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ORIGINAL ARTICLE

Model-based dose optimization framework for bedaquiline, pretomanid and linezolid for the treatment of drug-resistant tuberculosis

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Aims: Bedaquiline, pretomanid and linezolid (BPaL) combination treatment against *Mycobacterium tuberculosis* is promising, yet safety and adherence concerns exist that motivate exploration of alternative dosing regimens. We developed a mechanistic modelling framework to compare the efficacy of the current and alternative BPaL treatment strategies.

Methods: Pharmacodynamic models for each drug in the BPaL combination treatment were developed using in vitro time-kill data. These models were combined with pharmacokinetic models, incorporating body weight, lesion volume, site-of-action distribution, bacterial susceptibility and pharmacodynamic interactions to assemble the framework. The model was qualified by comparing the simulations against the observed clinical data. Simulations were performed evaluating bedaquiline and linezolid approved (bedaquiline 400 mg once daily [QD] for 14 days followed by 200 mg three times a week, linezolid 1200 mg QD) and alternative dosing regimens (bedaquiline 200 mg QD, linezolid 600 mg QD).

Results: The framework adequately described the observed antibacterial activity data in patients following monotherapy for each drug and approved BPaL dosing. The simulations suggested a minor difference in median time to colony forming unit (CFU)-clearance state with the bedaquiline alternative compared to the approved dosing and the linezolid alternative compared to the approved dosing. Median time to non-replicating-clearance state was predicted to be 15 days from the CFU-clearance state.

Conclusions: The model-based simulations suggested that comparable efficacy can be achieved using alternative bedaquiline and linezolid dosing, which may improve safety and adherence in drug-resistant tuberculosis patients. The framework can be utilized to evaluate treatment optimization approaches, including dosing regimen and duration of treatment predictions to eradicate both replicating- and non-replicating bacteria from lung and lesions.

KEYWORDS
combination therapy, drug-resistance, pharmacodynamic, pharmacokinetic, tuberculosis

1 | INTRODUCTION

The emergence of resistance to commonly used anti-tuberculosis (TB) drugs has been a global health challenge.[1] Historically, drug-resistant TB treatment regimens were associated with poor efficacy and safety outcomes. The new combination regimen of **bedaquiline**, **pretomanid** and **linezolid** (BPaL) showed high efficacy in patients with multi-drug-resistant TB (MDR-TB) and is now endorsed by the World Health Organization (WHO) for the treatment of MDR-TB.[2,3] The current approved BPaL dosing is based on a combination of bedaquiline 400 mg once daily (QD) for 14 days followed by 200 mg three times a week, pretomanid 200 mg QD and linezolid 1200 mg QD. The current linezolid dose is associated with safety concerns including peripheral and optic neuropathy and myelosuppression.[4,5] Moreover, the unconventional, three times a week, bedaquiline dosing schedule leads to patient non-adherence which ultimately affects treatment efficacy and emergence of resistance.[6] To overcome these safety and adherence concerns associated with the approved BPaL dosing regimen, alternative treatment optimization approaches are being evaluated, including bedaquiline 200 mg QD for 8 weeks followed by 100 mg QD and linezolid 600 mg QD.[7,8] The recently completed ZeNix study evaluating the suggested alternative bedaquiline and linezolid dosing demonstrated overall improved benefit–risk ratio following an alternative, simplified and lower, bedaquiline and linezolid dosing regimen compared to the approved dosing regimen.[8] Although the alternative linezolid dosing schedule was associated with overall improved benefit–risk ratio, a slightly higher percentage (5%) of favourable outcomes was reported at the approved dosing compared to the alternative dosing. Additionally, the precise treatment effect could not be assessed in the ZeNix study due to several limitations, such as smaller sample size and lack of comparator arm. Overall, it is evident that the current BPaL dosing regimen may not be optimal for all patients, and improvements are needed to ensure that every patient can receive the maximum benefits with minimal risks.

The BPaL treatment is associated with variable efficacy and safety outcomes across MDR-TB patients.[3,8,9] Mechanistic understanding of the relationship between patient- or disease-related factors and treatment outcome can help rationalize BPaL treatment optimization approaches to increase favourable treatment outcomes. Standard recommended BPaL treatment duration is 6–9 months with extension allowed as needed for up to 26 weeks.[3,8,10] Although the majority (~90%) of the patients achieve culture conversion during the first 2 months of therapy, some patients have also relapsed or had treatment failure after 26 months of therapy.[3,8] Mechanistically, relapse can be attributed to non-replicating persisting *Mycobacterium tuberculosis* (Mtb) subpopulation. TB patients' treatment response is measured in sputum samples. Non-replicating Mtb subpopulation persists within cavitary lung lesions of TB patients and as such often is not measurable. Thus, predictions of BPaL treatment response on non-replicating Mtb within cavitary lesions can help rationalize BPaL treatment duration to avoid relapse. To this end, a mechanistic pharmacokinetic (PK)–pharmacodynamic (PD)-response modelling framework that includes patient-, disease- and drug-related factors to enable predictions of BPaL anti-bacterial efficacy on replicating and non-replicating Mtb subpopulation is needed. Such a framework can help evaluate treatment optimization and individualization approaches for BPaL combination dosing regimen, schedule and duration selection based on the relevant factors in MDR-TB patients.

To date, quantitative pharmacology approaches have exploited some relationships between patient- and disease-related covariates, PK and response for bedaquiline, pretomanid and linezolid individually.[11–14] These models, however, did not include several key mechanistic components, such as Mtb susceptibility, target site drug exposures and PD interactions between the BPaL combination regimen. In this work, we aimed to combine the relevant mechanistic components to develop a quantitative framework for BPaL

What is already known about this subject

- The bedaquiline, pretomanid and linezolid (BPaL) combination treatment regimen is promising against drug-resistant tuberculosis.
- The currently used approved bedaquiline and linezolid dosing schedule in the BPaL combination regimen is associated with safety and adherence concerns.
- Alternative bedaquiline and linezolid dosing regimens, including simplified regimens and lower doses, have shown improved benefit–risk profile, although the precise treatment effect is uncertain due to a limited sample size and lack of a comparator arm.
- BPaL treatment optimization approaches are desirable to optimize treatment benefit, to minimize safety concerns and to avoid relapse following BPaL treatment.

What this study adds

- A mechanistic modelling framework for BPaL predicted minor differences in anti-Mtb efficacy between current approved and alternative dosing regimens.
- The modelling framework allowed predictions of time to non-replicating-clearance state, which can be utilized to evaluate treatment duration to eradicate non-replicating bacteria from lung lesions.
- This framework can be utilized to explore further treatment optimization and individualization approaches for drug-resistant tuberculosis patients.

combination, including dynamics of replicating and non-replicating Mtb, patient-related and other covariates and their effects on drug exposures, target site drug exposures, individual drug effects and PD drug interactions. The developed framework was then applied to perform anti-Mtb activity predictions for both replicating and non-replicating Mtb following the current approved and alternative BPaL dosing regimens in MDR-TB patients.

