prediction intervals compared to the base model (Appendix 1, Figures 3 and 4), suggesting improved precision in the predicted percentiles. The 10th, 50th, and 90th percentiles of observed concentrations were better captured within the model-derived intervals, and the number of outlier regions was substantially reduced.

Collectively, these improvements in spline alignment, residual distribution, and narrower prediction intervals indicate that the final model demonstrated improved GOF and predictive performance compared to the base model.

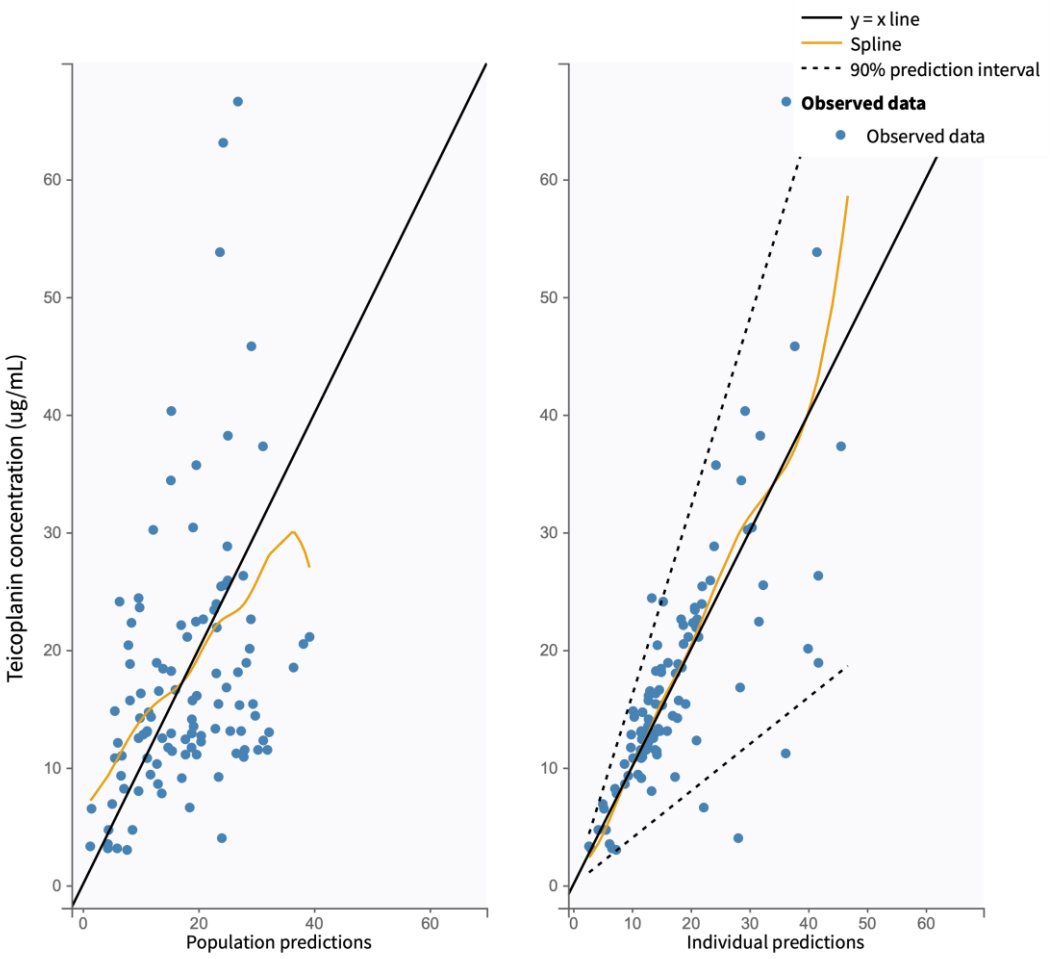

Figure 3. Observed versus prediction teicoplanin concentrations for the final model.
Scatter plots of observed teicoplanin concentrations versus population predictions (left) and individual predictions (right). The solid black line represents the line of identity (y = x). The yellow spline indicates a locally weighted regression fit to the data. The dashed lines in the individual prediction panel represent the 90% prediction interval.

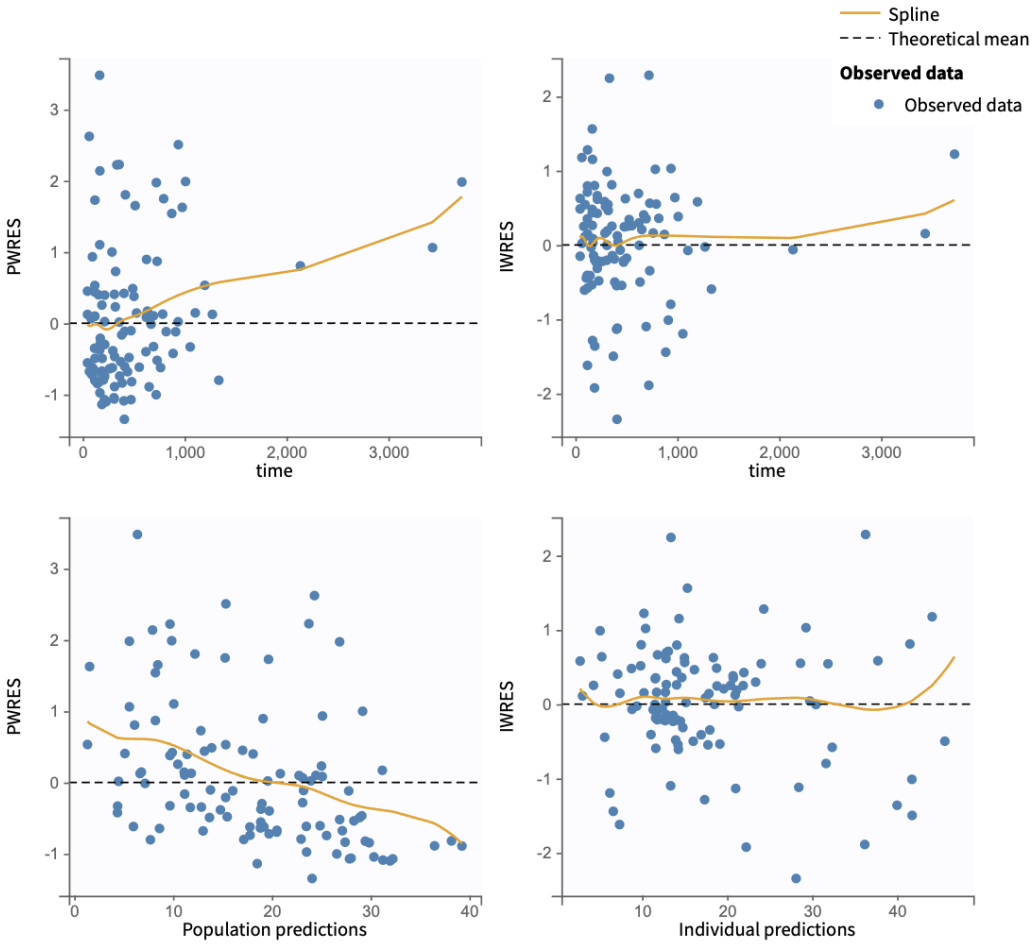

Figure 4. Scatter plots of residuals for the final model.
Scatterplots of population-weighted residuals (PWRES, left panels) and individual-weighted residuals (IWRES, right panels) versus time and predicted concentrations. The solid yellow line represents a spline smoother; the dashed line indicates the theoretical mean (y = 0).

3.5 Simulation

To reflect the final population PK model in which body weight was identified as the only significant covariate, all simulations were stratified by body weight, which were categorized into five weight-based groups: <4 kg, 4–10 kg, 10–30 kg, 30–50 kg, and >50 kg. This stratification allowed for the evaluation of dosing strategies tailored to weight-related pharmacokinetic differences, thereby enhancing the precision of exposure predictions across pediatric subpopulations.

Although simulations were initially planned based on age groups (0–3, 3–6, 6–9, 9–12, 12–15, and 15–18 years), the final analysis was conducted according to weight groups, as age was not identified as a significant covariate. Simulation results stratified by age group are available in Appendix 4.

3.5.1 Simulation for Early Target Attainment

Based on the early target attainment strategy, simulations were first conducted using loading dose regimens consisting of 3, 4, or 5 doses administered at 12-hour intervals to identify the regimen that achieved the highest mean PTA within the 15–30 μg/mL at the end of the loading phase (47, 59, or 71 hours post-initial dose). Additionally, an alternative regimen of four doses at 6-hour intervals was explored to assess potential improvement in target attainment; however, no improvement in PTA was observed. These results are summarized in Table 15 and Figures 7–9.

In the <4 kg group, the regimen of 12 mg/kg q12h × 4 achieved the highest PTA of 57.23%, with 19.38% of patients exceeding 30 μg/mL and 23.39% remaining below 15 μg/mL. For the 4–10 kg group, 10 mg/kg q12h × 5 resulted in the highest PTA of 57.36%, with 24.75% >30 μg/mL and 17.89% <15 μg/mL. In the 10–30 kg group, 8 mg/kg q12h × 5 showed a PTA of 56.98%, with 17.54% above and 25.48% below the target range. The same LD regimen (8 mg/kg q12h × 5) provided the highest PTA in the 30–50 kg group as well, with 53.50% within the target range, and 27.28% >30 μg/mL and 19.22% <15 μg/mL. Lastly, in the >50 kg group, 6 mg/kg q12h × 5 achieved the highest PTA of 52.61%, while 13.92% and 33.47% of patients fell outside the upper and lower bounds of the target range, respectively. These loading dose regimens were fixed for subsequent maintenance dose evaluation.

Using these fixed loading regimens, simulations were conducted to identify the maintenance dose that achieved the highest PTA at Day 21 (Table 16 and Figures 10–13). In the <4 kg group, a maintenance dose of 12 mg/kg resulted in a PTA of 56.55%, with 17.53% of patients exceeding 30 μg/mL and 25.92% remaining below 15 μg/mL. For the 4–10 kg group, 10 mg/kg once daily yielded the highest PTA of 56.07%, with 16.48% and 27.45% of patients above and below the target range, respectively. In the 10–30 kg group, 8 mg/kg provided the highest PTA of 55.89%, with 14.33% above and 29.78% below the target range. The same maintenance dose of 8 mg/kg was also optimal in the 30–50 kg group, resulting in a PTA of 56.54%, with 29.21% >30 μg/mL and 14.26% <15 μg/mL. Finally, in the >50 kg group, a maintenance dose of 6 mg/kg produced the highest PTA of 59.34%, with 18.32% exceeding and 22.34% falling below the target range.

Following the selection of both optimal loading and maintenance dose combinations, the time-course of PTA was evaluated across Days 4, 7, 14, and 21 to confirm sustained target attainment throughout therapy, as summarized in Table 17. Across all weight groups, PTA values within the 15–30 μg/mL remained above 50% at every time point, supporting the adequacy and clinical feasibility of the selected regimens for ongoing therapy.

Table 15. Simulated mean PTA (%) for C_{min} with Different loading dose schedules across weight groups

LD q12h x 3

Mean PTA (%) at 47 Hours for Cmin in the <4 kg Group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	10.56	0.16	89.29	89.44
8	27.71	1.26	71.03	72.29
10	43.55	4.65	51.81	56.45
12	53.04	10.71	36.25	46.96
14	55.93	19.16	24.92	44.07
16	53.87	28.97	17.15	46.13
18	49.24	38.80	11.97	50.76

Mean PTA (%) at 47 Hours for Cmin in the 4-10 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	17.29	0.42	82.29	82.71
8	36.91	2.90	60.19	63.09
10	50.28	8.63	41.09	49.72
12	54.76	17.71	27.53	45.25
14	52.93	28.62	18.46	47.07
16	47.64	39.81	12.55	52.36
18	41.29	49.92	8.79	58.71

Mean PTA (%) at 47 Hours for Cmin in the 10-30 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	23.52	1.01	75.48	76.48
8	42.24	5.22	52.54	57.76
10	51.66	13.37	34.96	48.34
12	52.20	24.53	23.28	47.80
14	47.78	36.46	15.76	52.22
16	41.66	47.46	10.88	58.34
18	35.30	56.97	7.73	64.70

Mean PTA (%) at 47 Hours for Cmin in the 30-50 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	30.31	2.21	67.48	69.69
8	45.56	9.03	45.41	54.44
10	50.11	19.99	29.90	49.89
12	47.36	32.52	20.13	52.65
14	41.70	44.53	13.77	58.30
16	35.71	54.60	9.70	64.29
18	29.86	63.20	6.94	70.14

Mean PTA (%) at 47 Hours for Cmin in the >50 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	33.60	3.42	62.98	66.40
8	46.08	11.94	41.98	53.92
10	47.88	24.27	27.85	52.12
12	44.16	37.02	18.83	55.84
14	38.46	48.55	12.99	61.54
16	32.77	58.02	9.21	67.23
18	27.47	65.92	6.62	72.53

LD q12h x 4

Mean PTA (%) at 59 Hours for Cmin in the <4 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	18.93	0.45	80.62	81.07
8	39.72	3.17	57.11	60.28
10	53.29	9.54	37.17	46.71
12	57.23	19.38	23.39	42.77
14	54.29	30.99	14.72	45.71
16	47.71	42.89	9.40	52.29
18	40.27	53.61	6.13	59.73

Mean PTA (%) at 59 Hours for Cmin in the 4-10 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	28.86	1.27	69.88	71.14
8	49.24	6.54	44.22	50.76
10	56.79	16.82	26.39	43.21
12	54.31	30.13	15.57	45.70
14	46.90	43.62	9.48	53.10
16	38.25	55.78	5.97	61.75
18	30.34	65.74	3.92	69.66

Mean PTA (%) at 59 Hours for Cmin in the 10-30 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	36.65	2.79	60.57	63.36
8	52.96	11.05	36.00	47.04
10	54.67	24.45	20.88	45.33
12	48.21	39.43	12.36	51.79
14	39.45	52.93	7.62	60.55
16	31.03	64.00	4.97	68.97
18	24.09	72.59	3.32	75.91

Mean PTA (%) at 59 Hours for Cmin in the 30-50 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	43.45	5.63	50.92	56.55
8	52.84	18.06	29.10	47.16
10	48.95	34.10	16.95	51.05
12	40.69	49.08	10.24	59.32
14	32.04	61.49	6.47	67.96
16	24.81	70.90	4.28	75.19
18	19.18	77.90	2.91	80.82

Mean PTA (%) at 59 Hours for Cmin in the >50 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	45.84	8.25	45.91	54.16
8	50.74	23.04	26.22	49.27
10	44.89	39.72	15.39	55.11
12	36.42	54.09	9.49	63.58
14	28.56	65.40	6.04	71.44
16	22.18	73.78	4.04	77.82
18	17.24	80.02	2.75	82.76

LD q12h x 5

Mean PTA (%) at 71 Hours for Cmin in the <4 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	26.04	0.99	72.97	73.96
8	47.41	5.47	47.12	52.59
10	57.16	14.61	28.23	42.84
12	56.36	27.03	16.61	43.64
14	49.58	40.54	9.88	50.42
16	41.08	52.88	6.04	58.92
18	32.93	63.30	3.77	67.08

Mean PTA (%) at 71 Hours for Cmin in the 4-10 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	37.88	2.55	59.57	62.12
8	55.67	10.87	33.46	44.33
10	57.36	24.75	17.89	42.64
12	49.93	40.43	9.65	50.07
14	39.69	54.83	5.48	60.31
16	30.25	66.54	3.21	69.75
18	22.61	75.42	1.98	77.39

Mean PTA (%) at 71 Hours for Cmin in the 10-30 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	46.02	5.09	48.89	53.99
8	56.98	17.54	25.48	43.02
10	52.28	34.60	13.11	47.72
12	41.76	51.11	7.13	58.24
14	31.41	64.46	4.13	68.59
16	23.00	74.52	2.48	77.00
18	16.75	81.71	1.54	83.25

Mean PTA (%) at 71 Hours for Cmin in the 30-50 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	51.75	9.81	38.44	48.25
8	53.50	27.28	19.22	46.50
10	43.95	45.99	10.06	56.05
12	32.80	61.56	5.64	67.20
14	23.78	72.85	3.38	76.23
16	17.12	80.78	2.10	82.88
18	12.44	86.24	1.32	87.56

Mean PTA (%) at 71 Hours for Cmin in the >50 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	52.61	13.92	33.47	47.39
8	49.48	33.71	16.81	50.52
10	38.77	52.25	8.98	61.23
12	28.33	66.53	5.14	71.67
14	20.47	76.42	3.11	79.53
16	14.87	83.19	1.94	85.13
18	10.90	87.85	1.25	89.10

LD q6h x 4

Mean PTA (%) at 41 Hours for Cmin in the <4 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	35.77	2.74	61.49	64.23
8	51.82	10.92	37.26	48.18
10	54.09	23.97	21.95	45.92
12	48.33	38.51	13.16	51.67
14	40.08	51.77	8.15	59.92
16	31.99	62.74	5.28	68.02
18	25.15	71.37	3.48	74.85

Mean PTA (%) at 41 Hours for Cmin in the 4-10 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	42.78	5.37	51.84	57.22
8	52.80	17.30	29.90	47.20
10	49.45	33.10	17.45	50.55
12	41.28	48.16	10.56	58.72
14	32.60	60.70	6.70	67.40
16	25.47	70.10	4.43	74.53
18	19.72	77.28	3.01	80.29

Mean PTA (%) at 41 Hours for Cmin in the 10-30 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	45.65	8.49	45.86	54.35
8	50.33	23.30	26.38	49.67
10	44.54	39.89	15.56	55.46
12	36.27	54.14	9.60	63.74
14	28.47	65.38	6.16	71.53
16	22.26	73.62	4.12	77.74
18	17.32	79.87	2.81	82.68

Mean PTA (%) at 41 Hours for Cmin in the 30-50 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	46.36	12.94	40.69	53.64
8	46.57	29.96	23.48	53.43
10	39.48	46.39	14.13	60.52
12	31.85	59.31	8.84	68.15
14	25.03	69.23	5.74	74.97
16	19.62	76.52	3.86	80.38
18	15.49	81.86	2.65	84.51

Mean PTA (%) at 41 Hours for Cmin in the >50 kg group				
LD (mg/kg)	15-30 µg/mL (%)	>30 µg/mL (%)	<15 µg/mL (%)	Total Out-of-Target (%)
6	45.57	16.17	38.27	54.43
8	44.00	33.75	22.25	56.00
10	37.05	49.48	13.47	62.95
12	29.81	61.73	8.45	70.19
14	23.53	70.93	5.54	76.47
16	18.52	77.75	3.73	81.48
18	14.66	82.78	2.56	85.34

Green shading indicates the loading dose regimen with the highest PTA among all simulated dosing schedules.

LD, loading dose; q12h, every 12 hours; q6h, every 6 hours; C_{min}, minimum (trough) concentration; PTA, probability of target attainment; >30 µg/mL (%), proportion of individuals with C_{min} above the target range; <15 µg/mL (%), proportion of individuals with C_{min} below the target range; 15–30 µg/mL (%), proportion of individuals within the target concentration range; Total Out-of-Target (%), combined percentage of individuals with C_{min} <15 and >30 µg/mL.