2 | METHODS

The development of the mechanistic PK–PD framework for BPaL combination treatments was performed in four main steps. We first fit the multi-state TB model to in vitro time-kill data for bedaquiline, pretomanid and linezolid for fast- and slow-replicating subpopulations of Mtb separately. Then, the individual drug effect models were translated to TB patients by accounting for patient body weight, TB lesion volume in patient lungs, drug exposure predictions within lungs and lesions, and Mtb susceptibility profiles (i.e., minimum inhibitory concentrations [MIC]). Next, the PD interaction parameters were incorporated. Lastly, the model was combined with a previously developed model for correlation between two anti-Mtb activity measures, colony forming units (CFUs) and time to positivity (TTP) to allow for predictions of both outcome measures. Combination treatment simulations were performed for approved and alternative treatment schedules, and the results were compared against the observed clinical data. The overall process for the construction of the quantitative framework for BPaL combination therapy is illustrated in Figure 1.

2.1 | Mechanistic PD models

The published multi-state TB model which describes the growth dynamics of fast-, slow- and non-replicating Mtb populations was reproduced and used to describe bacterial growth dynamics in TB patients.[15] We digitized longitudinal bacterial CFU data from in vitro fast-multiplying (log-phase) and semi-dormant Mtb time-kill experiments at various concentrations of bedaquiline, pretomanid and pretomanid.[16–21] Experiment-specific growth rate parameters, fast-multiplying bacterial growth rate (kG) and system carrying capacity (B_{max}), were estimated using the untreated control data. Next, drug effects for bedaquiline, pretomanid and linezolid were separately estimated (Table S1). Linear and non-linear drug-induced kill functions on fast-, slow- and non-replicating Mtb populations were evaluated. As no data for slow-replicating bacteria were

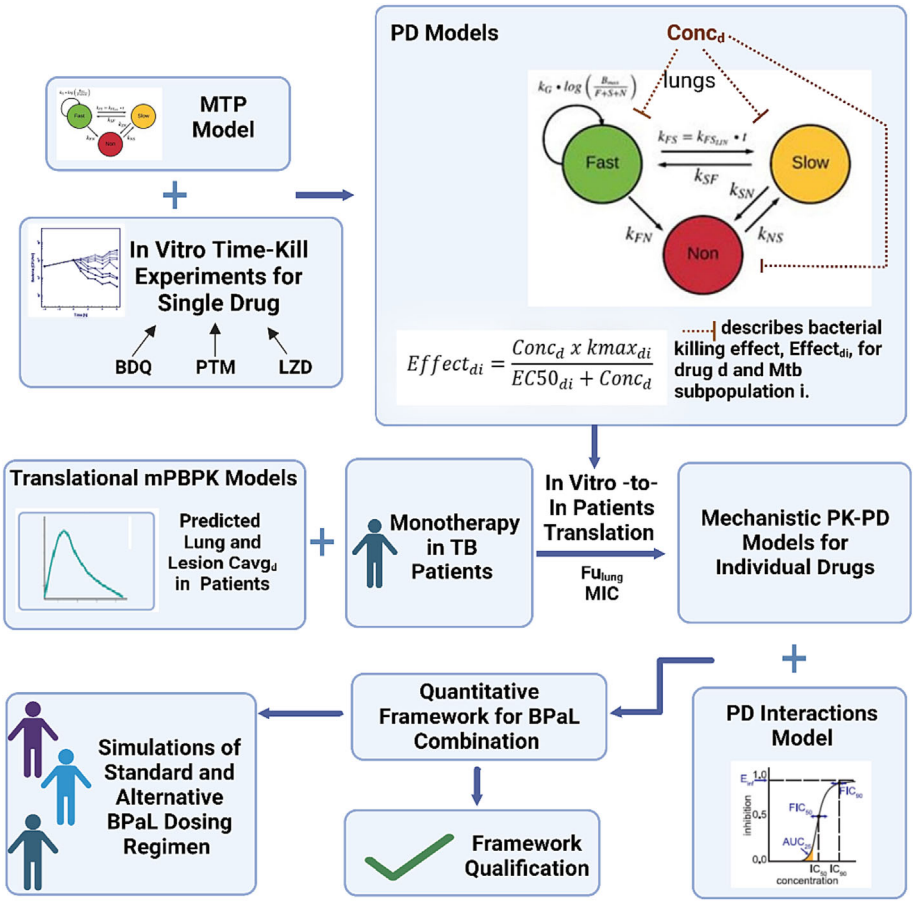

FIGURE 1 Overview of the bedaquiline, pretomanid and linezolid (BPaL) quantitative framework development process. BDQ, bedaquiline; Cavg$_d$, daily average concentrations of drug d at the site of action of TB patients (bedaquiline, pretomanid or linezolid); CFU, colony-forming unit of Mtb; Conc$_d$, in vitro concentrations of drug d; EBA, early bactericidal activity; Effect$_{di}$, bacterial killing effect of drug d for Mtb population i (fast-, slow- or non-replicating); Fu$_{lung}$, fraction unbound in lungs; LZD, linezolid; MDR, multi-drug resistant TB; MIC, minimum inhibitory concentrations; MTP, multistate tuberculosis pharmacometrics model[11,15]; PD, pharmacodynamic; PK, pharmacokinetic; PTM, pretomanid; TB, tuberculosis; TTP, time to liquid culture positivity. Figure created with Biorender.com.

available, the drug effect models for non-replicating Mtb were applied to the slow-replicating Mtb population. Models were selected based on objective function value, visual inspections of observed versus predictions plots, and plausibility and precision of the parameter estimates.

2.2 | Mechanistic PK–PD models

Sputum CFU data from bedaquiline, pretomanid and linezolid early bactericidal activity (EBA) studies, that is, clinical studies that evaluated monotherapy 14-day anti-Mtb effects, in pulmonary TB patients were obtained from the Platform for Aggregation of Clinical TB Studies (TB-PACTS; https://c-path.org/programs/tb-pacts/) database.[12,22–24] PK models and parameter estimates for bedaquiline and pretomanid from our prior work were used to simulate plasma and site of action, lungs and lesions, and concentration–time profiles.[14] A PK model for linezolid was reproduced from the literature to simulate plasma, lungs and lesion concentration–time profiles.[25] Body weights were sampled for the virtual patients from observed TB patients' body weight distribution from the data. TB lung lesion volumes were simulated using observed TB patients' cavity volume from the literature.[26] We simulated the PK of bedaquiline, pretomanid and linezolid monotherapy for various dose groups that were evaluated in the monotherapy clinical studies ($n = 500$ patients per simulated dose group), and target site exposure metrics for each virtual subject, daily average lung concentrations ($C_{avg\text{-}lung}$) and average lesion concentrations ($C_{avg\text{-}lesion}$) were calculated for use in the simulations of anti-Mtb activities. The multi-state TB pharmacometrics model and PK and PD models were combined for all three drugs for the simulations.[13,15]

Drug effects were introduced in the simulations at 150 days post-infection when the bacterial population was assumed to have reached a steady state. Drug effects were assumed to be driven by $C_{avg\text{-}lung}$ for fast- and slow-replicating Mtb and $C_{avg\text{-}lesion}$ for non-replicating Mtb. A lung tissue binding factor (Fu_{lung}) was incorporated to calculate free drug exposure at target sites to exert an anti-Mtb effect. Parameter estimates for Fu_{lung} were obtained from the literature.[27,28] Bacterial load, that is, CFU, simulations were performed according to the dosing schedules tested in the corresponding studies. CFU was calculated as the sum of predicted fast- and slow-replicating Mtb populations within lungs. The plots of predicted change in bacterial load were compared against the observed change in CFU over 14 days of monotherapy treatment for all three drugs.

The models for each drug used to perform monotherapy simulations were then combined to construct the framework for the simulation of combination therapies. PD interactions between each two-drug combination of the three drugs were incorporated using the adapted version of the Bliss independence model structure.[29,30] The parameter estimates were obtained from in vitro experiments-derived fractional inhibition coefficients for each two-drug combination[31] (Table 1).

2.3 | BPaL quantitative framework

Clinical studies often measure anti-microbial activity using solid culture (CFU) or liquid culture TTP. Therefore, a CFU-TTP correlation model has been previously developed by fitting a Gompertz model structure to the matched CFU and TTP clinical data from TB patients treated with rifampin.[32] We reproduced the CFU-TTP correlation model and added it within the quantitative frame to allow for simulations of CFU and TTP. As no in vitro time-kill experiments for M2 were available, M2 maximum kill rates for each bacterial subpopulation were assumed to be 5-fold lower than that of bedaquiline based on the literature.[33] Sensitivity analysis was conducted to evaluate the impact of bedaquiline-M2 effect scaling parameter (bdqm2scaling) by varying the scaling parameter and plotting typical CFU predictions (Figure S2). Overall, the final quantitative framework for BPaL included the dynamics of TB disease progression, drug distribution and available effective fraction into lung and lesions, individual drug effects, patient-related and other covariates, and PD drug interactions.

Virtual patient ($n = 500$) MICs for bedaquiline, pretomanid and linezolid were simulated by sampling from the observed MIC distribution for each drug from the Nix-TB study data from the TB-Pacts database.[3] Patient-specific covariates, PK, multi-state TB pharmacometrics model and PD parameters were simulated in a similar manner as monotherapy simulations described above. Then, drug effect parameters, k_{max} and EC_{50}, were adjusted for MIC by taking the ratio between the in-patient versus in vitro MIC for each drug and multiplying it by the parameter value.[29] Bacterial growth simulations were generated for up to 150 days using the abovementioned parameters. To qualify the quantitative framework, observed changes in microbiological measure, EBA-TTP from 0 to 14 day ($EBA\text{-}TTP_{0\text{-}14day}$) and 0 to 28 day ($EBA\text{-}TTP_{0\text{-}28day}$) following BPaL combination therapy were compared against the simulations for the dosing regimen studied in the Nix-TB study.[3] For the qualification task, typical B_{max} was set to match observed baseline median TTP in the study (Supporting Information S6).

2.4 | Simulations of the approved and alternative BPaL dosing regimen

The BPaL quantitative framework including the same simulated virtual population was used to perform simulations of the current approved and three alternative dosing scenarios. The alternative bedaquiline and linezolid dosing scenarios proposed in the literature were included in the simulations.[7,8] Overall, the following four dosing scenarios were simulated for 500 virtual subjects each: (1) bedaquiline 400 mg QD 14 days followed by 200 mg three times a week, pretomanid 200 mg QD, linezolid 600 mg BID; (2) bedaquiline 200 mg QD, pretomanid 200 mg QD, linezolid 600 mg BID; (3) bedaquiline 400 mg QD 14 days followed by 200 mg three times a week, pretomanid 200 mg QD, linezolid 600 mg QD; and (4) bedaquiline 200 mg QD, pretomanid 200 mg QD, linezolid 600 mg QD. Simulations were conducted

TABLE 1 Parameter estimates of bedaquiline, pretomanid and linezolid semi-mechanistic pharmacokinetic–pharmacodynamic (PK–PD) models.

Parameter	Description	Estimate	%RSE or assumption
Bedaquiline[a]			
BDQkmaxfst	Maximum kill rate for fast-replicating Mtb (1/day)	8.76	2.61
BDQkmaxS, BDQkmaxN	Maximum kill rate for slow- and non-replicating Mtb (1/day)	3.39	25.6
BDQEC50fst	Bedaquiline concentrations needed for half-maximum response for fast-replicating Mtb (mg/L)	0.12	11.7
BDQEC50S, BDQEC50N	Bedaquiline concentrations needed for half-maximum response for slow- and non-replicating Mtb (mg/L)	3.49	64.2
BDQTau	Delay in start of bedaquiline activity (days)	5.3	15.0
Fu_{lung}BDQ	Lung tissue binding factor	0.01	28
bdqm2scaling	Bedaquiline to M2 anti-bacterial effect scaling factor	0.2	Assumed 5-fold lower efficacy of M2 as compared to bedaquiline
Pretomanid[b]			
PTMkmaxfst	Maximum kill rate for fast-replicating Mtb (1/day)	2.97	8.34
PTMkmaxS, PTMkmaxN	Maximum kill rate for slow- and non-replicating Mtb (1/day)	0.709	36.4
PTMEC50fst	Pretomanid concentrations needed for half-maximum response for fast-replicating Mtb (mg/L)	0.156	21.3
PTMEC50S, PTMEC50N	Pretomanid concentrations needed for half-maximum response for slow- and non-replicating Mtb (mg/L)	12.5	69.2
Fu_{lung}PTM	Lung tissue binding factor	1	Assumed
Linezolid[c]			
LZDkmaxfst	Maximum kill rate for fast-replicating Mtb (1/day)	0.65	35.6
LZDkmaxS, LZDkmaxN	Maximum kill rate for slow- and non-replicating Mtb (1/day)	0.41	47.1
LZDEC50fst	Linezolid concentrations needed for half-maximum response for fast-replicating Mtb (mg/L)	0.8	58.3
LZDEC50S, LZDEC50N	Linezolid concentrations needed for half-maximum response for slow- and non-replicating Mtb (mg/L)	1.1	48.5
Fu_{lung}LZD	Lung tissue binding factor	0.29	28
Pharmacodynamic interactions			
FICBP	Interaction bedaquiline–pretomanid (synergy)	0.89	31
FICBL	Interaction bedaquiline–linezolid (antagonism)	1.13	
FICPL	Interaction pretomanid–linezolid (antagonism)	1.86	

Note: The multistate tuberculosis model structure and parameter estimated were fixed to the published estimates to describe Mtb growth dynamics.[15] The PK model structure and parameters were fixed to the published estimates to predict serum and lung site concentrations.[14,25]

[a]$kG = 1.52\ day^{-1}$ and $B_{max} = 6.5e+07\ mL^{-1}$ were estimated by fitting the multistate tuberculosis model to combined log-phase Mtb growth data in absence of bedaquiline.

[b]$B_{max} = 8.25e+09\ mL^{-1}$ was estimated by fitting the multistate tuberculosis model to combined log-phase Mtb growth data in absence of pretomanid.

[c]Linezolid hollow-fibre experiment showed no increase in Mtb load for the control group for the duration of the study; therefore, linezolid control data were best described by first-order natural death rates 0.542 and 0.275 day^{-1} for fast- and non-replicating bacteria, respectively.

for up to 14 weeks. Plots of bacterial load, CFU (total of fast- and slow-replicating Mtb), and non-replicating separately, over time following the start of treatment were generated. The time scales on the plots were selected for optimal presentation of the overall results. Time-to-Mtb clearance, defined as <1 CFU mL^{-1} or <1 non-replicating Mtb mL^{-1}, and proportions of virtual patients achieving Mtb clearance were calculated for each virtual patient and dosing combination.

2.5 | Software

All analyses were conducted in R (R for Windows, v4.1, https://www.r-project.org/) using RStudio (RStudio, v1-554, www.rstudio.com/). Data management and plotting were performed using the tidyverse package. Parameter optimization and model simulations were conducted using nlmixr and RxODE packages. Final model codes are provided in the Supporting Information S6.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.