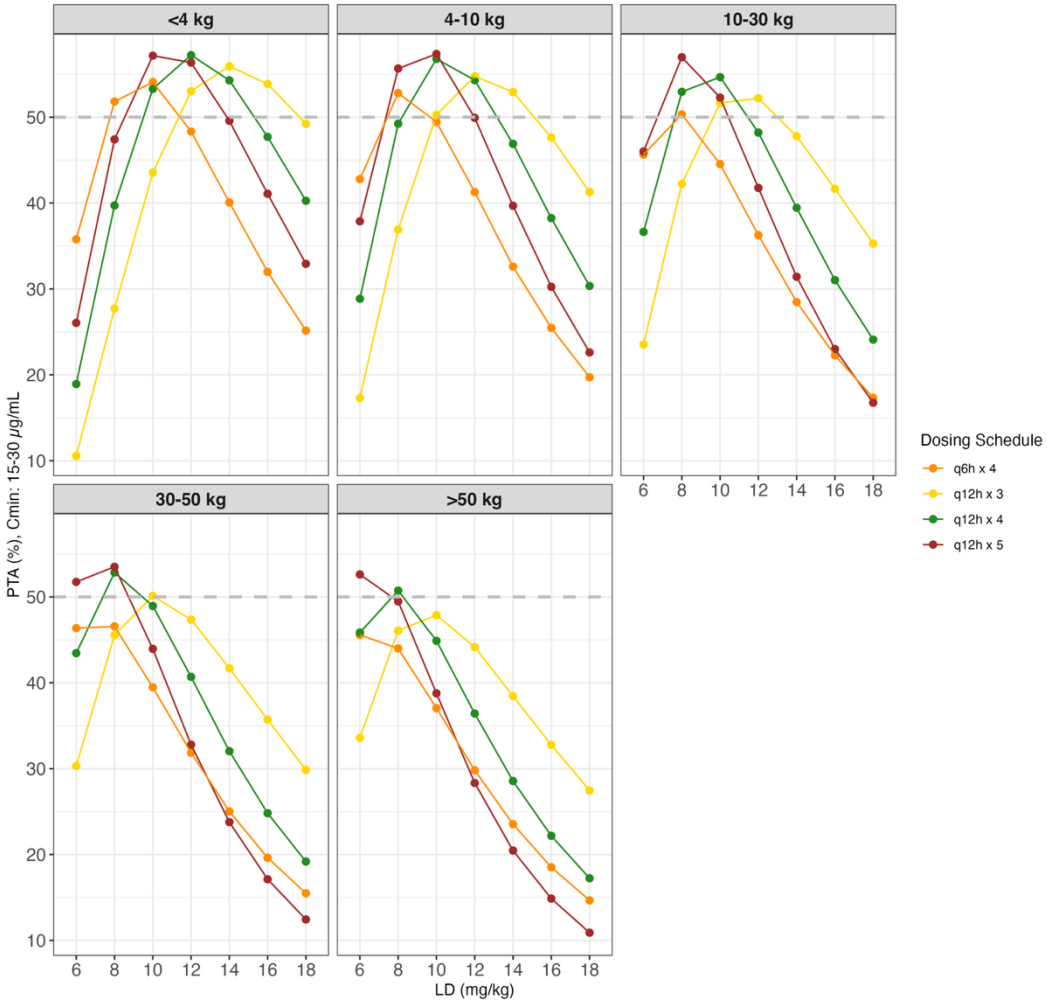

Figure 5. Mean PTA (%) for C_{min} 15–30 μg/mL with different loading dose schedules across weight groups.

Lines represent different loading dose schedules: yellow, 3 doses at 12-hour intervals; green, 4 doses at 12-hour intervals; brown, 5 doses at 12-hour intervals; orange, 4 doses at 6-hour intervals. The horizontal dashed line indicates the 50% PTA threshold.

PTA, probability of target attainment; C_{min}, minimum (trough) concentration; LD, loading dose; q12h, every 12 hours; q6h, every 6 hours.

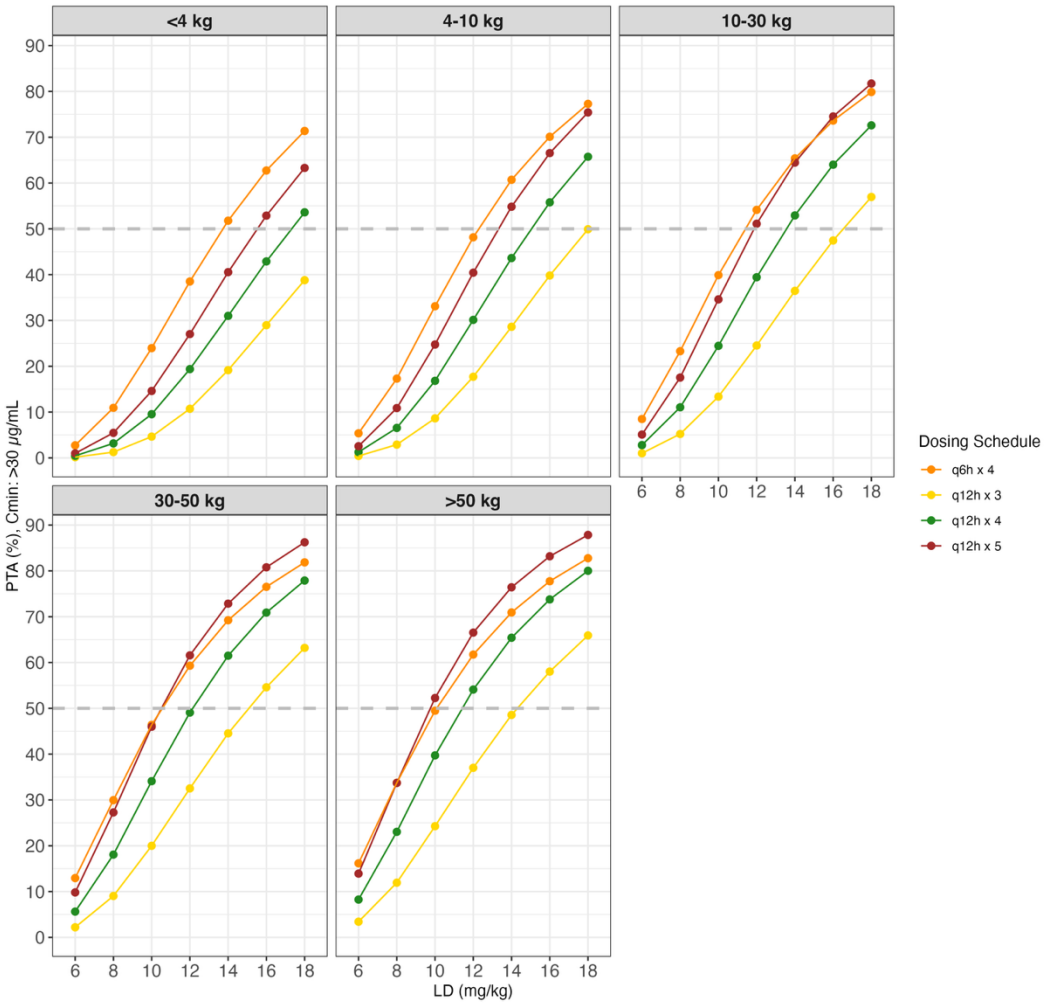

Figure 6. Mean PTA (%) for C_{min} >30 μg/mL with different loading dose schedules across weight groups.

Lines represent different loading dose schedules: yellow, 3 doses at 12-hour intervals; green, 4 doses at 12-hour intervals; brown, 5 doses at 12-hour intervals; orange, 4 doses at 6-hour intervals. The horizontal dashed line indicates the 50% PTA threshold.

PTA, probability of target attainment; C_{min}, minimum (trough) concentration; LD, loading dose; q12h, every 12 hours; q6h, every 6 hours.

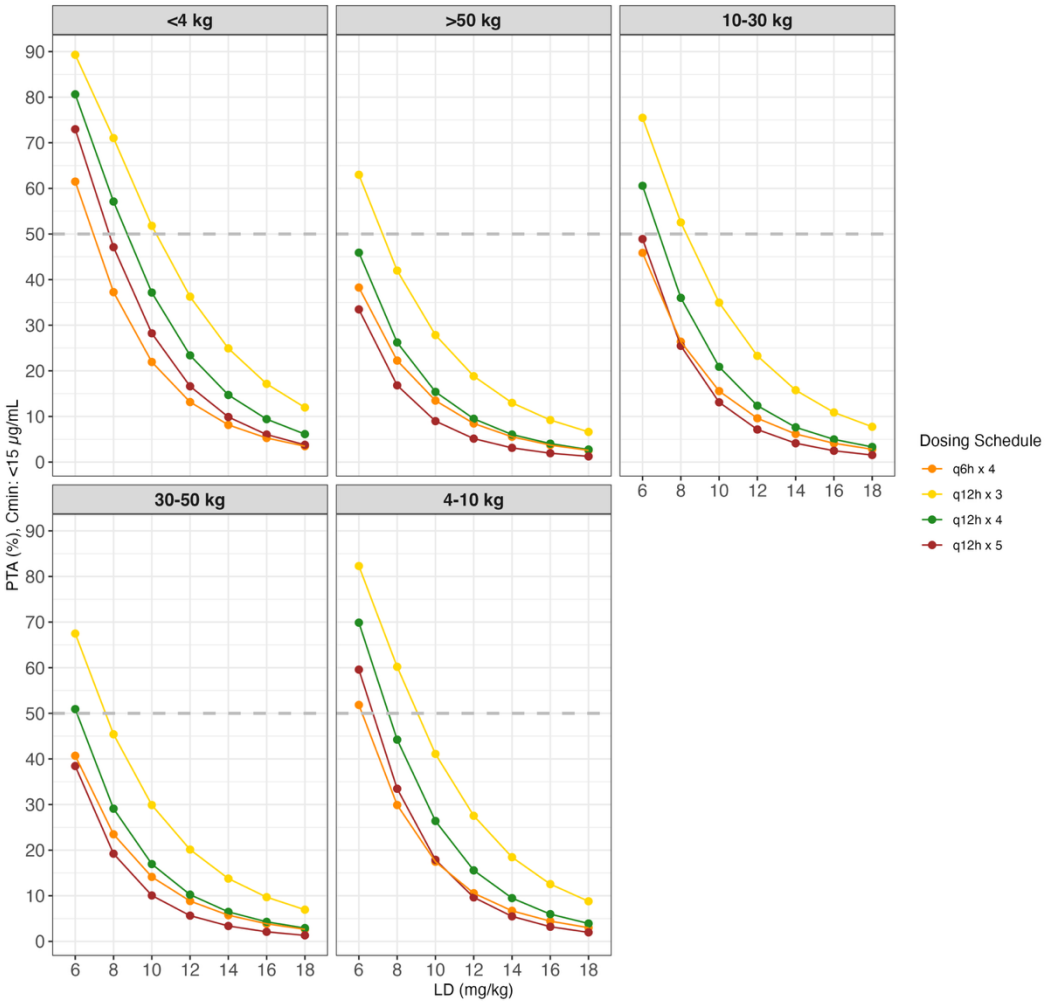

Figure 7. Mean PTA (%) for C_{min} <15 μg/mL with different loading dose schedules across weight groups.

Lines represent different loading dose schedules: yellow, 3 doses at 12-hour intervals; green, 4 doses at 12-hour intervals; brown, 5 doses at 12-hour intervals; orange, 4 doses at 6-hour intervals. The horizontal dashed line indicates the 50% PTA threshold.

PTA, probability of target attainment; C_{min}, minimum (trough) concentration; LD, loading dose; q12h, every 12 hours; q6h, every 6 hours.

Table 16. Simulated mean PTA (%) for C_{min} with different maintenance dose and fixed loading dose across weight groups at Day 21.

<4 kg group (LD 12 mg/kg q12h x 4 fixed)

Mean PTA(%) at Day 21 for Cmin in the <4 kg group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	17.52	0.55	81.93	82.48
8	36.65	3.01	60.34	63.35
10	50.64	8.75	40.61	49.36
12	56.55	17.53	25.92	43.45
14	55.46	28.22	16.32	44.55
16	50.46	39.31	10.23	49.54
18	43.75	49.79	6.46	56.25

4-10 kg group (LD 10 mg/kg q12h x 5 fixed)

Mean PTA(%) at Day 21 for Cmin in the 4-10 kg group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	28.08	1.66	70.26	71.93
8	47.20	6.90	45.91	52.80
10	56.07	16.48	27.45	43.93
12	55.25	28.83	15.92	44.75
14	48.87	41.84	9.29	51.13
16	41.09	53.63	5.28	58.91
18	33.05	63.89	3.06	66.95

10-30 kg group (LD 8 mg/kg q12h x 5 fixed)

Mean PTA(%) at Day 21 for Cmin in the 10-30 kg group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	41.36	4.18	54.46	58.64
8	55.89	14.33	29.78	44.11
10	55.59	29.05	15.36	44.41
12	47.59	44.65	7.77	52.41
14	37.53	58.54	3.93	62.47
16	28.14	69.84	2.03	71.86
18	20.60	78.30	1.10	79.40

30-50 kg group (LD 8 mg/kg q12h x 5 fixed)

Mean PTA(%) at Day 21 for Cmin in the 30-50 kg group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	55.17	11.19	33.64	44.83
8	56.54	29.21	14.26	43.46
10	45.29	48.91	5.80	54.71
12	32.22	65.35	2.43	67.78
14	21.55	77.40	1.05	78.45
16	14.09	85.43	0.48	85.91
18	9.07	90.71	0.22	90.93

>50 kg group (LD 6 mg/kg q12h x 5 fixed)

Mean PTA(%) at Day 21 for Cmin in the >50 kg group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	59.34	18.32	22.34	40.66
8	50.81	41.32	7.87	49.19
10	35.16	62.12	2.72	64.84
12	22.09	76.88	1.03	77.91
14	13.29	86.32	0.40	86.71
16	7.93	91.92	0.15	92.07
18	4.63	95.30	0.07	95.37

Green shading indicates the maintenance dose regimen with the highest PTA among all simulated dosing schedules.
LD, loading dose; MD, maintenance dose; q12h, every 12 hours; C_{min}, minimum (trough) concentration; PTA, probability of target attainment; >30 μg/mL (%), proportion of individuals with C_{min} above the target range; <15 μg/mL (%), proportion of individuals with C_{min} below the target range; 15–30 μg/mL (%), proportion of individuals within the target concentration range; Total Out-of-Target (%), combined percentage of individuals with C_{min} <15 and >30 μg/mL.

Table 17. Summary of simulated mean PTA (%) for C_{min} at Days 4, 7, 14, and 21 by weight group using selected loading and maintenenace dose.

<4 kg group (LD 12 mg/kg q12h x 4, MD 12 mg/kg q24h)

Mean PTA(%) for Cmin in the <4 kg group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
4	57.85	14.62	27.53	42.15
7	57.72	14.39	27.88	42.28
14	57.06	16.63	26.31	42.95
21	56.55	17.53	25.92	43.45

4-10 kg group (LD 10 mg/kg q12h x 5, MD 10 mg/kg q24h)

Mean PTA(%) for Cmin in the 4-10 kg group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
4	58.40	16.50	25.11	41.61
7	57.25	13.50	29.25	42.75
14	56.69	15.33	27.98	43.32
21	56.07	16.48	27.45	43.93

10-30 kg group (LD 8 mg/kg q12h x 5, MD 8 mg/kg q24h)

Mean PTA(%) for Cmin in the 10-30 kg group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
4	56.90	11.90	31.21	43.10
7	56.11	10.31	33.59	43.90
14	56.34	12.87	30.80	43.67
21	55.89	14.33	29.78	44.11

30-50 kg group (LD 8 mg/kg q12h x 5, MD 8 mg/kg q24h)

Mean PTA(%) for Cmin in the 30-50 kg group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
4	58.00	22.00	19.99	42.00
7	60.16	21.28	18.56	39.84
14	58.44	26.39	15.16	41.56
21	56.54	29.21	14.26	43.46

>50 kg group (LD 6 mg/kg q12h x 5, MD 6 mg/kg q24h)

Mean PTA(%) for Cmin in the >50 kg group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
4	54.88	10.84	34.28	45.12
7	58.09	11.00	30.91	41.91
14	59.97	15.51	24.52	40.03
21	59.34	18.32	22.34	40.66

LD, loading dose; MD, maintenance dose; q12h, every 12 hours; q24h, every 24 hours; C_{min}, minimum (trough) concentration; PTA, probability of target attainment; >30 μg/mL (%), proportion of individuals with C_{min} above the target range; <15 μg/mL (%), proportion of individuals with C_{min} below the target range; 15–30 μg/mL (%), proportion of individuals within the target concentration range; Total Out-of-Target (%), combined percentage of individuals with C_{min} <15 and >30 μg/mL.

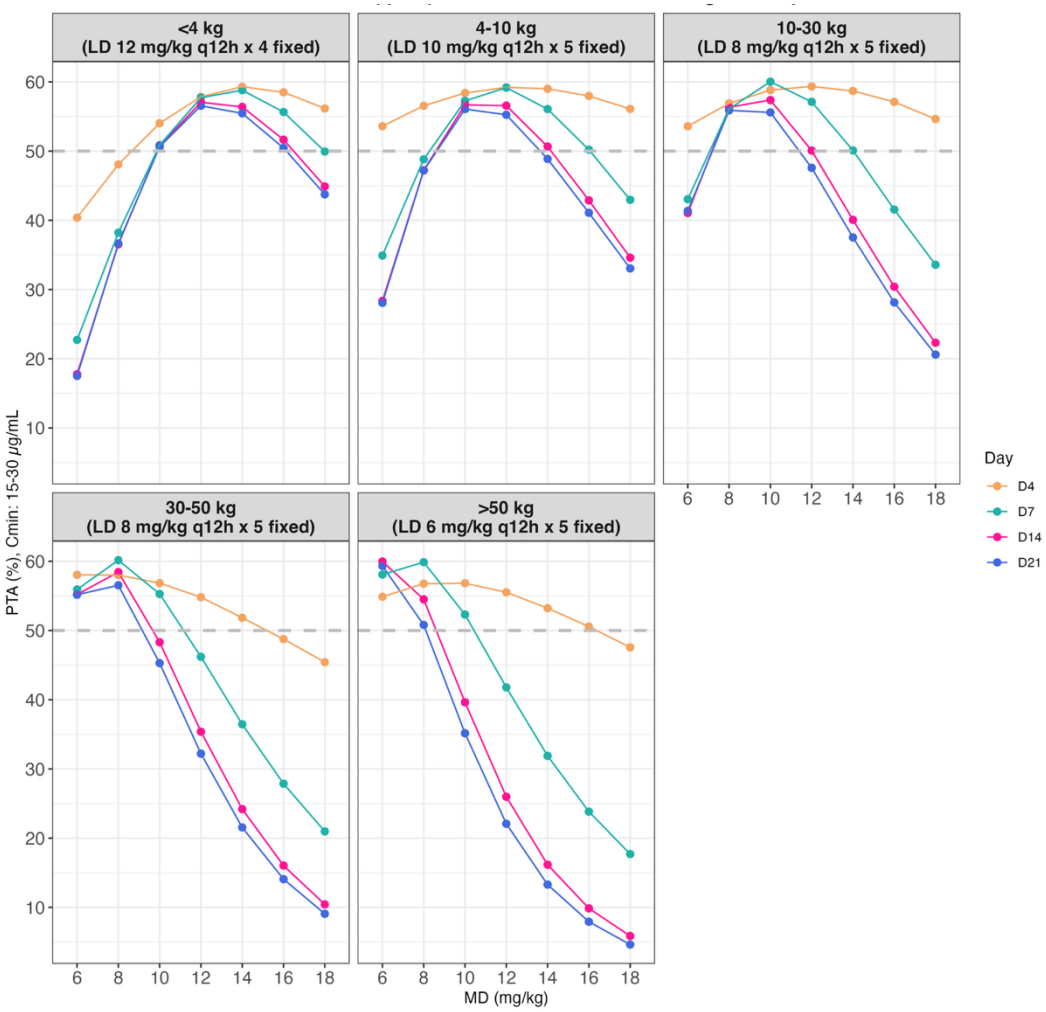

Figure 8. Mean PTA (%) for C_{min} 15–30 ug/mL across different maintenance doses using a fixed loading dose by weight groups.

Lines represent different sampling days: orange, Day 4; light green, Day 7; pink, Day 14; blue, Day 21. The horizontal dashed line indicates the 50% PTA threshold.

PTA, probability of target attainment; C_{min}, minimum (trough) concentration; LD, loading dose; MD, maintenance dose; q12h, every 12 hours.

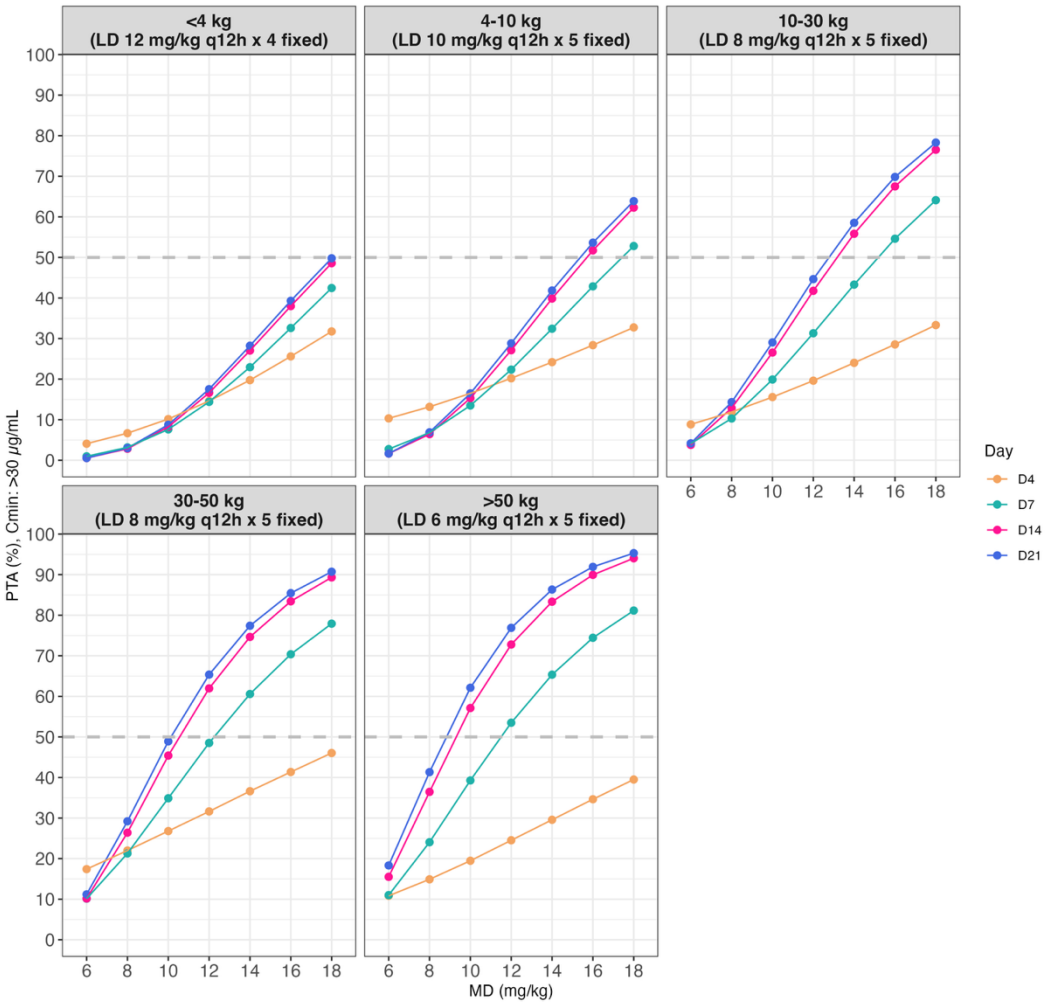

Figure 9. Mean PTA (%) for C_{min} >30 ug/mL across different maintenance doses using a fixed loading dose by weight groups.