3 | RESULTS

3.1 | Development of mechanistic PD models for in vitro time-kill data

The multi-state TB model was used as a base model structure to evaluate the drug effects of bedaquiline, pretomanid and linezolid using in vitro anti-Mtb activity data. Prior to adding drug effects, experiment-specific Mtb growth curves were estimated using control data. Estimation of both kG and B_{max} for bedaquiline experiments, and only B_{max} for pretomanid experiments best described the in vitro control data. Estimation of kG for the pretomanid control experiment was evaluated but resulted in a similar parameter estimate to that previously reported in the literature and was therefore fixed to the previously reported value.[15] Additionally, data from the hollow-fibre infection model were used for linezolid experiments, and the control data for the linezolid experiments were described by a first-order natural death term and the published multi-state TB model growth parameters.[20]

The non-linear model with separate drug-induced effects for each drug on fast-replicating and non-replicating Mtb provided improved fits over the linear models for all three drugs. No data for slow-replicating bacteria were available. Parameterization of drug effects was attempted separately for slow- and non-replicating Mtb populations using a multi-state TB model construct; however, the parameters were estimated with very high relative standard errors (RSEs). Thus, the model was simplified, and the same PD models and parameter estimates were applied to the slow-replicating and non-replicating Mtb populations. Delay in the induction of the bedaquiline effect has been previously described.[18] Therefore, a lag time in the bedaquiline model was evaluated and further improved the fit. The final model equations for all three drugs are provided in Supporting Information S6. The PD parameters for fast-replicating bacteria for all three drugs were estimated with good precision (%RSE < 40%). However, relatively large RSEs were noted for the parameters for slow- or non-replicating bacteria due to the limited data (Table 1). Overall, the models described the available data reasonably well (Figure 2).

3.2 | Mechanistic PK–PD models for individual drugs

Previously developed mechanistic PK models for bedaquiline, pretomanid and linezolid were combined with the PD models that were developed using the in vitro data to construct the mechanistic PK–PD framework. The framework was first used to simulate PK-EBA in TB patients at various doses of bedaquiline, pretomanid and linezolid separately (Table S1). For the EBA simulations, the PD parameters were not adjusted for MICs because all patients in the EBA studies for all three drugs had MIC ≤ lower limit of detection. The translated model overpredicted the anti-Mtb activity of bedaquiline. As bedaquiline strongly binds to plasma proteins and is widely distributed in tissue, a lung tissue binding factor parameter was introduced and estimated to be 0.01[33] (Table 1). The final model described well the median 14-day EBA data for bedaquiline at various doses (Figure 3). The lung tissue binding factors of 1 and 0.29 for pretomanid and linezolid, respectively, described well the median EBA data for both drugs.[27] The simulations confirmed that the developed framework predicts the central tendency in bedaquiline, pretomanid and linezolid EBA in TB patients separately. The framework was deemed reliable for the evaluation of the next steps of the analysis, that is, to simulate anti-Mtb activity following treatment with BPaL combination in MDR-TB patients.

3.3 | BPaL quantitative framework

The final quantitative framework for the BPaL combination that included a multi-state TB model, drug effect models for all three drugs, PD interactions between the three drugs, scaling of the drug effect for MIC, and CFU-TTP correlations model was used for the simulations of combination drug effect to compare against Nix-TB observed data. Overall, the framework reasonably described the observed anti-bacterial activity following BPaL combination therapy (Table 2, Figure S3). Median (95% prediction interval [PI]) time to CFU clearance status following the approved BPaL dosing was predicted as 38 (23–53) days which is in reasonable alignment with the reported median time to culture-negative status in the Nix-TB study (42 days) (Figure 4). Overall, this modelling framework was deemed appropriate to simulate anti-Mtb activity following approved and alternative BPaL dosing regimens.

3.4 | Simulations of anti-Mtb activity following BPaL at approved and alternative dosing in MDR-TB patients

The BPaL quantitative framework was used to perform and compare simulations of the current approved and three alternative dosing scenarios for up to 9 weeks (Figures 4 and 5). Bedaquiline QD dosing (bedaquiline 200 mg QD for 9 weeks followed by 100 mg QD) was predicted to achieve slightly faster CFU clearance when compared to approved bedaquiline dosing (400 mg QD for 14 days followed by 200 mg QD) (median [95% PI] time to <1 CFU mL^{-1} = 38 [23–53] *vs.* 40 [27–56] days). Linezolid 600 mg BID was predicted to yield slightly faster Mtb clearance as compared to linezolid 600 mg QD dosing (median [95% PI] time to <1 CFU mL^{-1} = 45 [26–58] *vs.* 43 [30–57] days). Overall clearance of non-replicating Mtb from the lesion was