Lines represent different sampling days: orange, Day 4; light green, Day 7; pink, Day 14; blue, Day 21. The horizontal dashed line indicates the 50% PTA threshold.

PTA, probability of target attainment; C_{min}, minimum (trough) concentration; LD, loading dose; MD, maintenance dose; q12h, every 12 hours.

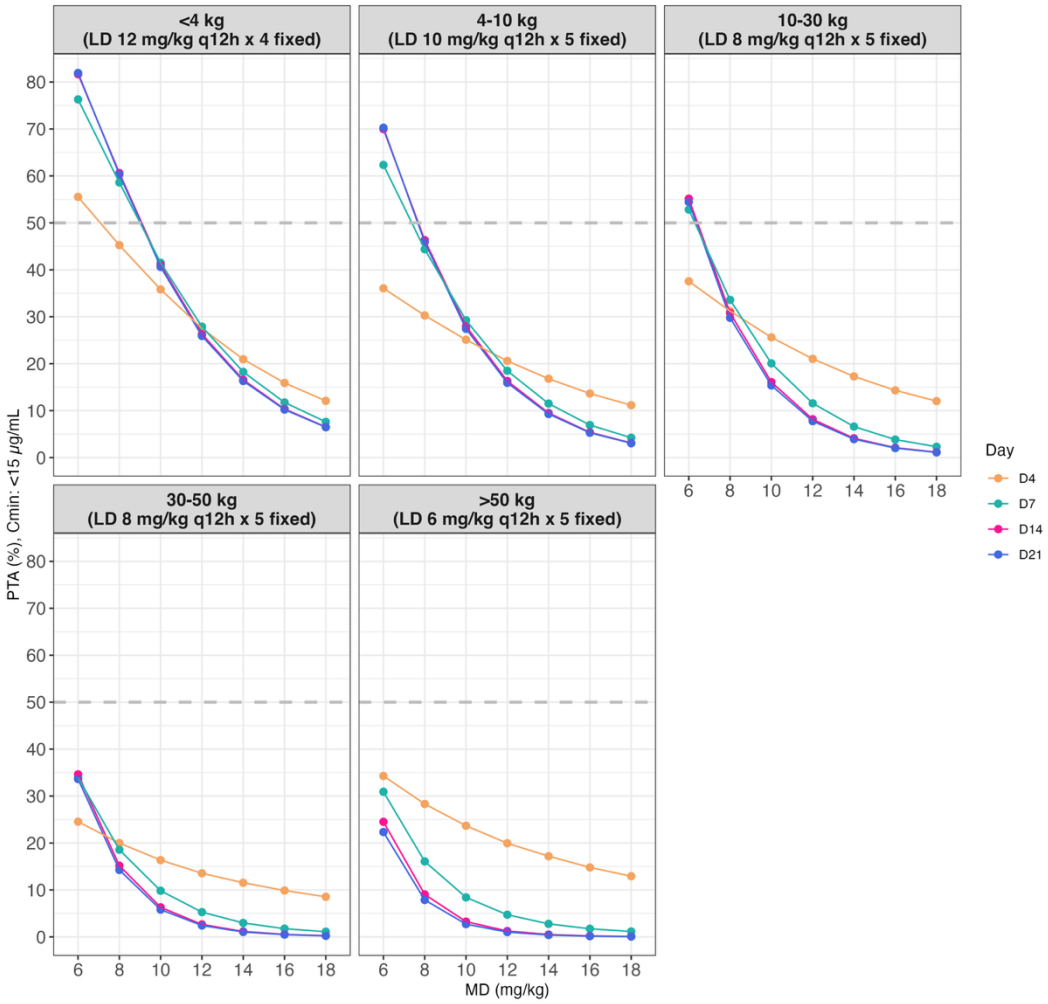

Figure 10. Mean PTA (%) for C_{min} <15 ug/mL across different maintenance doses (q24h) using a fixed loading dose by weight groups.

Lines represent different sampling days: orange, Day 4; light green, Day 7; pink, Day 14; blue, Day 21. The horizontal dashed line indicates the 50% PTA threshold.

PTA, probability of target attainment; C_{min}, minimum (trough) concentration; LD, loading dose; MD, maintenance dose; q12h, every 12 hours.

3.5.2 Simulation for Sustained Target Attainment Strategy

To identify regimens suitable for prolonged treatment, the sustained target attainment strategy began with simulations of various maintenance doses administered at 24-hour intervals to determine those achieving the highest PTA within the 15–30 μg/mL on Day 21. The simulation results are presented in Table 18 and Figures 13–15.

In the <4 kg group, a maintenance dose of 14 mg/kg once daily yielded the highest PTA of 52.24%, with 25.95% of individuals exhibiting C_{min} >30 μg/mL and 21.81% <15 μg/mL. For the 4–10 kg group, 10 mg/kg once daily achieved a PTA of 54.67%, with 18.06% above and 27.27% below the target range. The 10–30 kg group showed optimal results with 8 mg/kg once daily, producing a PTA of 54.83%, with 15.64% >30 μg/mL and 29.53% <15 μg/mL. The same dose of 8 mg/kg was also optimal in the 30–50 kg group, yielding a PTA of 54.97%, with 30.61% above and 14.43% below the target range. Lastly, for the >50 kg group, a dose of 6 mg/kg resulted in the highest PTA of 58.06%, with 19.62% and 22.33% of patients exceeding and falling below the therapeutic range, respectively. These optimal maintenance doses were subsequently fixed for further evaluation of loading dose strategies.

Using the fixed maintenance regimens identified above, loading dose simulations were conducted to determine the dosing regimens that achieved the highest PTA at 47 hours (Table 19 and Figures 16–18). For the <4 kg group, a loading dose of 14 mg/kg produced a PTA of 56.77%, with 21.18% >30 μg/mL and 22.05% <15 μg/mL. In the 4–10 kg group, 12 mg/kg administered three times at 12-hour intervals resulted in a PTA of 56.21%, with 19.44% above and 24.35% below the target range. The 10–30 kg group achieved the highest PTA of 53.80% with 10 mg/kg, accompanied by 14.66% >30 μg/mL and 31.54% <15 μg/mL. The same loading dose of 10 mg/kg also yielded the highest PTA in the 30–50 kg group (51.94%), with 21.57% and 26.49% of individuals exceeding and falling below the target range, respectively. Finally, in the >50 kg group, a loading dose of 10 mg/kg produced a PTA of 49.75%, with 25.99% >30 μg/mL and 24.26% <15 μg/mL.

Following the identification of optimal loading and maintenance dose combinations, the time course of PTA was evaluated across Days 4, 7, 14, and 21 to confirm the consistency of target attainment over the course of treatment (Table 20). All weight groups consistently achieved mean PTA values above 50% within the 15–30 μg/mL range at each time point, supporting the adequacy and clinical feasibility of the selected regimens for long-term therapeutic use.

Table 18. Simulated mean PTA (%) for C_{min} with different maintenance dose across weight groups.

<4 kg group

Mean PTA(%) at Day 21 for Cmin in the <4 kg group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	15.81	0.55	83.63	84.19
8	32.88	2.96	64.16	67.12
10	45.54	8.37	46.08	54.46
12	51.84	16.37	31.79	48.16
14	52.24	25.95	21.81	47.76
16	49.29	35.84	14.88	50.72
18	44.52	45.30	10.18	55.49

4–10 kg group

Mean PTA(%) at Day 21 for Cmin in the 4–10 kg group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	28.75	1.84	69.41	71.25
8	47.09	7.71	45.20	52.91
10	54.67	18.06	27.27	45.33
12	53.27	30.59	16.14	46.74
14	46.97	43.40	9.63	53.03
16	39.56	54.80	5.64	60.45
18	31.99	64.65	3.36	68.01

10–30 kg group

Mean PTA(%) at Day 21 for Cmin in the 10–30 kg group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	41.70	4.66	53.65	58.30
8	54.83	15.64	29.53	45.17
10	53.63	30.86	15.51	46.37
12	45.56	46.36	8.08	54.44
14	36.02	59.77	4.22	63.98
16	27.28	70.47	2.25	72.72
18	20.16	78.59	1.25	79.84

30–50 kg group

Mean PTA(%) at Day 21 for Cmin in the 30–50 kg group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	54.56	11.79	33.66	45.44
8	54.97	30.61	14.43	45.03
10	43.57	50.31	6.12	56.43
12	30.99	66.34	2.67	69.01
14	20.96	77.83	1.21	79.04
16	13.88	85.58	0.55	86.13
18	9.12	90.60	0.28	90.88

>50 kg group

Mean PTA(%) at Day 21 for Cmin in the <50 kg group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	58.06	19.62	22.33	41.94
8	48.76	43.14	8.10	51.24
10	33.52	63.53	2.95	66.48
12	21.15	77.68	1.17	78.85
14	12.95	86.58	0.47	87.06
16	7.91	91.90	0.19	92.09
18	4.76	95.16	0.09	95.24

Green shading indicates the maintenance dose regimen with the highest PTA among all simulated dosing schedules.
MD, maintenance dose; C_{min}, minimum (trough) concentration; PTA, probability of target attainment; >30 μg/mL (%), proportion of individuals with C_{min} above the target range; <15 μg/mL (%), proportion of individuals with C_{min} below the target range; 15–30 μg/mL (%), proportion of individuals within the target concentration range; Total Out-of-Target (%), combined percentage of individuals with C_{min} <15 and >30 μg/mL.

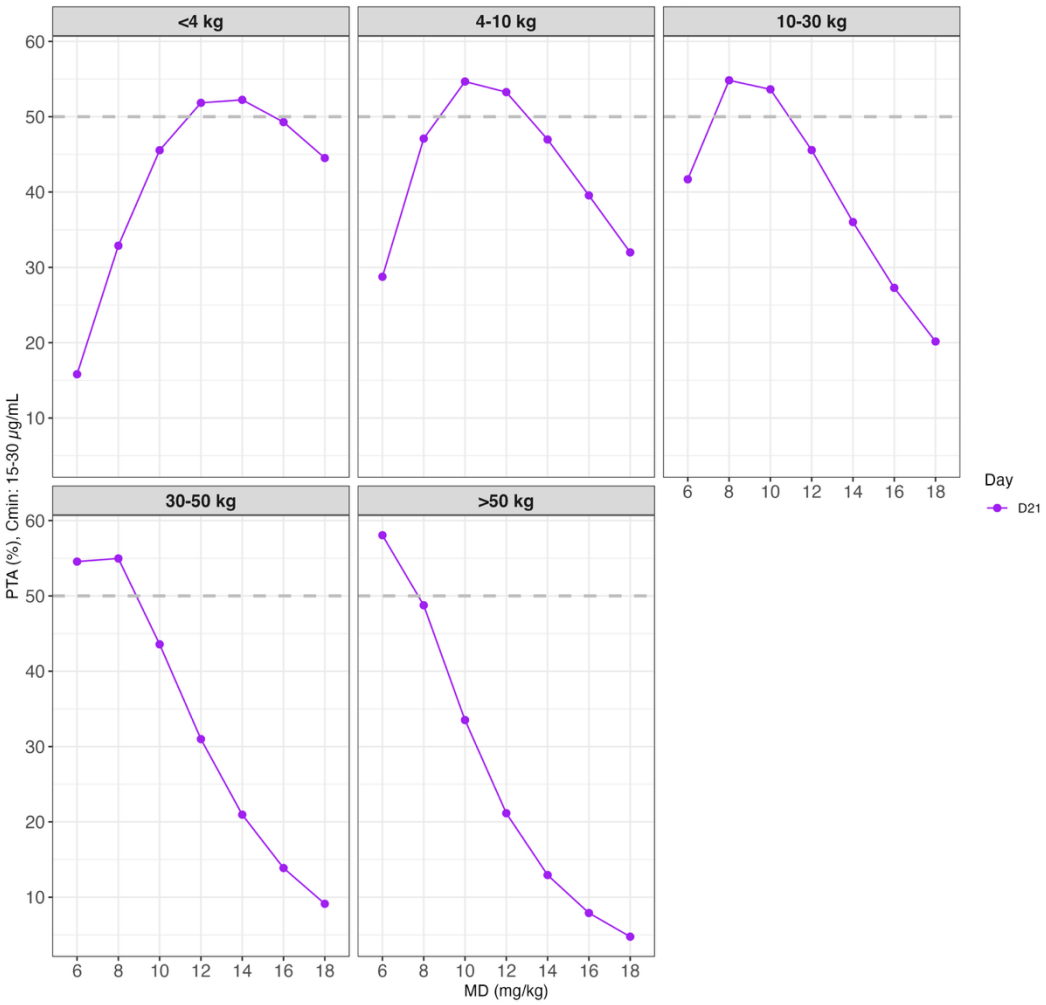

Figure 11. Mean PTA (%) for C_{min} 15–30 ug/mL across different maintenance doses (q24h) by weight groups.

Purple line represents sampling day on Day 21. The horizontal dashed line indicates the 50% PTA threshold.
PTA, probability of target attainment; C_{min}, minimum (trough) concentration; MD, maintenance dose.

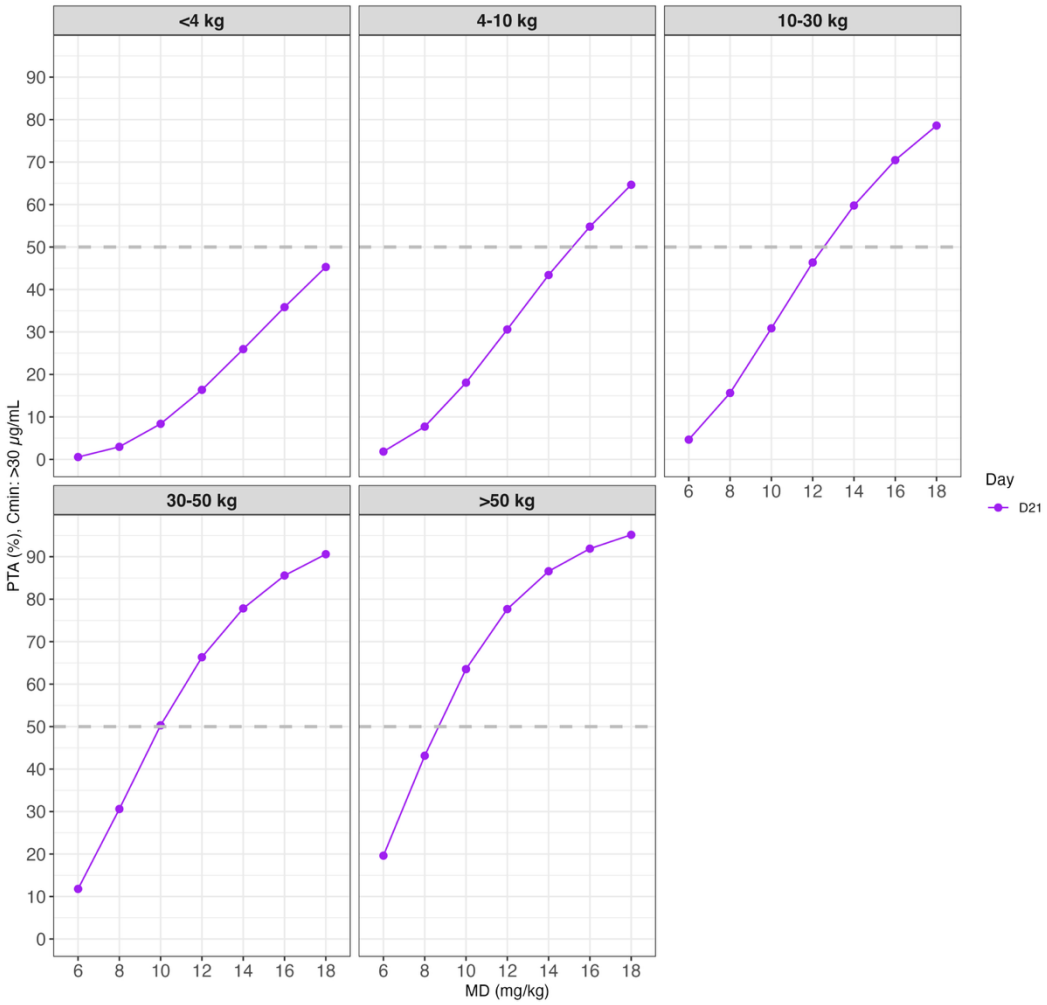

Figure 12. Mean PTA (%) for C_{min} >30 ug/mL across different maintenance doses (q24h) by weight groups.

Purple line represents sampling day on Day 21. The horizontal dashed line indicates the 50% PTA threshold.
PTA, probability of target attainment; C_{min}, minimum (trough) concentration; MD, maintenance dose.

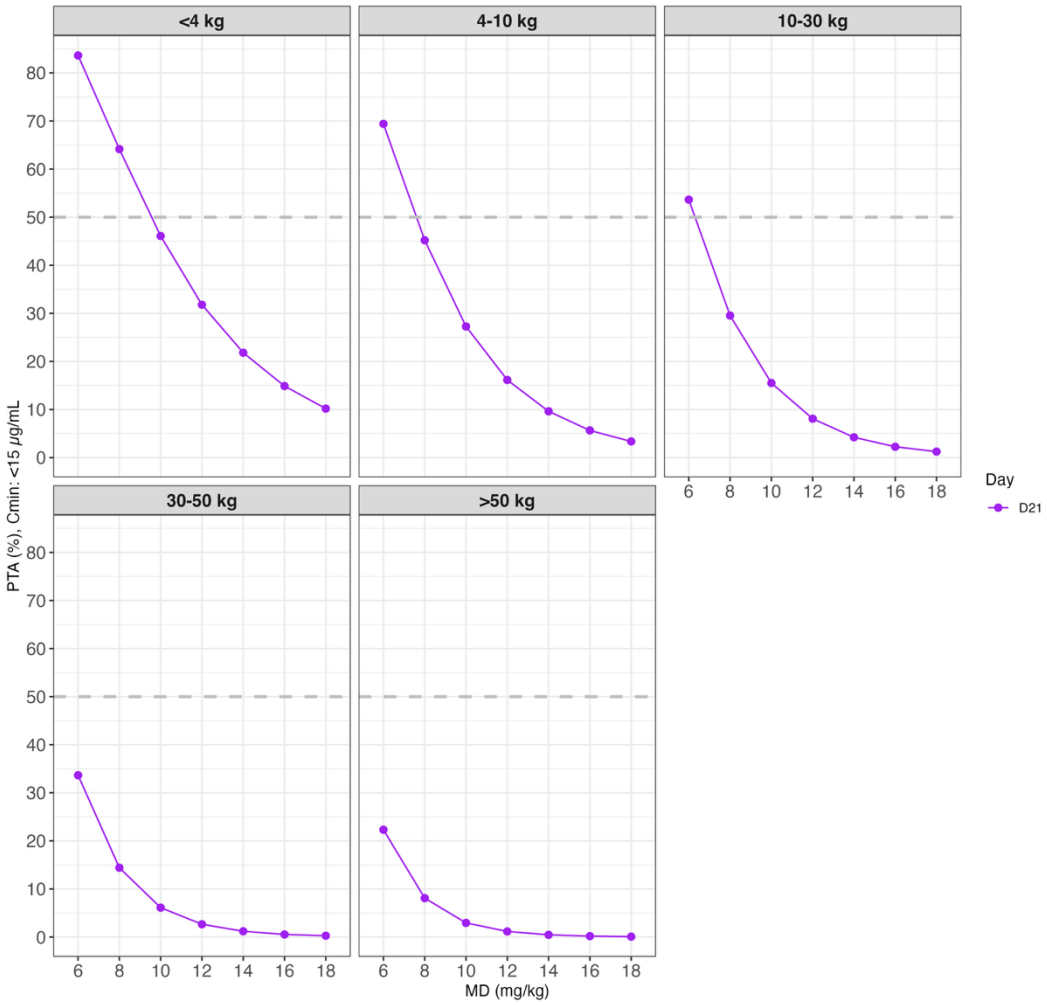

Figure 13. Mean PTA (%) for C_{min} <15 ug/mL across different maintenance doses (q24h) by weight groups.