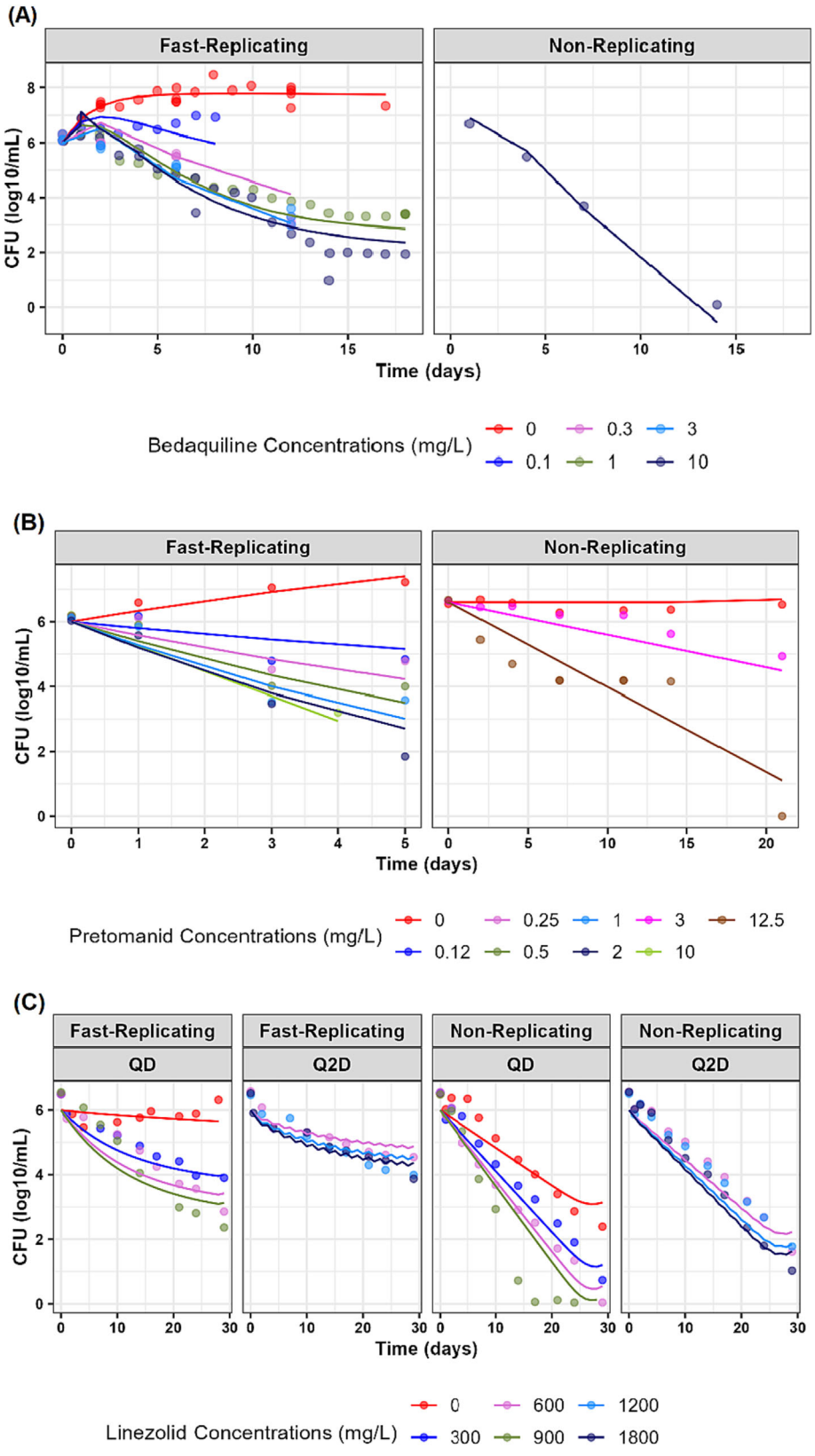

FIGURE 2 Model fitting of the semi-mechanistic pharmacodynamic (PD) models to in vitro anti-Mtb activity data: (A) bedaquiline, (B) pretomanid, (C) linezolid. The model described the observed in vitro experimental data well. Lines show the predicted data and points show observed data. CFU, colony-forming unit.

correlated with CFU clearance (combined fast- and slow-replicating Mtb). Median time to <1 non-replicating Mtb mL^{-1} was predicted to be an additional 15 days from the CFU clearance state (Figure 4). No clear correlation was predicted in time-to-Mtb clearance and individual MIC following BPaL combination therapy at the approved regimen (Figure S4).

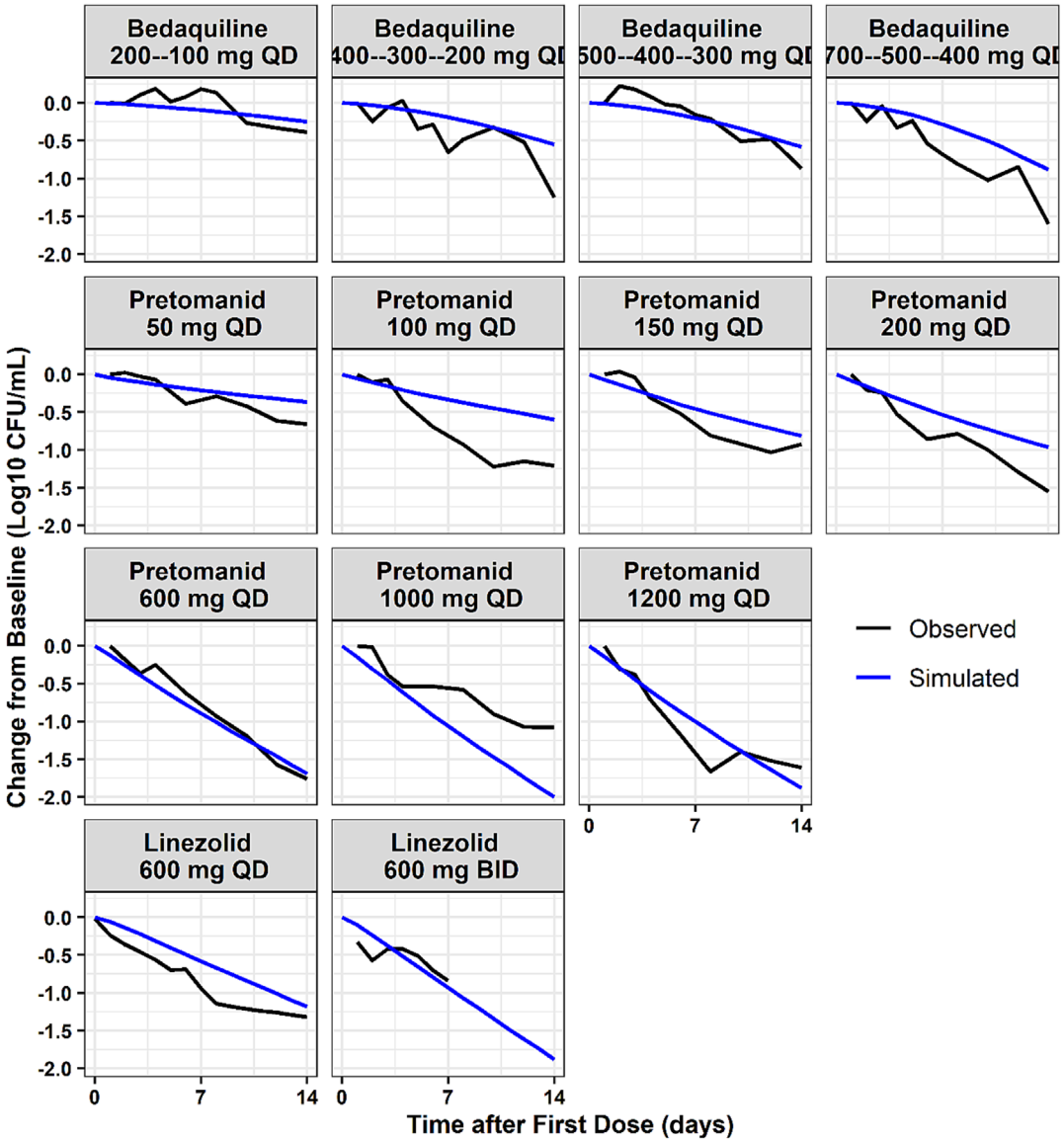

FIGURE 3 Evaluation of the bedaquiline, pretomanid and linezolid semi-mechanistic pharmacokinetic–pharmacodynamic (PK–PD) models using early bactericidal activity studies data from pulmonary tuberculosis (TB) patients. The in vitro to in vivo translated, semi-mechanistic PK–PD models recapitulate the early bactericidal activity in TB patients. Bedaquiline was administered with an increasing daily dose, that is, Panel 1 represents a group that received 200 mg on Day 1 and 100 mg on Day 2 onwards. Lines represent median. BID, twice daily; CFU, colony-forming unit; QD, once daily.

TABLE 2 Observed and predicted early bactericidal activity as measured by time to culture positivity (EBA-TTP) (1/day) following bedaquiline, pretomanid and linezolid combination therapy.

Linezolid treatment group	Metric	Observed median (95% CI)	Simulated median (95% PI)
600 mg BID	$EBA\text{-}TTP_{0\text{-}14days}$	−0.68 (−2.40 to 0.14)	−0.85 (−0.94 to −0.71)
	$EBA\text{-}TTP_{0\text{-}28days}$	−0.58 (−0.97 to −0.40)	−0.51 (−0.52 to −0.41)
1200 mg QD	$EBA\text{-}TTP_{0\text{-}14days}$	−0.63 (−1.42 to −0.07)	−0.85 (−0.93 to −0.75)
	$EBA\text{-}TTP_{0\text{-}28days}$	−0.45 (−0.92 to −0.12)	−0.51 (−0.52 to −0.46)

Abbreviations: BID, twice daily; CI, confidence interval; PI, prediction interval; QD, once daily.

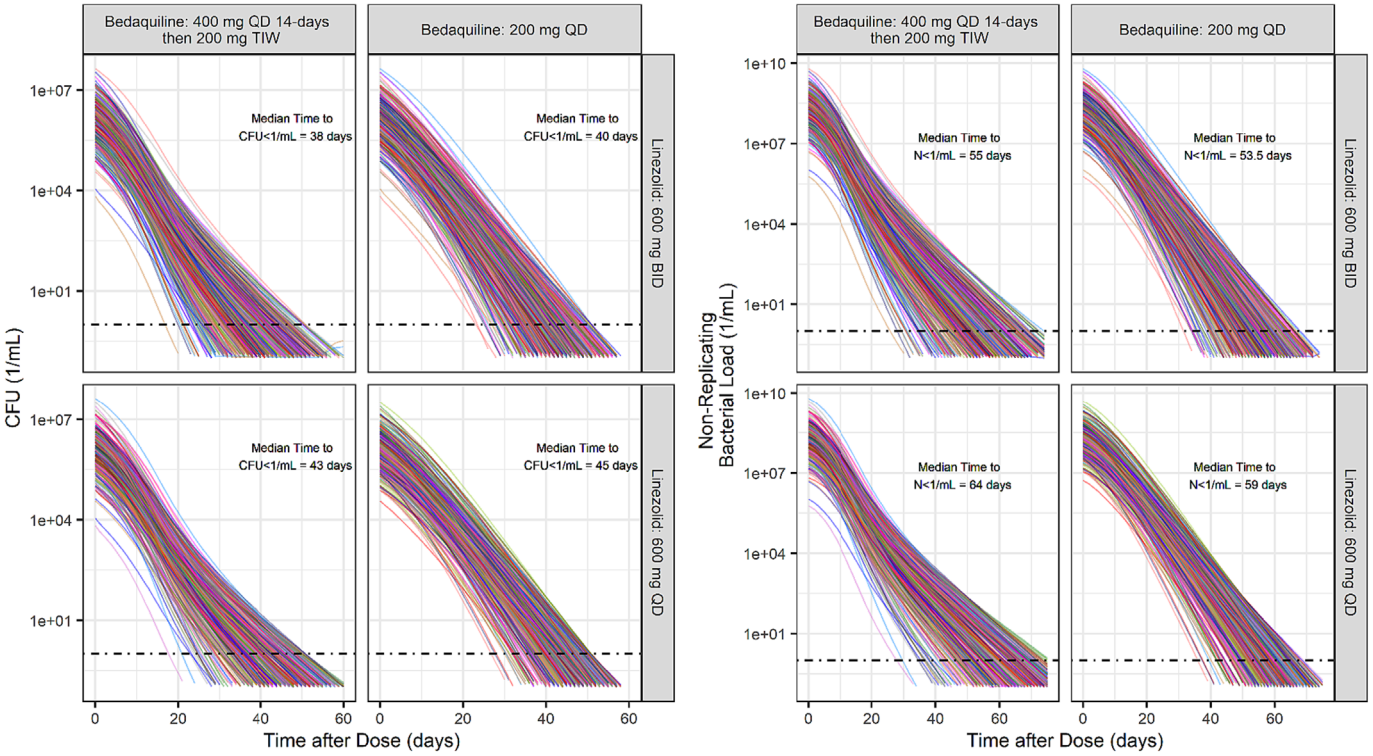

FIGURE 4 Spaghetti plots of anti-Mtb activity simulations using the bedaquiline, pretomanid and linezolid (BPaL) quantitative framework for the approved and alternative dosing regimens. Each BPaL combination dosing regimen was simulated for 500 virtual patients and bacterial load time course predictions are plotted for each virtual patient. CFU represents total fast- and slow-multiplying Mtb, BID = twice daily, QD = once daily, TIW = three times a week. Dashed lines represent 1 CFU or non-replicating Mtb mL^{-1}. Minor difference was predicted in Mtb clearance with bedaquiline QD dosing when compared to approved bedaquiline dosing. Similarly, minor difference was predicted in Mtb clearance following linezolid 600 mg BID as compared to linezolid 600 mg QD dosing. Median time to <1 non-replicating Mtb mL^{-1} was predicted to be an additional 15 days from the CFU clearance state.

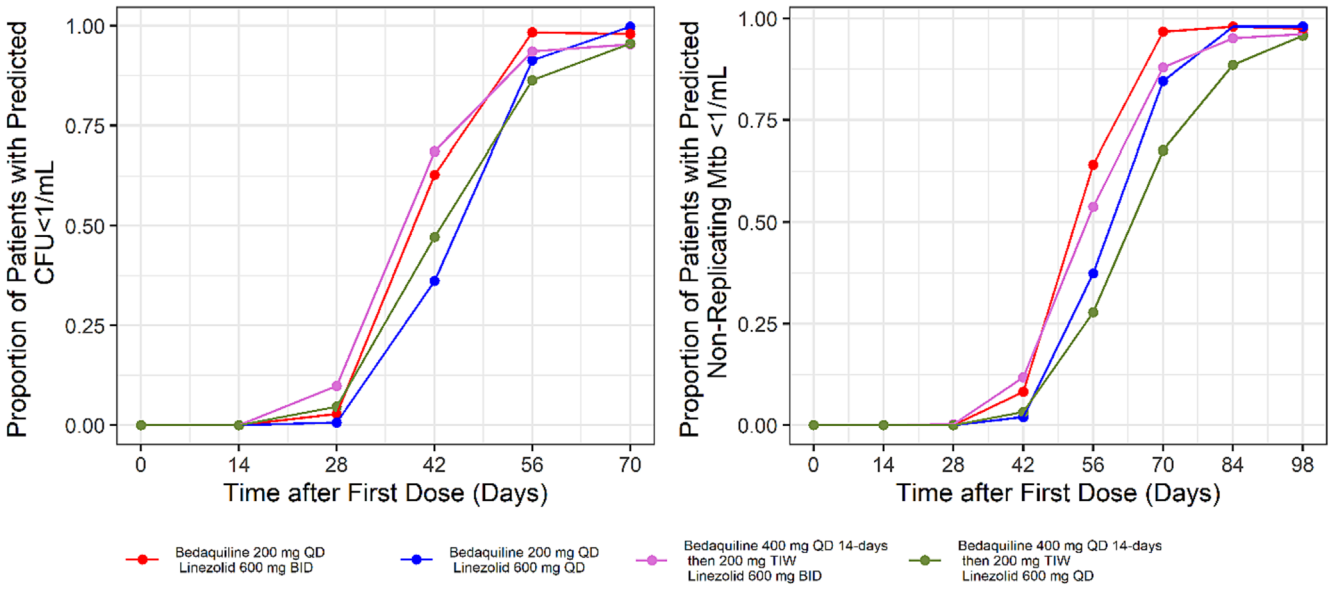

FIGURE 5 Predicted proportions of patients with colony-forming unit (CFU) and non-replicating Mtb < 1 mL^{-1}. Comparable proportions of patients were predicted to achieve Mtb clearance following bedaquiline once daily (QD) dosing versus bedaquiline approved dosing. Similarly, comparable proportions of patients were predicted to achieve Mtb clearance following linezolid QD dosing versus linezolid approved dosing.

4 | DISCUSSION

In this work, we developed a quantitative framework for the BPaL combination that included key components that play a role in the overall response to the therapy. The framework reasonably described anti-Mtb activity data for monotherapy of each drug in pulmonary TB patients and BPaL combination therapy in MDR-TB patients. We applied the framework to predict the treatment effects of the approved and alternative BPaL dosing scenarios.