Purple line represents sampling day on Day 21. The horizontal dashed line indicates the 50% PTA threshold.
PTA, probability of target attainment; C_{min}, minimum (trough) concentration; MD, maintenance dose.

Table 19. Simulated mean PTA (%) for C_{min} with different loading dose and fixed maintenance dose across weight groups at 47 hours.

<4 kg group (MD 14 mg/kg q24h fixed)

Mean PTA(%) at 47 Hours for Cmin in the <4 kg group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	11.88	0.19	87.94	88.12
8	29.85	1.53	68.61	70.15
10	45.99	5.34	48.67	54.01
12	54.88	12.07	33.06	45.12
14	56.77	21.18	22.05	43.23
16	53.95	31.39	14.67	46.05
18	48.47	41.64	9.90	51.53

4–10 kg group (MD 10 mg/kg q24h fixed)

Mean PTA(%) at 47 Hours for Cmin in the 4–10 kg group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	18.94	0.51	80.56	81.07
8	39.28	3.32	57.40	60.72
10	52.55	9.67	37.78	47.45
12	56.21	19.44	24.35	43.80
14	53.39	31.03	15.58	46.61
16	47.19	42.60	10.22	52.81
18	40.00	53.17	6.83	60.00

10–30 kg group (MD 8 mg/kg q24h fixed)

Mean PTA(%) at 47 Hours for Cmin in the 10–30 kg group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	25.44	1.15	73.41	74.56
8	44.70	5.79	49.51	55.30
10	53.80	14.66	31.54	46.20
12	53.39	26.59	20.03	46.61
14	47.99	39.10	12.91	52.01
16	40.96	50.49	8.55	59.04
18	33.76	60.40	5.84	66.24

30–50 kg group (MD 8 mg/kg q24h fixed)

Mean PTA(%) at 47 Hours for Cmin in the 30–50 kg group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	32.49	2.44	65.07	67.51
8	48.20	9.79	42.01	51.80
10	51.94	21.57	26.49	48.06
12	48.14	34.94	16.92	51.86
14	41.51	47.46	11.03	58.49
16	34.58	57.99	7.42	65.42
18	28.14	66.73	5.13	71.86

>50 kg group (MD 6 mg/kg q24h fixed)

Mean PTA(%) at 47 Hours for Cmin in the >50 kg group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	35.86	3.70	60.45	64.14
8	48.66	12.80	38.55	51.34
10	49.75	25.99	24.26	50.25
12	44.84	39.55	15.61	55.16
14	38.09	51.60	10.31	61.91
16	31.57	61.46	6.98	68.43
18	25.60	69.52	4.88	74.40

Green shading indicates the loading dose regimen with the highest PTA among all simulated dosing schedules.

LD, loading dose; MD, maintenance dose; C_{min}, minimum (trough) concentration; PTA, probability of target attainment; q24h, every 24 hours; >30 μg/mL (%), proportion of individuals with C_{min} above the target range; <15 μg/mL (%), proportion of individuals with C_{min} below the target range; 15–30 μg/mL (%), proportion of individuals within the target concentration range; Total Out-of-Target (%), combined percentage of individuals with C_{min} <15 and >30 μg/mL.

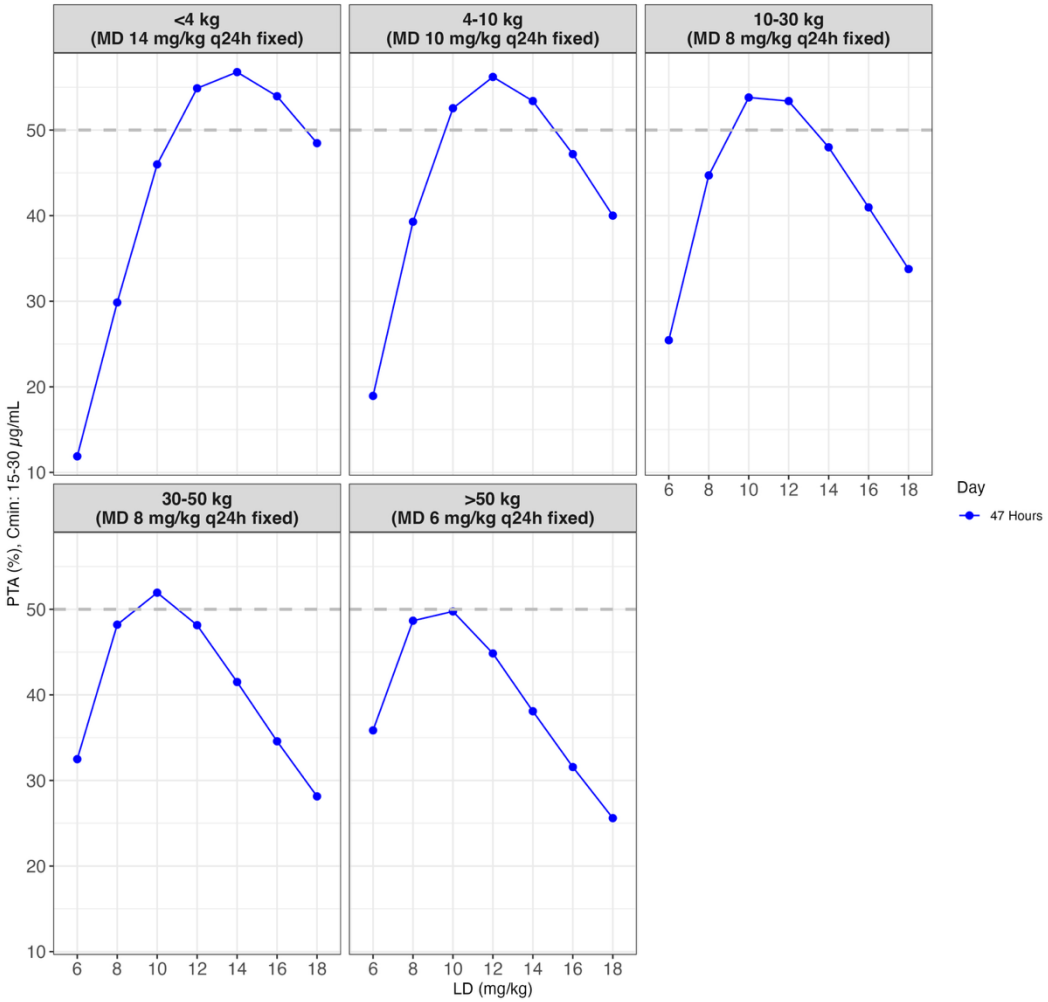

Figure 14. Mean PTA (%) for C_{min} 15–30 ug/mL across different loading doses (q12h x 3) using a fixed maintenance dose by weight groups.

Blue line represents sampling day at 47 hours. The horizontal dashed line indicates the 50% PTA threshold.

PTA, probability of target attainment; C_{min}, minimum (trough) concentration; LD, loading dose; MD, maintenance dose; q12h, every 12 hour.

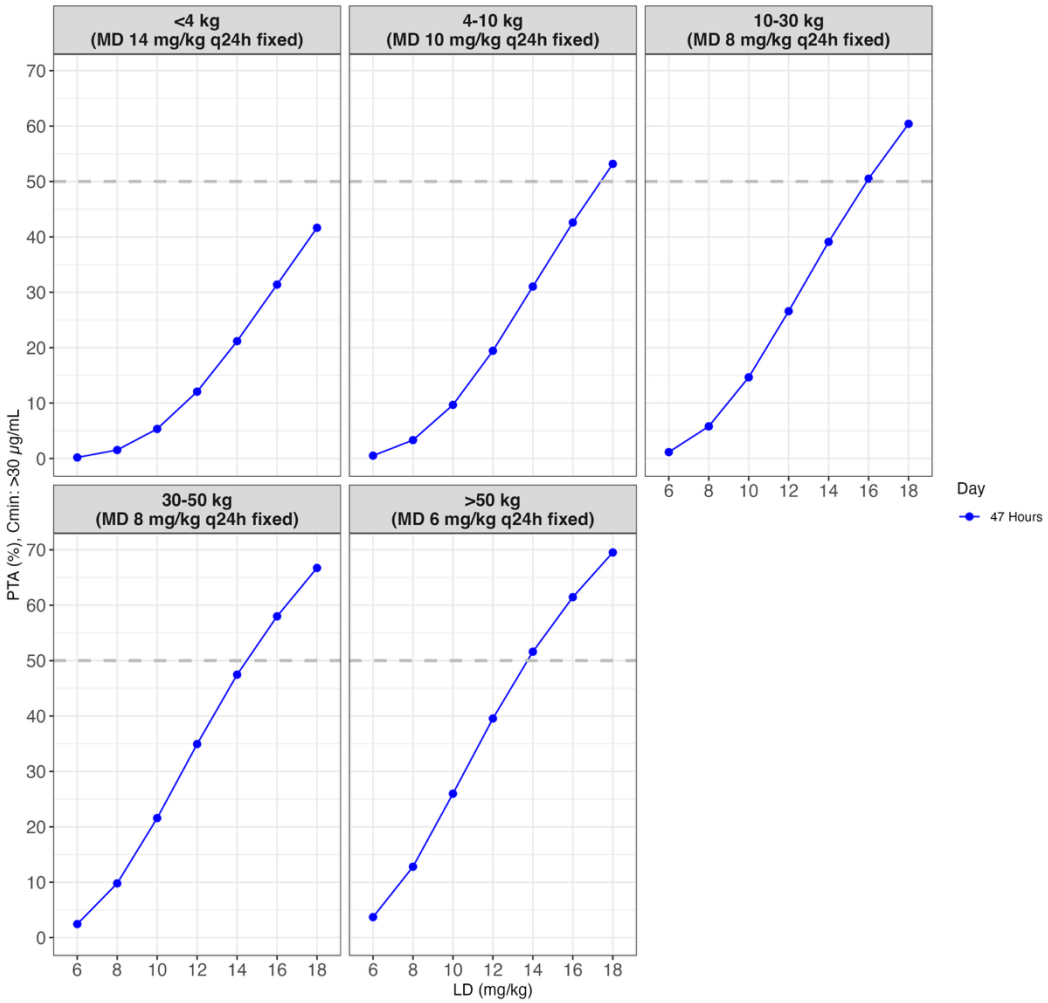

Figure 15. Mean PTA (%) for C_{min} >30 ug/mL across different loading doses (q12h x 3) using a fixed maintenance dose by weight groups.

Blue line represents sampling day at 47 hours. The horizontal dashed line indicates the 50% PTA threshold.

PTA, probability of target attainment; C_{min}, minimum (trough) concentration; LD, loading dose; MD, maintenance dose; q12h, every 12 hours.

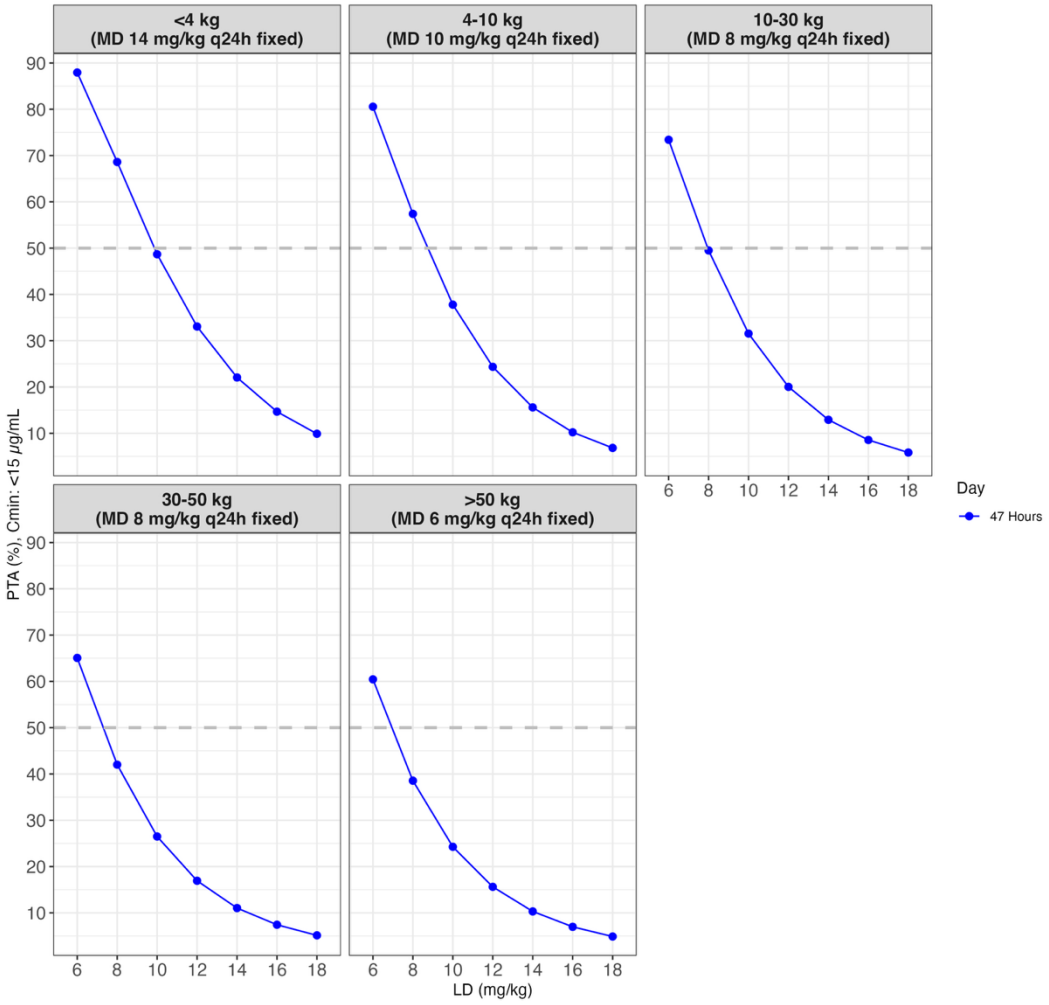

Figure 16. Mean PTA (%) for C_{min} <15 ug/mL across different loading doses (q12h x 3) using a fixed maintenance dose by weight groups.

Blue line represents sampling day at 47 hours. The horizontal dashed line indicates the 50% PTA threshold.

PTA, probability of target attainment; C_{min}, minimum (trough) concentration; LD, loading dose; MD, maintenance dose; q12h, every 12 hours.

Table 20. Summary of simulated mean PTA (%) for C_{min} at Days 4, 7, 14, and 21 by weight group using selected loading and maintenance dose.

<4 kg group
(LD 14 mg/kg q12h x 3, MD 14 mg/kg q24h)

Mean PTA(%) for Cmin in the <4 kg group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
4	57.01	17.68	25.32	42.99
7	55.62	21.23	23.16	44.38
14	52.96	25.10	21.94	47.04
21	52.14	26.06	21.80	47.86

4–10 kg group
(LD 12 mg/kg q12h x 3, MD 10 mg/kg q24h)

Mean PTA(%) for Cmin in the 4–10 kg group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
4	56.81	12.22	30.97	43.19
7	56.49	13.73	29.78	43.51
14	55.35	17.00	27.65	44.65
21	54.50	18.30	27.20	45.50

10–30 kg group
(LD 10 mg/kg q12h x 3, MD 8 mg/kg q24h)

Mean PTA(%) for Cmin in the 10–30 kg group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
4	54.78	9.32	35.90	45.22
7	55.56	10.77	33.66	44.44
14	55.36	14.45	30.19	44.64
21	54.56	16.08	29.36	45.44

30–50 kg group
(LD 10 mg/kg q12h x 3, MD 8 mg/kg q24h)

Mean PTA(%) for Cmin in the 30–50 kg group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
4	59.29	17.93	22.78	40.71
7	59.67	21.69	18.65	40.34
14	56.55	28.45	15.00	43.45
21	54.44	31.26	14.30	45.56

>50 kg group
(LD 10 mg/kg q12h x 3, MD 6 mg/kg q24h)

Mean PTA(%) for Cmin in the >50 kg group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
4	58.39	16.15	25.46	41.61
7	59.02	15.07	25.91	40.98
14	58.48	18.61	22.91	41.52
21	57.31	20.97	21.72	42.69

LD, loading dose; MD, maintenance dose; q12h, every 12 hours; q24h, every 24 hours; C_{min}, minimum (trough) concentration; PTA, probability of target attainment; >30 μg/mL (%), proportion of individuals with C_{min} above the target range; <15 μg/mL (%), proportion of individuals with C_{min} below the target range; 15–30 μg/mL (%), proportion of individuals within the target concentration range; Total Out-of-Target (%), combined percentage of individuals with C_{min} <15 and >30 μg/mL.

4. Discussion

The need for population pharmacokinetic studies of teicoplanin in pediatric patients arises from the considerable interindividual variability in drug disposition due to age, weight, renal function, and the maturation of elimination pathways (Yamada et al., 2022; Ramos-Martín et al., 2014). Despite teicoplanin's favorable safety profile and widespread use in treating MRSA infections, several studies have demonstrated that current pediatric dosing recommendations frequently fail to achieve therapeutic targets in children (Zhao et al., 20215; Sun et al., 2020; Yamada et al., 2016; Ogawa et al., 2013). This highlights the need for dosing strategies that are tailored to pediatric pharmacokinetics. While previous pediatric studies have attempted to optimize teicoplanin regimens using population pharmacokinetic models and Monte Carlo simulations, many of these studies have focused on early trough concentrations (typically Day 3 or 5), or assessed only the probability of exceeding specific trough thresholds such as >10 or >15 μg/mL (Zhao et al., 2015; Zhang et al., 2023; Kim et al., 2024). However, these methods do not evaluate whether drug concentrations are consistently maintained within the recommended therapeutic range of 15–30 μg/mL. This may overlook the risks of subtherapeutic or supratherapeutic exposures, especially in prolonged infections such as infective endocarditis that require sustained treatment over two to three weeks.

To address these limitations, this study aimed to optimize teicoplanin loading and maintenance dosing regimens in pediatric patients by evaluating both early and sustained target attainment at multiple clinically relevant timepoints (Days 4, 7, 14, and 21). Two simulation strategies were conducted. The first strategy focused on early target attainment, where an appropriate loading dose is critical to rapidly achieve therapeutic concentrations, especially in serious infections where early bacterial clearance is important. The second strategy focused on sustained target attainment, emphasizing the importance of maintenance dosing in maintaining trough levels within the therapeutic range over prolonged treatment durations, such as those required for infective endocarditis. This approach allowed us to propose weight-stratified dosing strategies that are better aligned with real-world clinical needs and provide a more comprehensive basis for individualized dosing in pediatric patients.

A one-compartment model with first-order elimination best described the teicoplanin concentration–time data, with body weight identified as the most significant covariate. The estimated volume of distribution (V = 11.982 L; 0.93 L/kg normalized to the median body weight of 12.825 kg) aligns with the established literature range of 0.9–1.6 L/kg (Wilson, 2000), suggesting adequate estimation even with sparse sampling. Clearance was estimated at 0.22 L/h (17.16 mL/h/kg), slightly above the previously reported range of 10–14 mL/h/kg (Wilson, 2000). This may reflect the high variability in renal function or the limited number of samples per subject. However, the relative standard error of the clearance estimate was acceptable, and the overall improvement in goodness-of-fit plots from the base model supports the adequacy of the final parameter estimates.

Based on this model, we performed simulations to evaluate various loading and maintenance dosing strategies for achieving early and sustained target trough concentrations. While three loading doses of 10 mg/kg q12h remain the current standard regimen, our simulations demonstrated that this regimen resulted in lower PTA values across all weight groups as shown in Table 15—43.55% in <4 kg, 50.28% in 4–10 kg, 51.66% in 10–30 kg, 50.11% in 30–50 kg, and 47.88% in >50 kg—when compared to more intensive regimens identified in our analysis. These findings suggest that the standard three-dose loading regimen may be insufficient to achieve early therapeutic exposure in pediatric populations.

Although regimens with the highest PTA were identified, the results also highlight the potential clinical relevance of alternative dosing strategies (Tables 15–16). For example, in the <4 kg group, the selected loading dose of 12 mg/kg q12h × 4 achieved the highest PTA (57.23%), but a lower dose of 10 mg/kg reduced the proportion of patients with >30 μg/mL from 19.38% to 9.54%, whereas a higher dose of 14 mg/kg decreased the proportion <15 μg/mL from 23.39% to 14.72%. In the 4–10 kg group, 8 mg/kg q12h × 5 lowered the >30 μg/mL rate from 24.75% (at 10 mg/kg) to 10.87%, while 12 mg/kg reduced the <15 μg/mL rate from 17.89% to 9.65%. Similarly, in the 10–30 kg group, 6 mg/kg reduced the >30 μg/mL proportion to 5.09%, and 10 mg/kg reduced the <15 μg/mL to 13.11%. For the 30–50 kg group, reducing the loading dose from 8 to 6 mg/kg decreased the >30 μg/mL rate from 27.28% to 9.81%, whereas increasing to 10 mg/kg lowered the <15 μg/mL to 10.06%. In the >50 kg group, although 6 mg/kg yielded the highest PTA, an 8 mg/kg regimen reduced the <15 μg/mL rate from 33.47% to 16.81%.

Once optimal loading doses were selected for each weight group, maintenance dosing simulations revealed a consistent trend: lower maintenance doses reduced the risk of supratherapeutic trough concentrations (>30 μg/mL), while higher maintenance doses reduced the likelihood of subtherapeutic levels (<15 μg/mL). These findings were consistent across both early and sustained exposure strategies (Tables 18–19). These suggests that although a specific dosing combinations may yield the highest PTA, alternative regimens may offer a more appropriate balance of efficacy and safety depending on the clinical needs, particularly in pediatric patients where toxicity risk may vary with age and renal function. Thus, the final dose selection must consider individual clinical needs, including infection severity, renal function, and the availability of TDM, to ensure an appropriate balance of efficacy and safety.

Despite these alternatives, similar dosing combinations were identified under both simulation strategies. In the early target attainment approach, the following loading dose–maintenance dose combinations achieved the highest PTA: <4 kg: 12 mg/kg q12h × 4 and 12 mg/kg q24h; 4–10 kg: 10 mg/kg q12h × 5 and 10 mg/kg q24h; 10–30 kg and 30–50 kg: 8 mg/kg q12h × 5 and 8 mg/kg q24h; and >50 kg: 6 mg/kg q12h × 5 and 6 mg/kg q24h. In contrast, the sustained target attainment approach yielded slightly more higher loading doses: <4 kg: 14 mg/kg q12h × 3 and 14 mg/kg q24h; 4–10 kg: 12 mg/kg q12h × 3 and 10 mg/kg q24h; 10–30 kg and 30–50 kg: 10 mg/kg q12h × 3 and 8 mg/kg q24h; >50 kg: 10 mg/kg q12h × 3 and 6 mg/kg q24h.

These results are consistent with findings from previous pediatric population pharmacokinetic studies. Gao et al. (2020) recommended three loading doses of 12 mg/kg q12h followed by a maintenance dose of 8 mg/kg q24h for children with mild renal impairment. Zhao et al. (2015) suggested age-based loading regimens, recommending 18 mg/kg for infants, 14 mg/kg for children, and 12 mg/kg for adolescents. Byrne et al. (2017) also proposed five loading doses of 15 mg/kg q12h in adult patients with hematologic malignancies, and Ogawa et al. (2013) suggested that an extended loading dose regimen could maximize the therapeutic effects of teicoplanin in patients with systemic MRSA infections. These prior studies align with our results, further supporting the need for optimized dosing regimens to overcome underdosing in pediatric populations.

Our study had several limitations. First, the timing of TDM sampling had to be assumed, as actual sampling times were not consistently recorded in the electronic medical records. In accordance with institutional guidelines recommending sample collection just before the next dose, we assumed samples were collected 30 minutes prior to dosing. However, since sampling times were uniformly defaulted to 12:00 in the electronic medical records, actual sampling may have occurred earlier or later, introducing timing-related bias. In particular, if samples were collected earlier than assumed, measured concentrations may have been lower than the true trough levels, potentially leading to underestimation of drug concentrations. Second, although infusion end times were available for some patients, the data were incomplete for many others. Therefore, we uniformly assumed a 30-minute infusion duration for all patients based on the available data. Third, despite over 4,000 pediatric patients receiving teicoplanin during the study period, only 123 had any recorded serum concentrations, and just 34 had at least two concentrations required for pharmacokinetic modeling. This sparse sampling and patients likely reflect current clinical practice, where teicoplanin TDM is not routinely performed in many pediatric centers despite increasing recognition of subtherapeutic exposures (Ramos-Martín et al., 2014). This may be due to teicoplanin's favorable safety profile compared to vancomycin, including a lower risk of nephrotoxicity, rare incidence of red man syndrome, and convenience of once-daily outpatient administration (Svetitsky et al., 2009), which may have contributed to the sparse sampling and limited data availability in our analysis. Finally, although teicoplanin is primarily eliminated via renal clearance, eGFR of our study population ranged from 25.26 to 169.85 mL/min/1.73 m^2. This high variability may have limited our ability to detect eGFR as a statistically significant covariate. Future studies with more stratified renal function groups and larger, balanced cohorts may better characterize the influence of renal function on teicoplanin pharmacokinetics and enhance the robustness of pharmacokinetic models.

5. Conclusion

In conclusion, our findings suggest that more optimized teicoplanin dosing regimens may be needed to optimize treatment in pediatric patients. The simulation results indicate that the currently recommended loading regimen of 10 mg/kg q12h × 3 and maintenance dose of 6–10 mg/kg q24h may be insufficient to achieve early therapeutic concentrations or for sustained target attainment, particularly in younger or low-weight children. By leveraging a population pharmacokinetic model that identified body weight as the most significant covariate, we proposed alternative weight-based dosing strategies that offer improved target attainment while balancing the risk of subtherapeutic or supratherapeutic exposure.

These results highlight the clinical utility of model-informed precision dosing approaches in pediatrics, where developmental and physiological variability can affect drug pharmacokinetics. However, exposure alone does not guarantee efficacy or safety. Therefore, future studies should aim to incorporate pharmacodynamic endpoints, such as AUC_{0-24}/MIC ratios or bacteriological response rates, to better define optimal dosing regimens. Furthermore, larger prospective studies with more comprehensive and accurate TDM data, increased number of samplings, and outcome-based clinical validation will be essential to refine and support the implementation of individualized teicoplanin dosing strategies in real-world pediatric settings.

References

Alford, E. L., Chhim, R. F., Crill, C. M., Hastings, M. C., Ault, B. H., & Shelton, C. M. (2014). Glomerular filtration rate equations do not accurately predict vancomycin trough concentrations in pediatric patients. *Annals of Pharmacotherapy*, *48*(6), 691–696.

Anderson, B., & Holford, N. (2007). Mechanism-Based concepts of size and maturity in Pharmacokinetics. The Annual Review of Pharmacology and Toxicology, 48(1), 303–332.

Byrne, C., Roberts, J., McWhinney, B., Ryder, S., Fennell, J., O'Byrne, P., Deasy, E., Egan, S., Desmond, R., Enright, H., D'Arcy, D., & McHugh, J. (2017). Population pharmacokinetics of teicoplanin and attainment of pharmacokinetic/pharmacodynamic targets in adult patients with haematological malignancy. Clinical Microbiology and Infection, 23(9), 674.e7-674.e13.

Cavalcanti, A. B., Goncalves, A. R., Almeida, C. S., Bugano, D. D., & Silva, E. (2010). Teicoplanin versus vancomycin for proven or suspected infection. Cochrane Library.

Cazaubon, Y., Venisse, N., Mimoz, O., Maire, P., Ducher, M., Bourguignon, L., & Goutelle, S. (2017). Population pharmacokinetics of teicoplanin administered by subcutaneous or intravenous route and simulation of optimal loading dose regimen. *Journal of Antimicrobial Chemotherapy*, *72*(10), 2804–2812.

Chen, C., Xie, M., Gong, J., Yu, N., Wei, R., Lei, L., Zhao, S., Li, R., Dong, X., Zhang, X., Zhou, Y., Li, S., & Cui, Y. (2023). Population pharmacokinetic analysis and dosing regimen optimization of teicoplanin in critically ill patients with sepsis. Frontiers in Pharmacology, 14.

Choi, J., Yoon, S. H., Park, H. J., Lee, S., & Kim, Y. (2023). Optimal Use and Need for therapeutic drug monitoring of teicoplanin in Children: a Systematic review. Journal of Korean Medical Science, 38(7).

Committee on Fetus and Newborn. (2004). Age terminology during the perinatal period. Pediatrics, 114(5), 1362–1364.

Craig, W. A. (2003). Basic pharmacodynamics of antibacterials with clinical applications to the use of B-lactams, glycopeptides, and linezolid. Infectious Disease Clinics of North America, 17(3), 479–501.

De Cock, R. F. W., Piana, C., Krekels, E. H. J., Danhof, M., Allegaert, K., & Knibbe, C. a. J. (2010). The role of population PK–PD modelling in paediatric clinical research. *European Journal of Clinical Pharmacology*, *67*(S1), 5–16.

Eckardt, K., Berns, J. S., Rocco, M. V., & Kasiske, B. L. (2009). Definition and Classification of CKD: The debate should be about Patient Prognosis—A position Statement from KDOQI and KDIGO. American Journal of Kidney Diseases, 53(6), 915–920.

European Medicines Agency. (2022). Targocid Summary of Product Characteristics. Retrieved March 24, 2025, from https://www.medicines.org.uk/emc/product/2926/smpc

Gao, L., Xu, H., Ye, Q., Li, S., Wang, J., Mei, Y., Niu, C., Kang, T., Chen, C., & Wang, Y. (2020). Population pharmacokinetics and dosage optimization of teicoplanin in children with different renal functions. *Frontiers in Pharmacology, 11*.

Hanai, Y., Oda, K., Ueda, T., Matsumoto, K., Murakami, L., Uekusa, S., Ohashi, H., Nishimura, K., Takesue, Y., & Matsuo, K. (2024). Optimal teicoplanin trough concentration with therapeutic Drug monitoring in Children: a Systematic review and Meta-analysis. Therapeutic Drug Monitoring, 46(6), 699–709.

Hanai, Y., Takahashi, Y., Niwa, T., Mayumi, T., Hamada, Y., Kimura, T., Matsumoto, K., Fujii, S., & Takesue, Y. (2021). Clinical practice guidelines for therapeutic drug monitoring of teicoplanin: a consensus review by the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. Journal of Antimicrobial Chemotherapy, 77(4), 869–879.

Holford, N., Heo, Y.-A., & Anderson, B. (2013). A Pharmacokinetic Standard for Babies and Adults. Journal of Pharmaceutical Sciences, 102(9), 2941–2952.

Kaasch, A. J., Rieg, S., Kuetscher, J., Brodt, H., Widmann, T., Herrmann, M., Meyer, C., Welte, T., Kern, P., Haars, U., Reuter, S., Hübner, I., Strauss, R., Sinha, B., Brunkhorst, F. M., Hellmich, M., Fätkenheuer, G., Kern, W. V., & Seifert, H. (2013). Delay in the administration of appropriate antimicrobial therapy in Staphylococcus aureus bloodstream infection: a prospective multicenter hospital-based cohort study. *Infection*, *41*(5), 979–985.

Kato, H., Hamada, Y., Hagihara, M., Hirai, J., Nishiyama, N., Koizumi, Y., Yamagishi, Y., Matsuura, K., & Mikamo, H. (2016). Retrospective study of teicoplanin loading regimen that rapidly achieves target 15–30 μg/mL serum trough concentration. Journal of Infection and Chemotherapy, 22(5), 308–313.

Kim, Y., Jo, K., Lee, J., Jang, J., Choe, E., Kang, G., Zang, D., & Lee, D. (2024). Beyond One-Size-Fits-All: Tailoring Teicoplanin regimens for normal renal function patients using population pharmacokinetics and Monte Carlo simulation. Pharmaceutics, 16(4), 499.

Lukas, J. C., Karikas, G., Gazouli, M., Kalabalikis, P., Hatzis, T., & Macheras, P. (2004). Pharmacokinetics of teicoplanin in an ICU population of children and infants. Pharmaceutical Research, 21(11), 2064–2071.

Nakamura, A., Takasu, O., Sakai, Y., Sakamoto, T., Yamashita, N., Mori, S., Morita, T., Nabeta, M., Hirayu, N., Yoshiyama, N., Moroki, M., Tashiro, K., & Kannae, M. (2015). Development of a teicoplanin loading regimen that rapidly achieves target serum concentrations in critically ill patients with severe infections. Journal of Infection and Chemotherapy, 21(6), 449–455.

Ogawa, R., Kobayashi, S., Sasaki, Y., Makimura, M., & Echizen, H. (2013). Population

pharmacokinetic and pharmacodynamic analyses of teicoplanin in Japanese patients with systemic MRSA infection. *International Journal of Clinical Pharmacology and Therapeutics, 51*(05), 357–366.

Ramos-Martín, V., Paulus, S., Siner, S., Scott, E., Padmore, K., Newland, P., Drew, R. J., Felton, T. W., Docobo-Pérez, F., Pizer, B., Pea, F., Peak, M., Turner, M. A., Beresford, M. W., & Hope, W. W. (2014). Population pharmacokinetics of teicoplanin in children. *Antimicrobial Agents and Chemotherapy*, *58*(11), 6920–6927.

Schwartz, G. J., Schneider, M. F., Maier, P. S., Moxey-Mims, M., Dharnidharka, V. R., Warady, B. A., Furth, S. L., & Muñoz, A. (2012). Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney International, 82(4), 445–453.

Shi, R., & Derendorf, H. (2010). Pediatric dosing and body size in biotherapeutics. Pharmaceutics, 2(4), 389–418.

Siddiqui, A. H., & Koirala, J. (2023). *Methicillin-Resistant Staphylococcus aureus*. StatPearls - NCBI Bookshelf.

Sosio, M., Kloosterman, H., Bianchi, A., De Vreugd, P., Dijkhuizen, L., & Donadio, S. (2003). Organization of the teicoplanin gene cluster in Actinoplanes teichomyceticus. Microbiology, 150(1), 95–102.

Strenger, V., Hofer, N., Rodl, S., Honigl, M., Raggam, R., Seidel, M. G., Dornbusch, H. J., Sperl, D., Lackner, H., Schwinger, W., Sovinz, P., Benesch, M., Urlesberger, B., & Urban, C. (2013). Age- and gender-related differences in teicoplanin levels in paediatric patients. Journal of Antimicrobial Chemotherapy.

Sun, D., Zhang, T., Mi, J., Dong, Y., Liu, Y., Zhang, Y., Zhang, D., Wang, T., Cheng, H., & Dong, Y. (2020). Therapeutic Drug Monitoring and Nephrotoxicity of Teicoplanin Therapy in Chinese Children: A Retrospective Study. Infection and Drug Resistance, Volume 13, 4105–4113.

Svetitsky, S., Leibovici, L., & Paul, M. (2009). Comparative Efficacy and Safety of Vancomycin versus Teicoplanin: Systematic Review and Meta-Analysis. *Antimicrobial Agents and Chemotherapy*, *53*(10), 4069–4079.

Ueda, T., Takesue, Y., Nakajima, K., Ichki, K., Wada, Y., Komatsu, M., Tsuchida, T., Takahashi, Y., Ishihara, M., Kimura, T., Uchino, M., & Ikeuchi, H. (2013). High-dose regimen to achieve novel target trough concentration in teicoplanin. Journal of Infection and Chemotherapy, 20(1), 43–47.

Ueda, T., Takesue, Y., Nakajima, K., Ichiki, K., Ishikawa, K., Takai, Y., Yamada, K., Tsuchida, T., Otani, N., Takahashi, Y., Ishihara, M., Takubo, S., Ikeuchi, H., Uchino, M., & Kimura, T. (2020). Clinical efficacy and safety in patients treated with teicoplanin with a target trough concentration of 20 μg/mL using a regimen of 12 mg/kg for five doses within the initial 3 days. BMC Pharmacology

and Toxicology, 21(1).

Wang, S., Lin, F., Ruan, J., Ye, H., & Wang, L. (2018). Pharmacokinetics of multiple doses of teicoplanin in Chinese elderly critical patients. Expert Review of Clinical Pharmacology, 11(5), 537–541.

Wilson, A. P. (2000). Clinical Pharmacokinetics of Teicoplanin. Clinical Pharmacokinetics, 39(3), 167–183.

Wood, M. J. (1996). The comparative efficacy and safety of teicoplanin and vancomycin. Journal of Antimicrobial Chemotherapy, 37(2), 209–222.

Yamada, T., Emoto, C., Fukuda, T., Motomura, Y., Inoue, H., Ohga, S., & Ieiri, I. (2022). Optimal Teicoplanin dosing regimen in neonates and children developed by leveraging Real-World clinical information. Therapeutic Drug Monitoring, 44(3), 404–413.

Yamada, T., Kubota, T., Yonezawa, M., Nishio, H., Kanno, S., Yano, T., Kobayashi, D., Egashira, N., Takada, H., Hara, T., & Masuda, S. (2016). Evaluation of teicoplanin trough values after the recommended loading dose in children with associated safety analysis. The Pediatric Infectious Disease Journal, 36(4), 398–400.

Zhang, T., Sun, D., Shu, Z., Duan, Z., Liu, Y., Du, Q., Zhang, Y., Dong, Y., Wang, T., Hu, S., Cheng, H., & Dong, Y. (2020). Population Pharmacokinetics and Model-Based dosing optimization of Teicoplanin in pediatric patients. Frontiers in Pharmacology, 11.

Zhang, X., Chen, Y., Wang, Y., Chen, C., Chen, Y., Xu, F., Dai, Y., Shi, D., Lin, G., Yu, X., Xiang, D., & Zhang, C. (2023). Model-based dosing optimization and therapeutic drug monitoring practices of teicoplanin in patients with complicated or non-complicated methicillin-resistant staphylococcus aureus infection. British Journal of Clinical Pharmacology.

Zhao, W., Zhang, D., Storme, T., Baruchel, A., Declèves, X., & Jacqz-Aigrain, E. (2015). Population pharmacokinetics and dosing optimization of teicoplanin in children with malignant haematological disease. British Journal of Clinical Pharmacology, 80(5), 1197–1207.

Appendices

Appendix 1. Visual Diagnostic Plots of Base Model

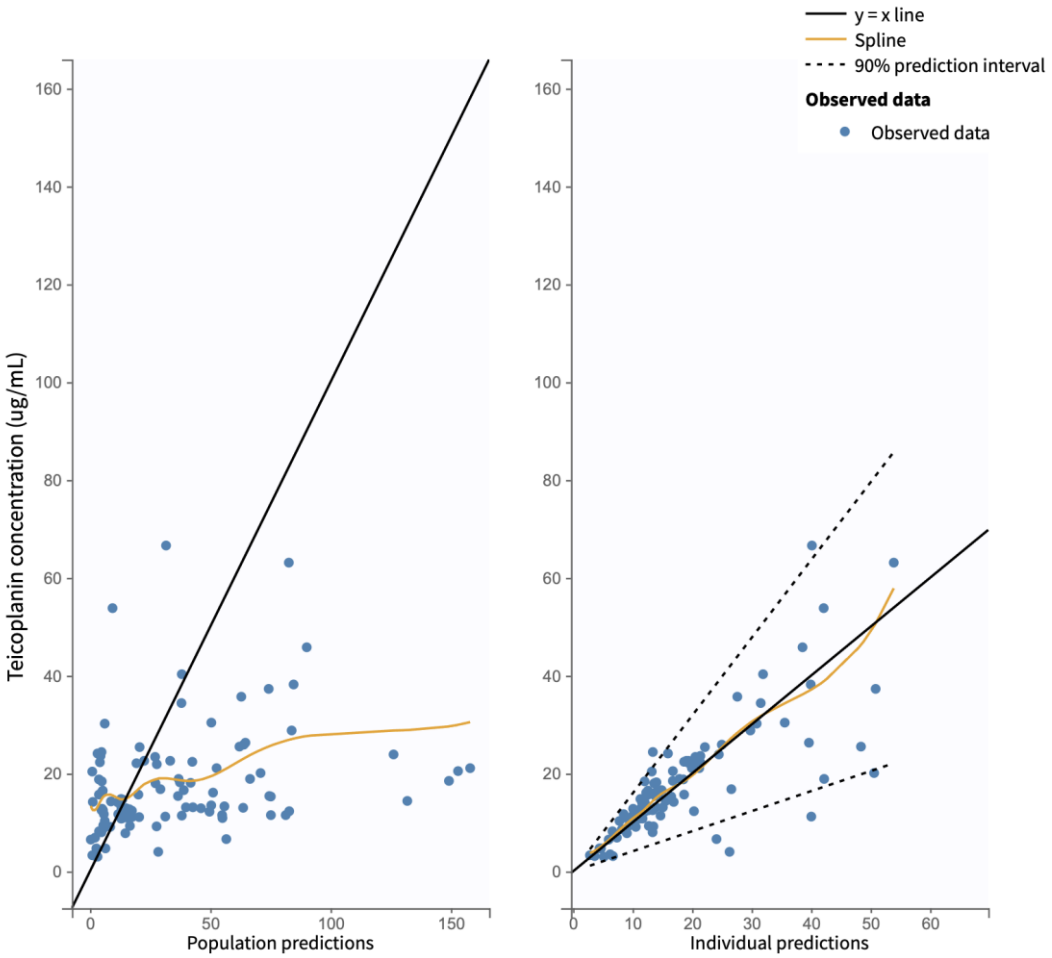

Figure 1. Observed versus prediction teicoplanin concentrations for the base model.
Scatter plots of observed teicoplanin concentrations versus population predictions (left) and individual predictions (right). The solid black line represents the line of identity (y = x). The yellow spline indicates a locally weighted regression fit to the data. The dashed lines in the individual prediction panel represent the 90% prediction interval.