The BPaL quantitative framework can be used for the rational design of BPaL dose optimization strategies in TB patients, including MDR-TB. The approved bedaquiline dose in the BPaL regimen includes 400 mg QD for 14 days followed by 200 mg three times a week for at least 6–9 weeks. This unconventional, three times a week, dosing schedule and long treatment duration may lead to patient non-adherence.[34] Additionally, bedaquiline has been reported to have delayed onset of anti-Mtb activity. Therefore, alternative bedaquiline dosing, 200 mg QD for 9 weeks followed by 100 mg QD, has been proposed. Prior analyses predicted comparable safety concerns associated with alternative bedaquiline dosing and approved dosing.[35] Our simulations suggested a minor difference in Mtb clearance following bedaquiline QD dosing compared to the approved dosing. Linezolid has been a key drug in more than five drug combination regimens and was widely used for the treatment of MDR-TB before the availability of bedaquiline and pretomanid. Despite the reasonable efficacy against MDR-TB, linezolid has high toxicity potential.[2] Our simulations suggested a slightly slower Mtb clearance following BPaL administration including linezolid 600 mg QD when compared to 600 mg BID. These simulations are in alignment with the ZeNix study, where 89% and 84% of the patients had favourable outcomes following BPaL including 1200 and 600 mg QD linezolid, respectively. In the same study, fewer adverse events and dose modifications were reported in the group with linezolid 600 mg compared to 1200 mg QD.[8] Altogether, this suggests that alternative BPaL dosing, including bedaquiline 200 mg QD and linezolid 600 mg QD, may be appropriate for most MDR-TB patients.

Our modelling framework incorporates predictions of drug penetration within lungs and cavitary lesions where drug concentrations within lungs drive fast- and slow-replicating Mtb killing, and drug concentrations within lesions drive non-replicating Mtb killing. Our model-based predictions for the effects of BPaL combination on non-replicating Mtb suggested an approximately additional 15 days of BPaL therapy to achieve a non-replicating clearance state from the CFU clearance state. Thus, additional clinical evaluations of the BPaL regimen for longer treatment periods after the CFU-negative state and its impact on tolerance, resistance or relapse rate can be beneficial.[36]

We assumed that the M2 target site exposure-driven maximum kill rate for all three Mtb subpopulations is 5-fold lower than that of bedaquiline.[33] The observed plasma M2-bedaquiline exposure ratio has been reported to be 0.25–0.32.[33] Based on our translational mPBPK model, plasma, lungs and lesion M2-bedaquiline exposure ratios were predicted to be 0.18, 1.11 and 1.02, respectively.[14] These results provide an overview of the relative role of M2 as compared to bedaquiline on Mtb clearance.

In our model, we used synergistic PD interaction between bedaquiline and pretomanid, and antagonist PD interaction between linezolid and bedaquiline as well as linezolid and pretomanid based on the robust DiaMOND drug interaction evaluation methodology from the literature.[31] Previously, mixed results have been reported for this type of PD interactions between each two-drug combination of bedaquiline, pretomanid and linezolid perhaps owing to different experimental conditions.[37–39] Our model predictions agree with the consistently reported experimental and clinical findings that reported three-drug combination, BPaL, to be synergistically effective against Mtb.

A key assumption in our model was that we assumed the same drug effect parameters for the slow- or non-replicating Mtb population for all three drugs as in vitro time-kill data were not available for the slow-replicating Mtb population in the literature. Such data are often not measured, and simpler bacterial growth models with two Mtb populations have been developed using murine experimental data.[40] As our model was calibrated using a multi-state TB model construct and parameterization and in vitro data from fast- and slow-replicating Mtb experiments, our parameter estimates and thus simulations capture relative contributions of treatment on the killing of each Mtb subpopulation (Figure S5). Future work on the development and validation of two Mtb subpopulation models using in vitro data, and on the development of bioanalytical methods to enable measurements of all three Mtb subpopulations can be useful.

Bedaquiline and pretomanid pulmonary drug concentration data from TB patients are not available to date; therefore, lung and lesion penetration of these two drugs were obtained using translational mPBPK models.[14] Additionally, lung tissue content and drug physicochemical properties affect the fraction of drug available at target sites to exert the anti-Mtb effect. Anti-bacterial activity data following monotherapy agreed well with the predictions for bedaquiline and linezolid by accounting for unbound drug fractions in lungs that were measured experimentally.[27] However, a similar approach for pretomanid underpredicted the drug effects. Therefore, this parameter was assumed to be 1 for pretomanid which provided a reasonable fit to the data. Overall, although the lung and lesion penetration component of our framework could not be qualified against observed data, our model is qualified against observed anti-Mtb activity data following the monotherapy of each drug.

Our BPaL quantitative framework includes key factors that play a role in treatment outcome, such as patient body weight, plasma PK, TB lesion volume, drug penetration and available effective fraction into lung and lesion, Mtb susceptibility and PD interactions amongst all three drugs. Thus, the framework can be utilized to further explore the relationship between these factors and individual parameter estimates to understand the key factors affecting treatment outcomes. The mechanistic understanding included in this quantitative framework combined with data-driven estimation approaches, such as Bayesian estimation, may provide a thorough understanding of individual variability towards the goal of treatment individualization. Model-informed therapeutic drug monitoring approaches have been

proposed and are being evaluated for precision dosing approaches to account for variability in PK to enable optimal plasma drug exposures in the treatment of TB patients.[41,42] Additionally, variability in disease-related and treatment-response-related factors may affect treatment response.[9] Further data-driven, model-informed evaluations using our mechanistic framework as a foundation can provide insights into such factors and help identify patients at higher risk of poor treatment response and factors affecting poor treatment response.[9] Understanding such relationships can help develop further dose optimization or individualization algorithms.

In conclusion, we present a quantitative framework for predicting dosing regimens of BPaL combination treatment in TB patients, including MDR-TB patients. Our quantitative framework adequately described the observed anti-Mtb activity data following monotherapy for each drug and the BPaL combination regimen. The simulations suggested a minor difference in median time-to-Mtb clearance with the bedaquiline alternative compared to the approved dosing (40 *vs.* 38 days). Similarly, the simulations suggested a minor difference in median time-to-Mtb clearance with the linezolid alternative compared to the approved dosing (45 *vs.* 43 days). Overall, these results suggest that relatively comparable efficacy can be achieved using alternative bedaquiline and linezolid dosing that may improve safety and adherence in MDR-TB patients. Median time to <1 non-replicating mL^{-1} was predicted to be approximately 15 days from the CFU clearance state. These predictions can be utilized to evaluate treatment duration to eradicate non-replicating bacteria from lung lesions to avoid relapse and emergence of resistance.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. The analysis was performed by Krina Mehta. The first draft of the manuscript was written by Krina Mehta. All authors reviewed and edited the manuscript. All authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interests to declare.

DATA AVAILABILITY STATEMENT

All data used in the analysis were either obtained from literature (as cited) or were obtained from the TB-PACTS database (https://c-path.org/programs/tb-pacts/). Final model codes are provided in the Supporting information.