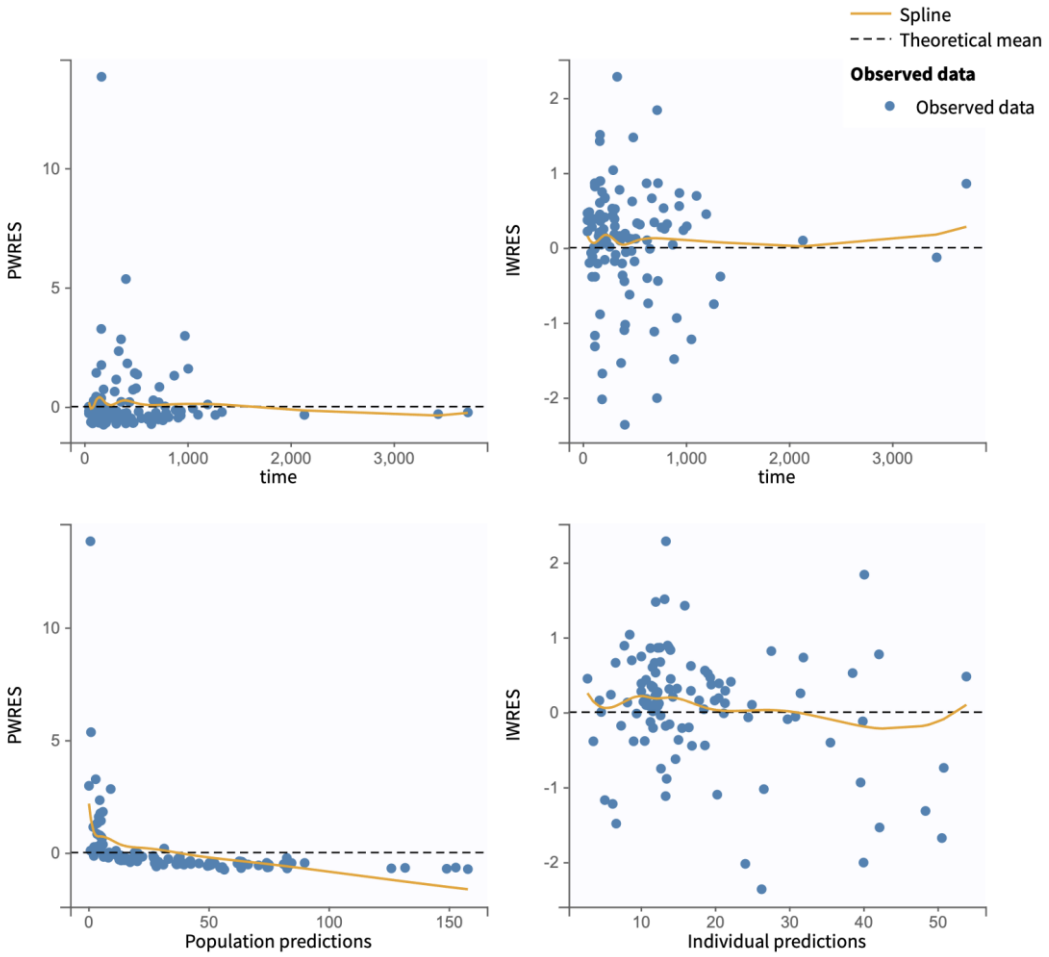

Figure 2. Scatter plots of residuals for the base model

Scatterplots of population-weighted residuals (PWRES, left panels) and individual-weighted residuals (IWRES, right panels) versus time and predicted concentrations. The solid yellow line represents a spline smoother; the dashed line indicates the theoretical mean (y = 0).

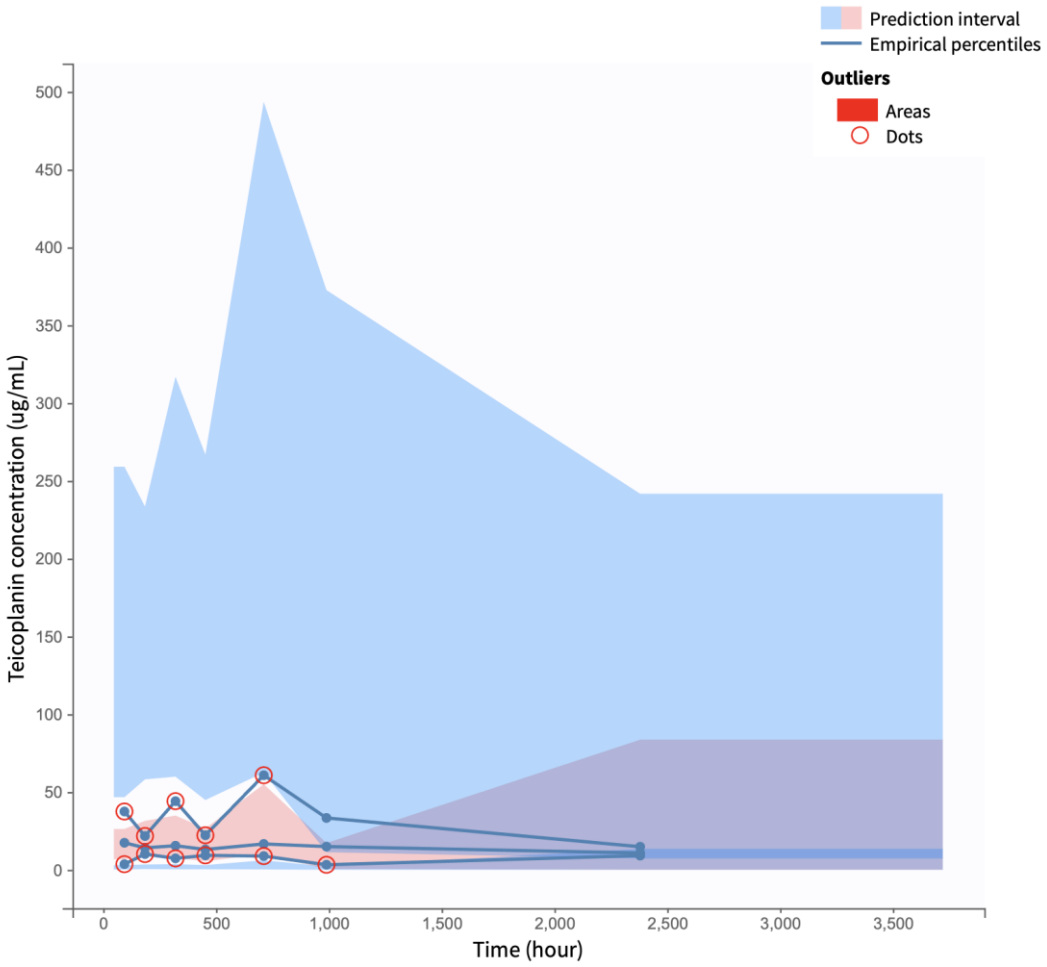

Figure 3. Visual predictive check for the base model.
Blue solid lines indicate empirical percentiles of the observed teicoplanin concentrations. Shaded areas indicate the 90% prediction intervals from 500 simulations: pink for the 50th percentile, and blue for the 10th and 90th percentiles. Red areas and dots indicate empirical percentiles falling outside the prediction intervals.

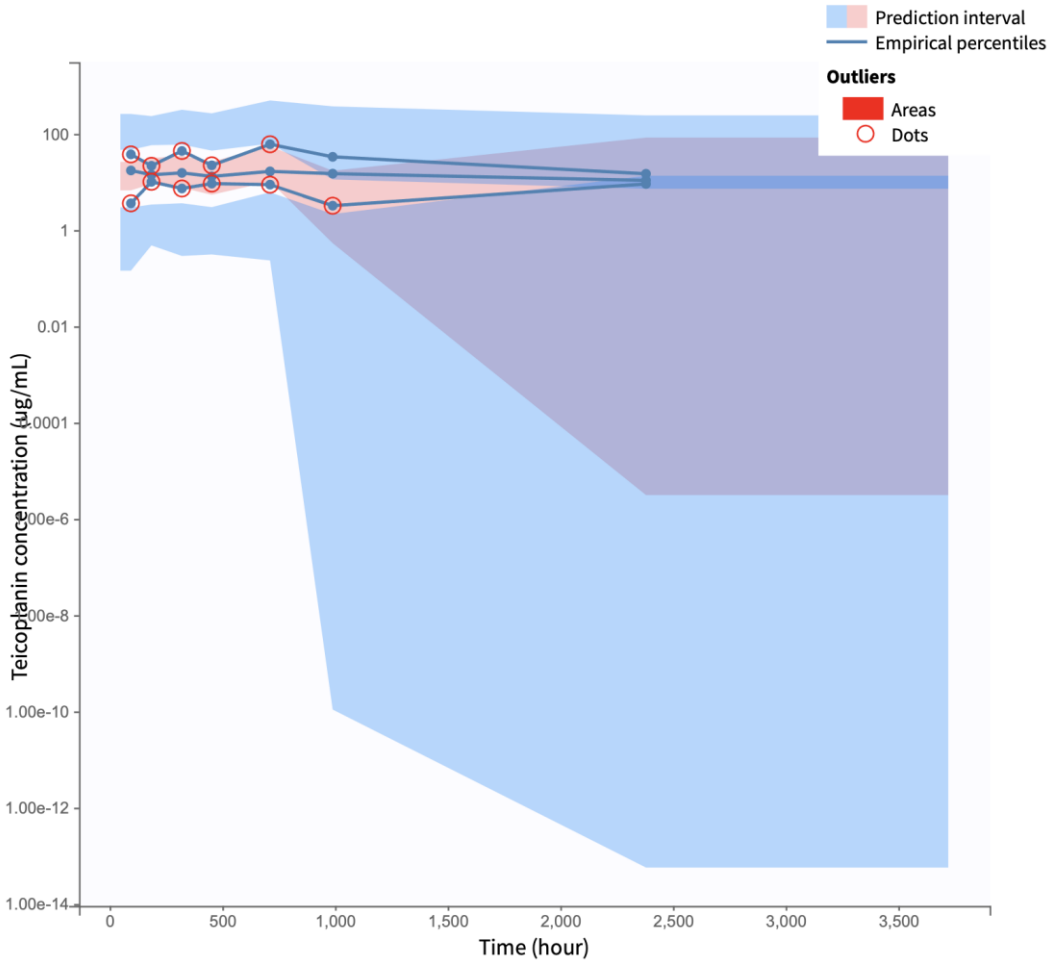

Figure 4. Visual predictive check on a logarithmic scale for the base model.
Blue solid lines indicate empirical percentiles of the observed teicoplanin concentrations. Shaded areas indicate the 90% prediction intervals from 500 simulations: pink for the 50th percentile, and blue for the 10th and 90th percentiles. Red areas and dots indicate empirical percentiles falling outside the prediction intervals.

Appendix 2. R code for calculating the mean PTA (%)

```
# Required libraries
library(readr)
library(dplyr)

# Load the simulation output CSV file
file_path <- "endpoint_Percent_ids_in_target.csv"
df <- read_csv(file_path)

# Calculate mean PTA (%) for each dosing group
pta_results <- df %>%
   group_by(group) %>%
   summarise(
      PTA_Mean = mean(totalTrue)    # Mean percentage of IDs within target range
   ) %>%
   arrange(group)

# Display results
print(pta_results)
# Save the summary results as a new CSV file
write_csv(pta_results, "q12hx3_PTA(15-30)_below_4.csv")
```

Appendix 3. R code for visualizing mean PTA (%) plot

```
# Load required libraries
library(readr)
library(dplyr)
library(ggplot2)
library(stringr)

# Define file list for each LD scenario and weight group
files <- list(
"q6h x 4" = list(
"<4kg" = "q6hx4_PTA(15-30)_below_4kg.csv",
"4-10kg" = "q6hx4_PTA(15-30)_4to10kg.csv",
"10-30kg" = "q6hx4_PTA(15-30)_10to30kg.csv",
"30-50kg" = "q6hx4_PTA(15-30)_30to50kg.csv",
">50kg" = "q6hx4_PTA(15-30)_above_50kg.csv"
),
"q12h x 3" = list(
"<4kg" = "q12hx3_PTA(15-30)_below_4kg.csv",
"4-10kg" = "q12hx3_PTA(15-30)_4to10kg.csv",
"10-30kg" = "q12hx3_PTA(15-30)_10to30kg.csv",
"30-50kg" = "q12hx3_PTA(15-30)_30to50kg.csv",
">50kg" = "q12hx3_PTA(15-30)_above_50kg.csv"
),
"q12h x 4" = list(
"<4kg" = "q12hx4_PTA(15-30)_below_4kg.csv",
"4-10kg" = "q12hx4_PTA(15-30)_4to10kg.csv",
"10-30kg" = "q12hx4_PTA(15-30)_10to30kg.csv",
"30-50kg" = "q12hx4_PTA(15-30)_30to50kg.csv",
">50kg" = "q12hx4_PTA(15-30)_above_50kg.csv"
),
"q12h x 5" = list(
"<4kg" = "q12hx5_PTA(15-30)_below_4kg.csv",
"4-10kg" = "q12hx5_PTA(15-30)_4to10kg.csv",
"10-30kg" = "q12hx5_PTA(15-30)_10to30kg.csv",
"30-50kg" = "q12hx5_PTA(15-30)_30to50kg.csv",
">50kg" = "q12hx5_PTA(15-30)_above_50kg.csv"
)
)

# Define weight group labels for plotting
```

```
weight_group_labels <- c(
"<4kg"         = "<4 kg",
"4-10kg" = "4-10 kg",
"10-30kg"= "10-30 kg",
"30-50kg"= "30-50 kg",
">50kg"        = ">50 kg"
)

# Merge data from all files into one dataset
pta_data <- bind_rows(lapply(names(files), function(day) {
bind_rows(lapply(names(files[[day]]), function(weight_group) {
file_path <- files[[day]][[weight_group]]
df <- read_csv(file_path)
df$Day <- day
df$Weight_Group <- weight_group_labels[[weight_group]]
df$LD <- factor(df$group, levels = c("6mgkg", "8mgkg", "10mgkg", "12mgkg", "14mgkg",
"16mgkg", "18mgkg"),
labels = c("6", "8", "10", "12", "14", "16", "18"))
return(df)
}))
}))

# Format LD and Weight_Group for plotting
pta_data <- pta_data %>%
mutate(
LD = factor(LD, levels = c("6", "8", "10", "12", "14", "16", "18")),
Weight_Group = factor(Weight_Group, levels = c("<4 kg", "4-10 kg", "10-30 kg", "30-50 kg", ">50
kg"))
)

# Generate the PTA plot
ggplot(pta_data, aes(x = LD, y = PTA_Mean, color = Day, group = Day)) +
geom_point(size = 2) +
geom_line(size = 0.5) +
facet_wrap(~Weight_Group) +
scale_color_manual(
values = c("q6h x 4" = "darkorange", "q12h x 3" = "gold", "q12h x 4" = "forestgreen", "q12h x 5" =
"brown"),
breaks = c("q6h x 4", "q12h x 3", "q12h x 4", "q12h x 5")
) +
scale_y_continuous(breaks = seq(0, 100, by = 10)) +
```

```
geom_hline(yintercept = 50, linetype = "dashed", color = "gray", size = 1) +
labs(
title = "Mean PTA (%) for Cmin (15–30 µg/mL) Across Loading Dose Schedules and Weight Groups",
x = "Loading Dose (mg/kg)",
y = "PTA (%) for Cmin: 15–30 µg/mL",
color = "LD Schedule"
) +
theme_bw() +
theme(
plot.title = element_text(hjust = 0.5, size = 14, face = "bold"),
axis.text = element_text(size = 12),
legend.position = "right",
strip.text = element_text(size = 12, face = "bold")
)

# Save the figure as high-resolution PNG
ggsave(
filename = "pta_optLDfirst_15-30.png",
plot = last_plot(),
width = 10,
height = 10,
units = "in",
dpi = 300
)
```

Note: The same R script structure was applied to visualize the mean PTA (%) for maintenance dose simulations. Only the input filenames were modified to correspond to the maintenance dose datasets.

Appendix 4. Simulation conducted by age groups

Table 1. Simulated mean PTA (%) for C_{min} with different loading dose schedules across age groups.

LD q12h x 3

Mean PTA (%) at 47 Hours for Cmin in the 0 ≤ Age ≤ 3 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	14.58	0.32	85.09	85.42
8	32.90	2.28	64.83	67.10
10	47.12	7.07	45.81	52.88
12	53.69	14.91	31.41	46.31
14	53.90	24.71	21.39	46.10
16	50.13	35.18	14.70	49.87
18	44.76	44.97	10.27	55.25

Mean PTA (%) at 47 Hours for Cmin in the 3 ≤ Age < 6 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	23.41	0.96	75.63	76.59
8	42.22	5.10	52.68	57.78
10	51.77	13.19	35.04	48.23
12	52.35	24.37	23.28	47.65
14	47.86	36.37	15.78	52.14
16	41.80	47.32	10.88	58.20
18	35.39	56.87	7.73	64.61

Mean PTA (%) at 47 Hours for Cmin in the 6 ≤ Age < 9 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	27.58	1.59	70.82	72.42
8	44.65	7.22	48.13	55.35
10	51.25	17.01	31.75	48.75
12	49.59	29.18	21.23	50.41
14	44.23	41.34	14.44	55.77
16	38.02	51.87	10.11	61.98
18	31.94	60.85	7.21	68.06

Mean PTA (%) at 47 Hours for Cmin in the 9 ≤ Age < 12 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	30.12	2.15	67.74	69.89
8	45.52	8.86	45.62	54.48
10	50.22	19.72	30.07	49.78
12	47.51	32.26	20.23	52.49
14	41.87	44.30	13.83	58.13
16	35.90	54.38	9.73	64.11
18	30.06	62.99	6.95	69.94

Mean PTA (%) at 47 Hours for Cmin in the 12 ≤ Age < 15 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	30.67	2.34	66.99	69.33
8	45.66	9.31	45.03	54.35
10	49.89	20.43	29.69	50.11
12	47.03	33.01	19.96	52.97
14	41.32	45.00	13.68	58.68
16	35.39	54.97	9.64	64.61
18	29.61	63.50	6.90	70.39

Mean PTA (%) at 47 Hours for Cmin in the 15 ≤ Age ≤ 18 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	31.34	2.59	66.07	68.66
8	45.74	9.92	44.34	54.26
10	49.46	21.29	29.24	50.54
12	46.36	33.93	19.71	53.64
14	40.74	45.72	13.54	59.26
16	34.79	55.66	9.55	65.21
18	29.15	64.00	6.85	70.85

LD q12h x 4

Mean PTA (%) at 59 Hours for Cmin in the 0 ≤ Age ≤ 3 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	24.68	0.97	74.35	75.33
8	44.88	5.25	49.87	55.12
10	54.92	13.95	31.12	45.08
12	55.21	25.65	19.15	44.79
14	50.03	38.12	11.85	49.97
16	42.29	50.13	7.57	57.71
18	34.70	60.38	4.93	65.30

Mean PTA (%) at 59 Hours for Cmin in the 3 ≤ Age ≤ 6 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	36.65	2.69	60.66	63.35
8	53.05	10.86	36.09	46.95
10	54.83	24.26	20.91	45.17
12	48.31	39.34	12.36	51.70
14	39.61	52.74	7.65	60.39
16	31.13	63.91	4.96	68.87
18	24.21	72.48	3.31	75.79

Mean PTA (%) at 59 Hours for Cmin in the 6 ≤ Age ≤ 9 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	41.08	4.22	54.70	58.92
8	53.55	14.80	31.65	46.45
10	51.68	30.01	18.31	48.32
12	43.76	45.30	10.94	56.24
14	34.93	58.21	6.87	65.08
16	27.12	68.35	4.54	72.88
18	20.90	76.06	3.03	79.10

Mean PTA (%) at 59 Hours for Cmin in the 9 ≤ Age ≤ 12 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	43.30	5.49	51.21	56.70
8	52.92	17.76	29.32	47.08
10	49.13	33.82	17.05	50.87
12	40.90	48.79	10.31	59.10
14	32.29	61.22	6.49	67.71
16	25.00	70.68	4.32	75.00
18	19.31	77.78	2.92	80.73

Mean PTA (%) at 59 Hours for Cmin in the 12 ≤ Age ≤ 15 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	43.82	5.87	50.31	56.18
8	52.64	18.57	28.79	47.36
10	48.48	34.76	16.76	51.52
12	40.15	49.69	10.17	59.86
14	31.65	61.93	6.42	68.35
16	24.53	71.21	4.27	75.47
18	18.92	78.19	2.89	81.08

Mean PTA (%) at 59 Hours for Cmin in the 15 ≤ Age ≤ 18 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	44.17	6.42	49.40	55.83
8	52.17	19.61	28.22	47.83
10	47.82	35.73	16.45	52.18
12	39.40	50.60	10.00	60.60
14	30.97	62.67	6.35	69.03
16	23.99	71.78	4.23	76.01
18	18.59	78.55	2.86	81.41

LD q12h x 5

Mean PTA (%) at 71 Hours for Cmin in the 0 ≤ Age ≤ 3 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	32.70	2.00	65.30	67.30
8	51.71	8.79	39.50	48.29
10	56.68	20.72	22.60	43.32
12	52.50	34.70	12.80	47.50
14	43.88	48.62	7.50	56.12
16	34.97	60.50	4.53	65.03
18	27.14	70.05	2.82	72.86

Mean PTA (%) at 71 Hours for Cmin in the 3 ≤ Age ≤ 6 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	46.00	4.95	49.05	54.00
8	57.09	17.31	25.60	42.91
10	52.42	34.46	13.12	47.58
12	41.92	50.95	7.13	58.08
14	31.48	64.38	4.15	68.52
16	23.11	74.40	2.48	76.89
18	16.82	81.64	1.54	83.18

Mean PTA (%) at 71 Hours for Cmin in the 6 ≤ Age ≤ 9 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	50.00	7.46	42.55	50.00
8	55.67	22.93	21.40	44.33
10	47.56	41.34	11.10	52.44
12	36.39	57.45	6.16	63.61
14	26.65	69.75	3.61	73.35
16	19.18	78.60	2.22	80.82
18	13.89	84.72	1.39	86.11

Mean PTA (%) at 71 Hours for Cmin in the 9 ≤ Age ≤ 12 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	51.64	9.57	38.80	48.37
8	53.69	26.94	19.37	46.31
10	44.26	45.59	10.15	55.74
12	33.13	61.20	5.67	66.87
14	24.00	72.61	3.39	76.00
16	17.27	80.63	2.11	82.73
18	12.54	86.13	1.33	87.46

Mean PTA (%) at 71 Hours for Cmin in the 12 ≤ Age ≤ 15 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	51.91	10.18	37.91	48.09
8	53.10	27.96	18.94	46.90
10	43.37	46.70	9.93	56.63
12	32.33	62.10	5.57	67.67
14	23.40	73.28	3.33	76.61
16	16.87	81.06	2.07	83.13
18	12.25	86.45	1.31	87.75

Mean PTA (%) at 59 Hours for Cmin in the 15 ≤ Age ≤ 18 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	52.00	11.06	36.94	48.00
8	52.27	29.25	18.48	47.73
10	42.37	47.88	9.75	57.63
12	31.46	63.06	5.48	68.54
14	22.74	73.97	3.29	77.26
16	16.42	81.52	2.06	83.58
18	11.98	86.73	1.29	88.02

LD q6h x 4

Mean PTA (%) at 41 Hours for Cmin in the 0 ≤ Age ≤ 3 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	39.55	4.32	56.13	60.45
8	52.05	14.74	33.22	47.95
10	51.26	29.27	19.47	48.75
12	44.38	43.87	11.75	55.62
14	35.87	56.73	7.40	64.13
16	28.43	66.79	4.78	71.57
18	22.16	74.62	3.22	77.84

Mean PTA (%) at 41 Hours for Cmin in the 3 ≤ Age ≤ 6 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	45.59	8.41	46.00	54.41
8	50.37	23.21	26.43	49.64
10	44.60	39.82	15.58	55.40
12	36.39	54.00	9.62	63.61
14	28.55	65.29	6.16	71.46
16	22.31	73.57	4.12	77.69
18	17.32	79.86	2.82	82.68

Mean PTA (%) at 41 Hours for Cmin in the 6 ≤ Age ≤ 9 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	46.31	10.98	42.71	53.69
8	48.27	27.23	24.50	51.73
10	41.43	43.95	14.63	58.57
12	33.58	57.29	9.13	66.42
14	26.30	67.82	5.88	73.70
16	20.55	75.50	3.95	79.45
18	16.17	81.13	2.71	83.83

Mean PTA (%) at 41 Hours for Cmin in the 9 ≤ Age ≤ 12 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	46.33	12.81	40.87	53.67
8	46.70	29.76	23.54	53.30
10	39.63	46.21	14.16	60.37
12	32.01	59.14	8.86	67.99
14	25.12	69.13	5.74	74.88
16	19.67	76.46	3.87	80.33
18	15.56	81.79	2.65	84.44

Mean PTA (%) at 41 Hours for Cmin in the 12 ≤ Age ≤ 15 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	46.23	13.33	40.44	53.77
8	46.31	30.37	23.32	53.69
10	39.21	46.74	14.05	60.79
12	31.63	59.56	8.80	68.37
14	24.88	69.42	5.70	75.12
16	19.48	76.68	3.84	80.53
18	15.41	81.96	2.63	84.59

Mean PTA (%) at 59 Hours for Cmin in the 15 ≤ Age ≤ 18 Year Age Group				
LD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	46.11	13.95	39.94	53.89
8	45.81	31.10	23.09	54.19
10	38.76	47.31	13.93	61.25
12	31.23	60.06	8.72	68.78
14	24.55	69.78	5.68	75.45
16	19.27	76.91	3.82	80.73
18	15.24	82.14	2.62	84.76

Green shading indicates the loading dose regimen with the highest PTA among all simulated dosing schedules.
LD, loading dose; q12h, every 12 hours; q6h, every 6 hours; C_{min}, minimum (trough) concentration; PTA, probability of target attainment; >30 μg/mL (%), proportion of individuals with C_{min} above the target range; <15 μg/mL (%), proportion of individuals with C_{min} below the target range; 15–30 μg/mL (%), proportion of individuals within the target concentration range; Total Out-of-Target (%), combined percentage of individuals with C_{min} <15 and >30 μg/mL.

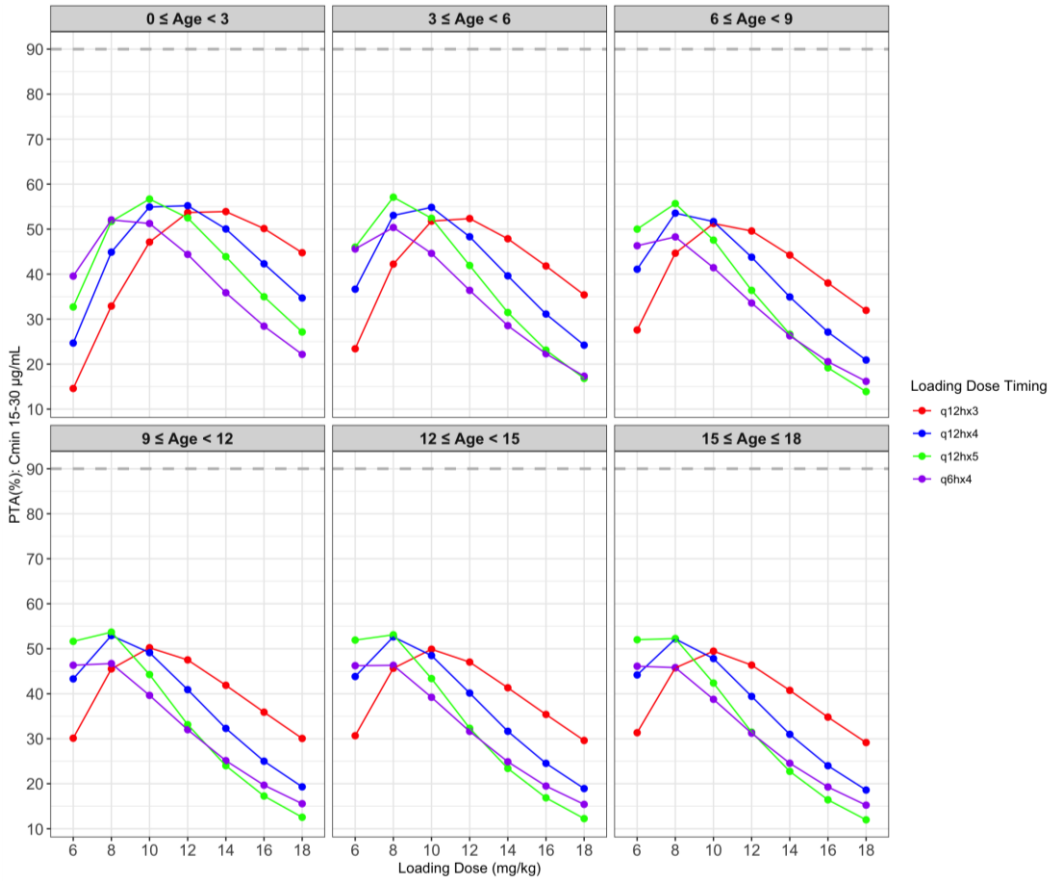

Figure 1. Mean PTA (%) for C_{min} 15–30 μg/mL with different loading dose schedules across age groups.

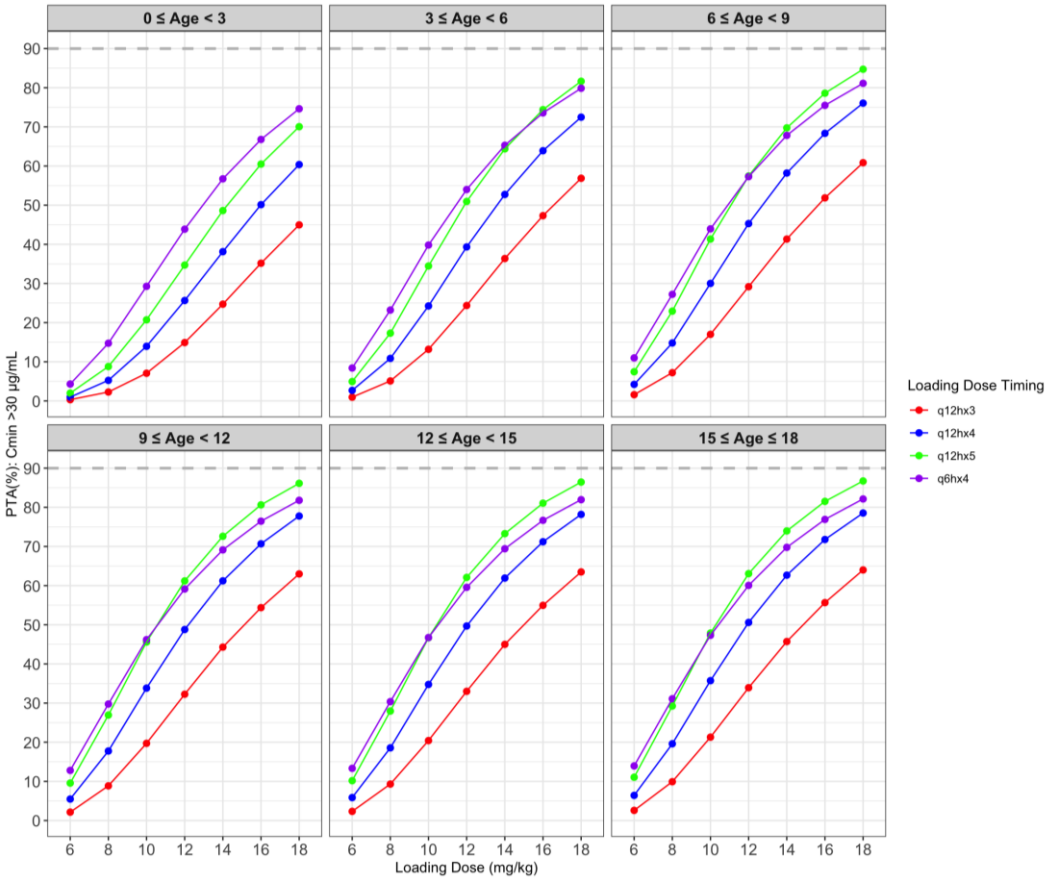

Figure 2. Mean PTA (%) for C_{min} >30 μg/mL with different loading dose schedules across age groups.

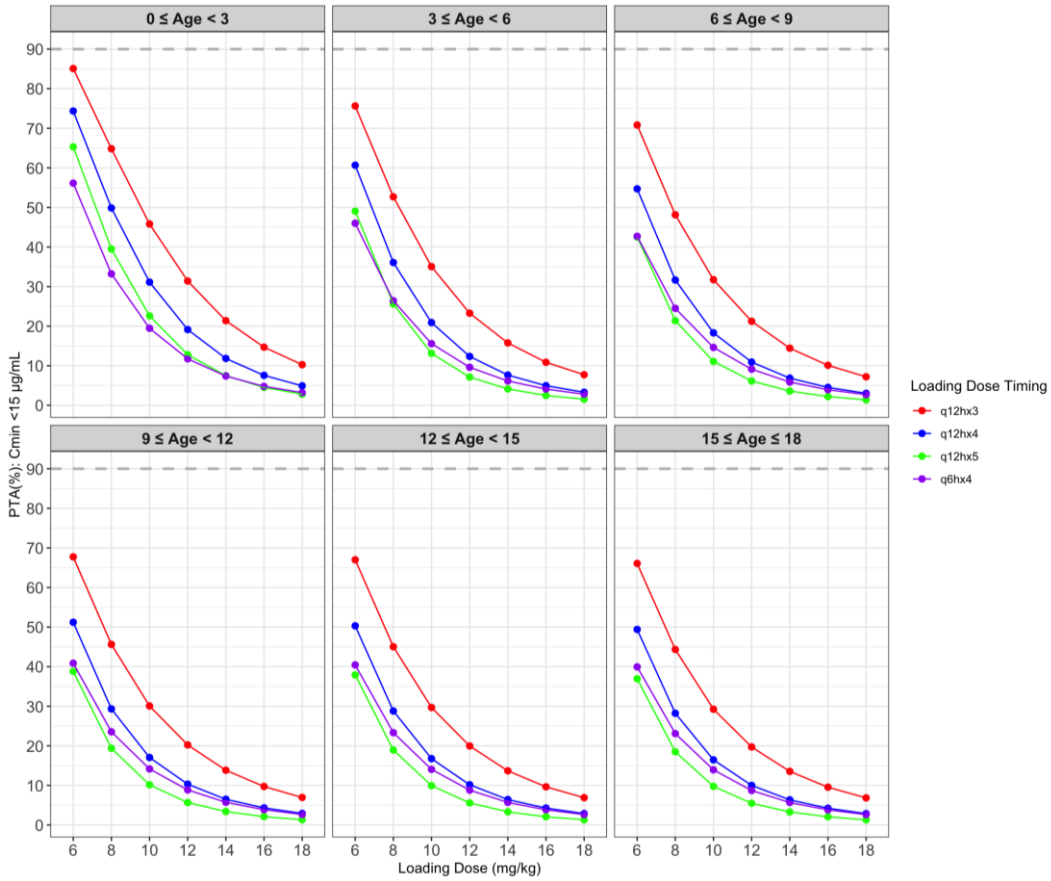

Figure 3. Mean PTA (%) for C_{min} <15 µg/mL with different loading dose schedules across age groups.

Table 2. Simulated mean PTA (%) for C_{min} with different maintenance dose and fixed loading dose across age groups at Das 5, 14, and 21.

0 ≤ Age < 3 (LD 10 mg/kg q12h x 5 fixed)

Mean PTA(%) at Day 5 for Cmin in the 0 ≤ Age < 3 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	38.34	4.24	57.42	61.66
8	46.60	7.22	46.18	53.40
10	52.87	11.33	35.79	47.13
12	56.39	16.60	27.01	43.61
14	57.40	22.57	20.04	42.60
16	56.20	29.11	14.70	43.80
18	53.22	36.02	10.77	46.78

Mean PTA(%) at Day 14 for Cmin in the 0 ≤ Age < 3 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	23.21	1.30	75.49	76.79
8	40.55	5.02	54.43	59.45
10	51.39	12.18	36.44	48.61
12	54.35	22.04	23.61	45.65
14	51.70	33.12	15.18	48.30
16	46.44	43.86	9.70	53.56
18	39.83	53.80	6.37	60.17

Mean PTA(%) at Day 21 for Cmin in the <4 kg group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	22.91	1.30	75.79	77.09
8	40.61	5.37	54.03	59.40
10	50.91	13.15	35.95	49.10
12	53.30	23.48	23.21	46.70
14	50.35	34.72	14.93	49.65
16	44.91	45.53	9.56	55.10
18	38.34	55.36	6.30	61.66

3 ≤ Age < 6 (LD 8 mg/kg q12h x 5 fixed)

Mean PTA(%) at Day 5 for Cmin in the 3 ≤ Age < 6 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	48.25	5.56	46.20	51.76
8	56.35	10.21	33.44	43.65
10	60.03	16.48	23.50	39.97
12	59.79	23.98	16.23	40.21
14	56.50	32.27	11.23	43.50
16	51.38	40.60	8.02	48.62
18	45.58	48.61	5.81	54.42

Mean PTA(%) at Day 14 for Cmin in the 3 ≤ Age < 6 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	40.75	3.63	55.63	59.25
8	56.57	12.40	31.03	43.43
10	57.87	26.07	16.06	42.13
12	50.53	41.35	8.12	49.47
14	40.42	55.48	4.10	59.58
16	30.58	67.33	2.09	69.42
18	22.48	76.40	1.13	77.52

Mean PTA(%) at Day 21 for Cmin in the 3 ≤ Age < 6 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	41.17	3.98	54.85	58.83
8	56.27	13.79	29.94	43.73
10	56.11	28.53	15.37	43.89
12	47.98	44.25	7.77	52.02
14	37.84	58.24	3.93	62.16
16	28.34	69.64	2.02	71.66
18	20.70	78.22	1.08	79.30

6 ≤ Age < 9 (LD 8 mg/kg q12h x 5 fixed)

Mean PTA(%) at Day 5 for Cmin in the 6 ≤ Age < 9 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	54.77	9.22	36.01	45.24
8	59.39	15.63	24.97	40.61
10	59.56	23.45	16.99	40.44
12	56.38	32.10	11.51	43.62
14	50.82	41.07	8.11	49.18
16	44.67	49.41	5.92	55.33
18	38.56	57.03	4.42	61.45

Mean PTA(%) at Day 14 for Cmin in the 6 ≤ Age < 9 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	49.97	6.63	43.40	50.03
8	59.35	19.60	21.05	40.65
10	53.77	36.60	9.64	46.23
12	42.42	53.26	4.32	57.58
14	30.97	67.04	1.99	69.03
16	21.65	77.40	0.95	78.35
18	14.81	84.71	0.48	85.19

Mean PTA(%) at Day 21 for Cmin in the 6 ≤ Age < 9 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	50.18	7.35	42.47	49.82
8	58.16	21.78	20.06	41.84
10	51.20	39.77	9.03	48.80
12	39.43	56.51	4.06	60.57
14	28.27	69.87	1.86	71.73
16	19.53	79.58	0.89	80.47
18	13.29	86.26	0.45	86.71

9 ≤ Age < 12 (LD 8 mg/kg q12h x 5 fixed)

Mean PTA(%) at Day 5 for Cmin in the 9 ≤ Age < 12 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	57.33	12.70	29.98	42.67
8	59.43	20.22	20.35	40.57
10	57.48	28.86	13.67	42.52
12	52.56	38.06	9.38	47.44
14	46.34	46.88	6.77	53.66
16	39.88	55.09	5.03	60.12
18	34.15	62.02	3.84	65.86

Mean PTA(%) at Day 14 for Cmin in the 9 ≤ Age < 12 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	54.87	9.77	35.36	45.13
8	58.56	25.80	15.64	41.44
10	48.82	44.61	6.58	51.19
12	36.02	61.22	2.77	63.98
14	24.79	74.00	1.22	75.21
16	16.52	82.91	0.57	83.48
18	10.77	88.97	0.26	89.23

Mean PTA(%) at Day 21 for Cmin in the 9 ≤ Age < 12 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	54.84	10.76	34.40	45.17
8	56.72	28.55	14.73	43.28
10	45.82	48.11	6.07	54.18
12	32.84	64.62	2.54	67.16
14	22.12	76.77	1.11	77.88
16	14.51	84.97	0.52	85.49
18	9.41	90.36	0.24	90.60

12 ≤ Age < 15 (LD 8 mg/kg q12h x 5 fixed)

Mean PTA(%) at Day 5 for Cmin in the 12 ≤ Age < 15 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	57.82	13.70	28.48	42.18
8	59.23	21.51	19.26	40.77
10	56.75	30.32	12.94	43.26
12	51.43	39.64	8.94	48.57
14	45.18	48.35	6.47	54.82
16	38.68	56.48	4.84	61.32
18	33.03	63.26	3.71	66.97

Mean PTA(%) at Day 14 for Cmin in the 12 ≤ Age < 15 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	55.96	10.70	33.35	44.04
8	58.13	27.53	14.35	41.87
10	47.41	46.69	5.90	52.59
12	34.28	63.28	2.44	65.72
14	23.29	75.66	1.05	76.71
16	15.31	84.20	0.49	84.69
18	9.84	89.94	0.22	90.16

Mean PTA(%) at Day 21 for Cmin in the 12 ≤ Age < 15 age group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	55.90	11.78	32.32	44.10
8	56.13	30.41	13.46	43.87
10	44.28	50.31	5.41	55.72
12	31.08	66.69	2.23	68.92
14	20.65	78.40	0.95	79.35
16	13.32	86.24	0.45	86.68
18	8.52	91.28	0.19	91.48

15 ≤ Age ≤ 18 (LD 8 mg/kg q12h x 5 fixed)

Mean PTA(%) at Day 5 for Cmin in the 15 ≤ Age ≤ 18 group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	57.91	15.08	27.01	42.09
8	58.58	23.22	18.19	41.42
10	55.49	32.27	12.24	44.51
12	49.94	41.52	8.54	50.06
14	43.64	50.12	6.24	56.36
16	37.43	57.89	4.68	62.57
18	31.83	64.55	3.62	68.17

Mean PTA(%) at Day 14 for Cmin in the 15 ≤ Age ≤ 18 group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	56.64	12.27	31.08	43.36
8	56.83	30.05	13.13	43.17
10	45.26	49.41	5.33	54.74
12	32.19	65.61	2.20	67.81
14	21.62	77.40	0.98	78.38
16	14.04	85.53	0.44	85.96
18	8.96	90.85	0.20	91.04

Mean PTA(%) at Day 21 for Cmin in the 15 ≤ Age ≤ 18 group				
MD (mg/kg)	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
6	56.52	13.51	29.98	43.48
8	54.67	33.09	12.25	45.34
10	42.03	53.09	4.88	57.97
12	28.99	69.01	2.00	71.01
14	18.98	80.14	0.88	81.02
16	12.15	87.46	0.39	87.85
18	7.66	92.17	0.17	92.34

Green shading indicates the maintenance dose regimen with the highest PTA among all simulated dosing schedules. LD, loading dose; MD, maintenance dose; q12h, every 12 hours; q24h, every 24 hours; C_{min}, minimum (trough) concentration; PTA, probability of target attainment; >30 μg/mL (%), proportion of individuals with C_{min} above the target range; <15 μg/mL (%), proportion of individuals with C_{min} below the target range; 15–30 μg/mL (%), proportion of individuals within the target concentration range; Total Out-of-Target (%), combined percentage of individuals with C_{min} <15 and >30 μg/mL.

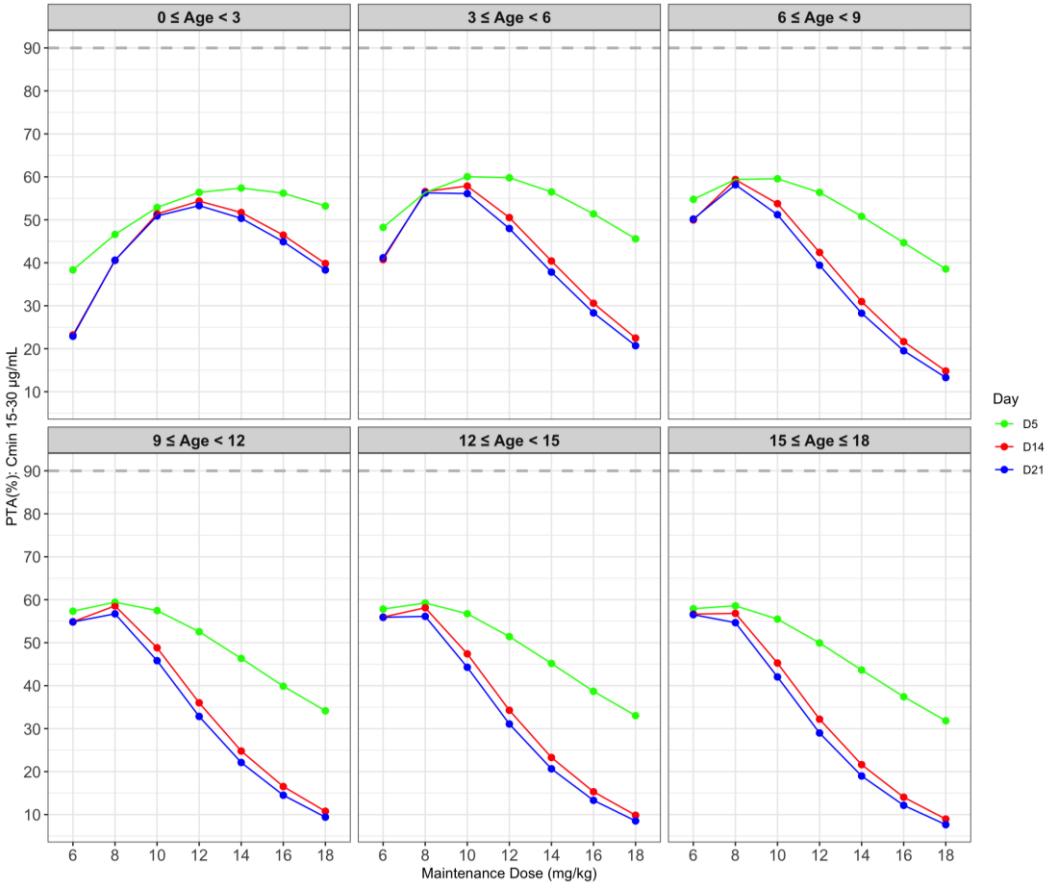

Figure 4. Mean PTA (%) for C_{min} 15–30 ug/mL across different maintenance doses using a fixed loading dose by age groups.

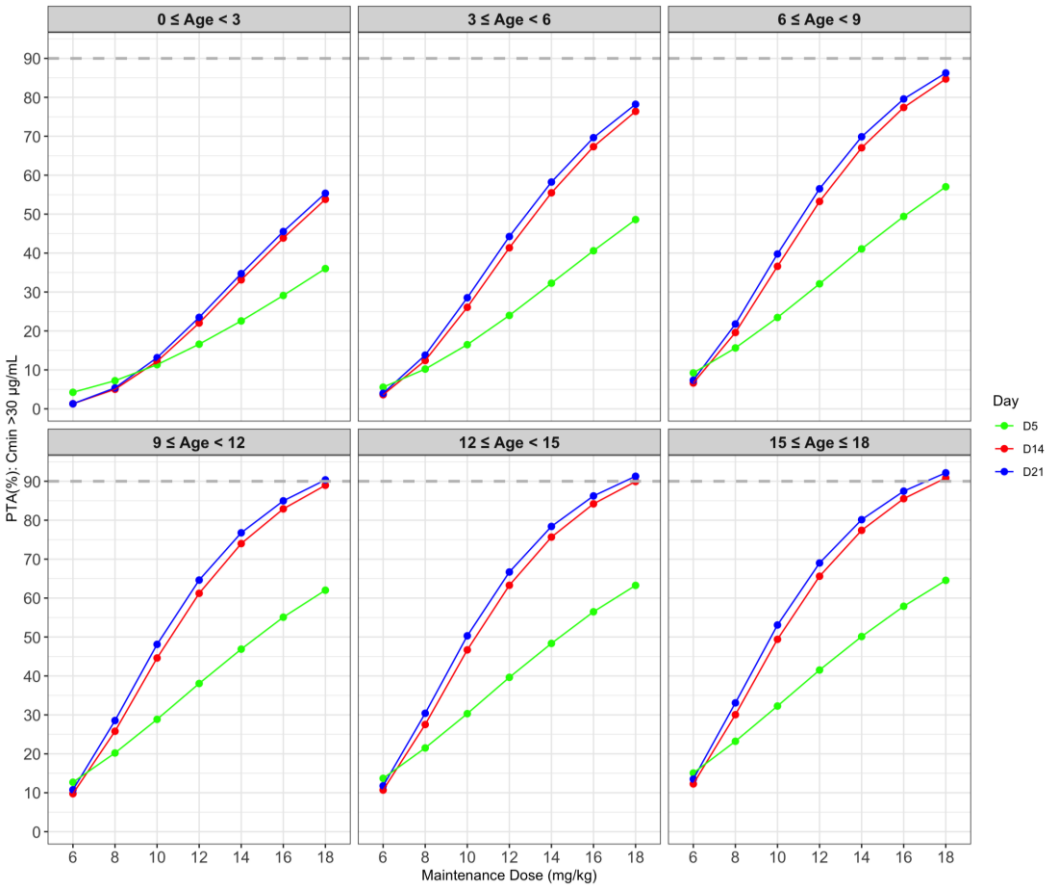

Figure 5. Mean PTA (%) for C_{min} >30 ug/mL across different maintenance doses using a fixed loading dose by age groups.

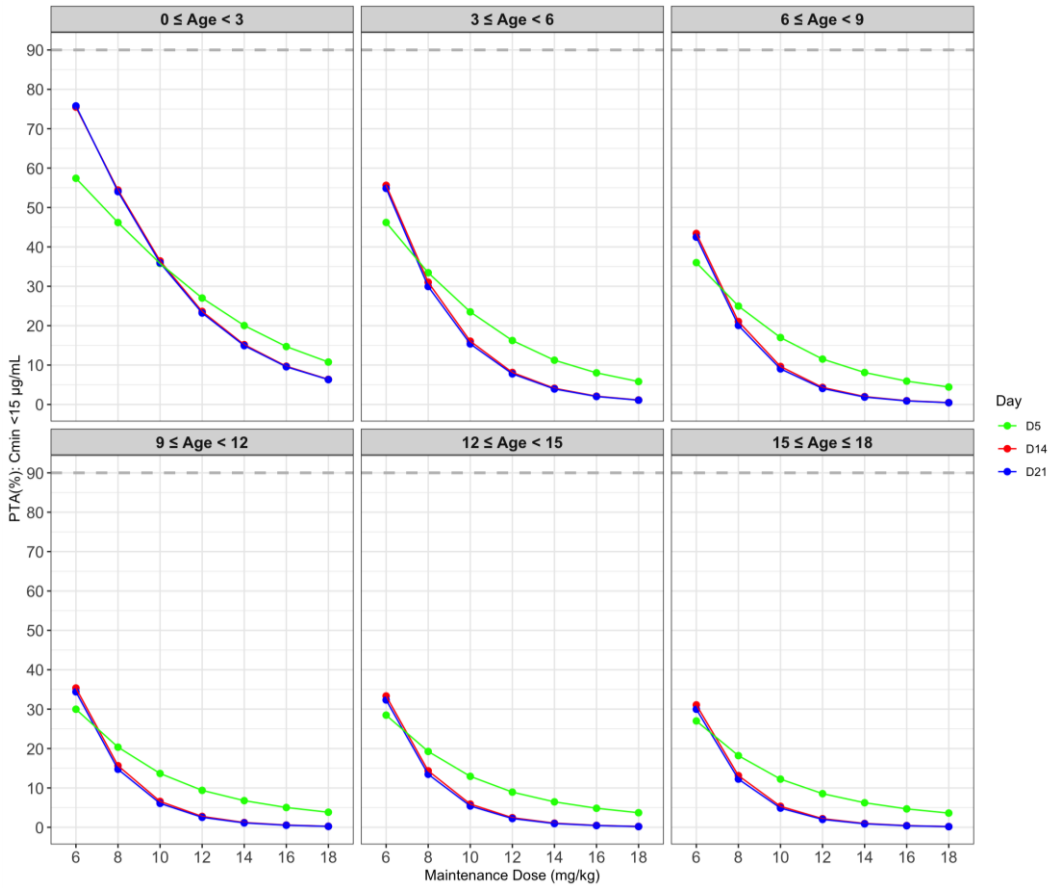

Figure 6. Mean PTA (%) for C_{min} <15 ug/mL across different maintenance doses using a fixed loading dose by age groups.

Table 3. Summary of simulated mean PTA (%) for C_{min} at Days 5, 14, and 21 by age group using selected loading and maintenance dose.

0 ≤ Age < 3
(LD 10 mg/kg q12h x 5, MD 12 mg/kg q24h)

Mean PTA(%) for Cmin in the 0 ≤ Age < 3 age group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
5	56.39	16.60	27.01	43.61
14	54.35	22.04	23.61	45.65
21	53.30	23.48	23.21	46.70

3 ≤ Age < 6
(LD 8 mg/kg q12h x 5, MD 8 mg/kg q24h)

Mean PTA(%) for Cmin in the 3 ≤ Age < 6 age group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
5	56.35	10.21	33.44	43.65
14	56.57	12.40	31.03	43.43
21	56.27	13.79	29.94	43.73

6 ≤ Age < 9
(LD 8 mg/kg q12h x 5, MD 8 mg/kg q24h)

Mean PTA(%) for Cmin in the 6 ≤ Age < 9 age group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
5	59.39	15.63	24.97	40.61
14	59.35	19.60	21.05	40.65
21	58.16	21.78	20.06	41.84

9 ≤ Age < 12
(LD 8 mg/kg q12h x 5, MD 8 mg/kg q24h)

Mean PTA(%) for Cmin in the 9 ≤ Age < 12 age group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
5	59.43	20.22	20.35	40.57
14	58.56	25.80	15.64	41.44
21	56.72	28.55	14.73	43.28

12 ≤ Age < 15
(LD 8 mg/kg q12h x 5, MD 8 mg/kg q24h)

Mean PTA(%) for Cmin in the 12 ≤ Age < 15 age group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
5	59.23	21.51	19.26	40.77
14	58.13	27.53	14.35	41.87
21	56.13	30.41	13.46	43.87

15 ≤ Age < 18
(LD 8 mg/kg q12h x 5, MD 6 mg/kg q24h)

Mean PTA(%) for Cmin in the 15 ≤ Age ≤ 18 age group				
Day	15-30 μg/mL (%)	>30 μg/mL (%)	<15 μg/mL (%)	Total Out-of-Target (%)
5	57.91	15.08	27.01	42.09
14	56.64	12.27	31.08	43.36
21	56.52	13.51	29.98	43.48

LD, loading dose; MD, maintenance dose; q12h, every 12 hours; q24h, every 24 hours; C_{min}, minimum (trough) concentration; PTA, probability of target attainment; >30 μg/mL (%), proportion of individuals with C_{min} above the target range; <15 μg/mL (%), proportion of individuals with C_{min} below the target range; 15–30 μg/mL (%), proportion of individuals within the target concentration range; Total Out-of-Target (%), combined percentage of individuals with C_{min} <15 and >30 μg/mL.

Abstract in Korean

한국 소아 환자의 Teicoplanin 초기 및 유지 용량 최적화를 위한 인구 약동학 모델링 및 시뮬레이션 연구

배경

Teicoplanin 은 메티실린 내성 황색포도상구균을 포함한 그람 양성균 감염 치료에 사용되며, 특히 소아에서 자주 처방된다. 최근 치료약물농도 모니터링(TDM) 가이드라인은 trough 농도 15-30 μg/mL 를 권고하지만, 다수의 소아 환자에서 목표 미달이 관찰되어 용량 조절의 필요성이 제기되고 있다. 기존 연구들은 투약 초기(3 일 또는 5 일)의 노출에 집중되었고, 장기 유지에 대한 근거는 부족하다. 이에 본 연구는 한국 소아 환자를 대상으로 현재 teicoplanin 용량의 적절성을 평가하고, 인구 약동학 모델 기반 시뮬레이션을 통해 초기 및 장기 목표 농도(15–30 ug/mL)를 달성할 수 있는 용량 전략을 탐색하고자 한다.

연구 방법론

본 후향적 연구는 2005 년 11 월 1 일부터 2025 년 1 월 1 일까지 신촌 세브란스병원에서 teicoplanin 을 투여받은 0-18 세 소아 환자를 대상으로 수행되었다. 전자의무기록을 통해 임상, 인구학적, 약물농도 데이터를 수집하여 인구 약동학 분석을 수행하였다. Monolix 의 SAEM 알고리즘으로 구조적 모델을 설정하고, 생리학적 타당성과 통계적 유의성에 따라 공변량을 선별하였다. 최종 모델 기반으로 Simulx 를 사용해 각 용량 조합에 대해 100 명 가상 환자를 대상으로 1,000 회 반복 시뮬레이션을 수행하였다. 시뮬레이션은 48-72 시간 내 목표 농도 도달 여부를 평가하는 ‘초기 목표 도달 전략’과, 21 일간의 치료 기간 동안 농도 유지 여부를 평가하는 ‘장기 유지 전략’으로 수행하였다. 초기 전략에서는 12 시간 간격으로 3-5 회 초기 용량 후 47-71 시간에 목표 농도 도달 확률(PTA)을 평가하고, 이후 적정 유지 용량과 함께 21 일차에서 유지 농도를 확인하였다. 반면 장기 유지 전략에서는 21 일차에서 최적 유지 용량을 먼저 선정하고, 이에 적합한 3 회 초기 용량을 47 시간 시점에서 평가하였다. 두 전략 모두 최종적으로 4, 7, 14, 21 일차에서 초기-유지 용량 조합의 적절성을 평가하였다.

결과

총 34 명 소아 환자에서 108 개의 teicoplanin 혈중 농도 자료를 분석하였다. 첫 TDM 시 목표 농도률은 32.4%, 전체 TDM 중 36.1%였으며, 3 세 미만에서 저농도 비율이 높게 나타났다. 단일 구회 모델이 가장 적합하였으며, 체중이 유의한 공변량으로 확인되었다(V_d: 11.98 L; CL: 0.22 L/h). OFV 는 805.9 에서 746 으로 감소하였다. 초기 전략에서는 <4 kg 군 12 mg/kg q12h x 4, 4–10, 10–50, >50 kg 군에서 각각 10, 8, 6 mg/kg q12h x 5 가 가장 높은 PTA(15–30 μg/mL)를 보이는 초기 용량으로 나타났다. 이에 적합한 유지 용량 (12, 10, 8, 6 mg/kg q24h)을 조합한 경우, 모든 체중군 및 시점에서 PTA 50% 이상 유지했다. 장기 유지 전략에서는 <4, 4–10, 10–50, >50 kg 체중군에서 각각 14, 10 8, 6 mg/kg q24h 가 가장 높은 PTA 를 보이는 유지 용량으로 확인되었다. 이에 적합한 초기 용량 (<4, 4-10, ≥10 kg 군에서 각각 14, 12, 10 mg/kg q12h x 3)을 적용한 경우에도 21 일까지 PTA 가 50% 이상 유지했다.

고찰

본 연구는 현행 teicoplanin 용량에서 소아에서 목표 농도 미달 사례가 빈번함을 확인하였으며, 특히 저연령 및 저체중군에서 이러한 경향이 두드러졌다. 인구 약동학 모델 기반 시뮬레이션으로 제안된 체중별 초기 및 유지 용량 조합은 저농도 및 과다 노출의 위험을 균형 있게 고려하면서 PTA 50% 이상을 유지하여 기존 용량보다 효과적일 가능성을 시사한다. 다만, 본 연구는 소규모 샘플과 TDM 시점 및 주입시간에 대한 가정으로 인해 혈중 농도 추정에 편향이 있었을 가능성이 있으며, 이로 인해 신기능 등 주요 공변량 분석에 한계가 있었을 가능성이 있다.

결론

본 연구는 한국 소아 환자에서 체중 기반 teicoplanin 초기 및 유지 용량 조합을 제안하였으며, 이를 통해 21 일간 전 체중군에서 PTA 50% 이상을 달성함을 시뮬레이션을 통해 확인하였다. 제안된 모델 기반 용량 전략은 소아 감염 치료의 효과와 안전성 향상에 기여할 수 있다. 향후 약동학-약력학 지표(AUC_{0-24}/MIC), 정밀하게 수집된 TDM 데이터, 임상적 치료 결과를 포함한 연구를 통해 실제 임상에서의 정밀 치료 기반 마련이 필요하다.

핵심 되는 말 : 테이코플라닌, 소아, 인구 약동학, 치료약물농도 모니터링, 메티실린 내성 황색포도상구균, 초기 용량, 유지 용량, 용량 최적화