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REFERENCES

1. Ou ZJ, Yu DF, Liang YH, et al. Trends in burden of multidrug-resistant tuberculosis in countries, regions, and worldwide from 1990 to 2017: results from the Global Burden of Disease study. *Infect Dis Poverty*. 2021;10(1):24. doi:10.1186/s40249-021-00803-w
2. World Health Organization (WHO). *WHO consolidated guidelines on tuberculosis. Module 4: treatment drug-resistant tuberculosis treatment*. World Health Organization; 2022.
3. Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med*. 2020;382(10):893-902. doi:10.1056/nejmoa1901814
4. van de Berg SEJ, Pelzer PT, van der Land AJ, et al. Acceptability, feasibility, and likelihood of stakeholders implementing the novel BPaL regimen to treat extensively drug-resistant tuberculosis patients. *BMC Public Health*. 2021;21(1):1404. doi:10.1186/s12889-021-11427-y
5. Imperial MZ, Nedelman JR, Conradie F, Savic RM. Proposed linezolid dosing strategies to minimize adverse events for treatment of extensively drug-resistant tuberculosis. *Clin Infect Dis*. 2022;74(10):1736-1747. doi:10.1093/cid/ciab699
6. Bloemberg GV, Keller PM, Stucki D, et al. Acquired resistance to bedaquiline and delamanid in therapy for tuberculosis. *N Engl J Med*. 2015;373(20):1986-1988. doi:10.1056/NEJMc1505196
7. Salinger DH, Nedelman JR, Mendel C, Spigelman M, Hermann DJ. Daily dosing for bedaquiline in patients with tuberculosis. *Antimicrob Agents Chemother*. 2019;63(11):e00463-19. doi:10.1128/AAC.00463-19
8. Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis. *N Engl J Med*. 2022;387(9):810-823. doi:10.1056/nejmoa2119430
9. Solans BP, Imperial MZ, Olugbosi M, Savic RM. Analysis of dynamic efficacy endpoints of the Nix-TB trial. *Clin Infect Dis*. 2023;76(11):1903-1910. doi:10.1093/cid/ciad051
10. Oelofse S, Esmail A, Diacon AH, et al. Pretomanid with bedaquiline and linezolid for drug-resistant TB: a comparison of prospective cohorts. *Int J Tuberc Lung Dis*. 2021;25(6):453-460. doi:10.5588/ijtld.21.0035
11. Svensson RJ, Simonsson USH. Application of the multistate tuberculosis pharmacometric model in patients with rifampicin-treated pulmonary tuberculosis. *CPT Pharmacometrics Syst Pharmacol*. 2016;5(5):264-273. doi:10.1002/psp4.12079
12. Lyons MA. Modeling and simulation of pretomanid pharmacodynamics in pulmonary tuberculosis patients. *Antimicrob Agents Chemother*. 2019;63(12):1-24. doi:10.1128/AAC.00732-19
13. Svensson EM, Karlsson MO. Modelling of mycobacterial load reveals bedaquiline's exposure-response relationship in patients with drug-resistant TB. *J Antimicrob Chemother*. 2017;72(12):3398-3405. doi:10.1093/jac/dkx317
14. Mehta K, Guo T, van der Graaf PH, van Hasselt JGC. Predictions of bedaquiline and pretomanid target attainment in lung lesions of tuberculosis patients using translational minimal physiologically based pharmacokinetic modeling. *Clin Pharmacokinet*. 2023;62(3):519-532. doi:10.1007/s40262-023-01217-7
15. Clewe O, Aulin L, Hu Y, Coates ARM, Simonsson USH. A multistate tuberculosis pharmacometric model: a framework for studying anti-tubercular drug effects in vitro. *J Antimicrob Chemother*. 2016;71(4):964-974. doi:10.1093/jac/dkv416
16. Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science*. 2005;307(5707):223-227. doi:10.1126/science.1106753
17. Koul A, Vranckx L, Dendouga N, et al. Diarylquinolines are bactericidal for dormant mycobacteria as a result of disturbed ATP homeostasis. *J Biol Chem*. 2008;283(37):25273-25280. doi:10.1074/jbc.M803899200
18. Koul A, Vranckx L, Dhar N, et al. Delayed bactericidal response of *Mycobacterium tuberculosis* to bedaquiline involves remodelling of bacterial metabolism. *Nat Commun*. 2014;5(1):3369. doi:10.1038/ncomms4369
19. Somasundaram S, Anand RS, Venkatesan P, Paramasivan CN. Bactericidal activity of PA-824 against *Mycobacterium tuberculosis* under anaerobic conditions and computational analysis of its novel

analogues against mutant Ddn receptor. *BMC Microbiol*. 2013;13(1):218. doi:10.1186/1471-2180-13-218
20. Drusano GL, Myrick J, Maynard M, et al. Linezolid kills acid-phase and nonreplicative-persister-phase *Mycobacterium tuberculosis* in a hollow-fiber infection model. *Antimicrob Agents Chemother*. 2018;62(8):e00221-18. doi:10.1128/AAC.00221-18
21. Food and Drug Administration (FDA). FDA briefing document. Pretomanid tablet, 200 mg: meeting of the Antimicrobial Drugs Advisory Committee (AMDAC). 2019. https://www.fda.gov/media/127592/download
22. Dietze R, Hadad DJ, McGee B, et al. Early and extended early bactericidal activity of linezolid in pulmonary tuberculosis. *Am J Respir Crit Care Med*. 2008;178(11):1180-1185. doi:10.1164/rccm.200806-892OC
23. Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. 14-Day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet*. 2012;380(9846):986-993. doi:10.1016/S0140-6736(12)61080-0
24. Diacon AH, Dawson R, du Bois J, et al. Phase II dose-ranging trial of the early bactericidal activity of PA-824. *Antimicrob Agents Chemother*. 2012;56(6):3027-3031. doi:10.1128/AAC.06125-11
25. Strydom N, Gupta SV, Fox WS, et al. Tuberculosis drugs' distribution and emergence of resistance in patient's lung lesions: a mechanistic model and tool for regimen and dose optimization. *PLoS Med*. 2019;16(4):e1002773. doi:10.1371/journal.pmed.1002773
26. Chen RY, Yu X, Smith B, et al. Radiological and functional evidence of the bronchial spread of tuberculosis: an observational analysis. *Lancet Microbe*. 2021;2(10):e518-e526. doi:10.1016/S2666-5247(21)00058-6
27. Sarathy JP, Via LE, Weiner D, et al. Extreme drug tolerance of *Mycobacterium tuberculosis* in caseum. *Antimicrob Agents Chemother*. 2018;62(2):e02266-17. doi:10.1128/AAC.02266-17
28. Sarathy JP, Zuccotto F, Hsinpin H, et al. Prediction of drug penetration in tuberculosis lesions. *ACS Infect Dis*. 2016;2(8):552-563. doi:10.1021/acsinfecdis.6b00051
29. Wicha SG, Huisinga W, Kloft C. Translational pharmacometric evaluation of typical antibiotic broad-spectrum combination therapies against *Staphylococcus aureus* exploiting in vitro information. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(8):515-522. doi:10.1002/psp4.12197
30. Lill D, Kümmel A, Mitov V, et al. Efficient simulation of clinical target response surfaces. *CPT Pharmacometrics Syst Pharmacol*. 2022;11(4):512-523. doi:10.1002/psp4.12779
31. Cokol M, Kuru N, Bicak E, Larkins-Ford J, Aldridge BB. Efficient measurement and factorization of high-order drug interactions in *Mycobacterium tuberculosis*. *Sci Adv*. 2017;3(10):e1701881. doi:10.1126/sciadv.1701881
32. Bowness R, Boeree MJ, Aarnoutse R, et al. The relationship between *Mycobacterium tuberculosis* MGIT time to positivity and cfu in sputum samples demonstrates changing bacterial phenotypes potentially reflecting the impact of chemotherapy on critical sub-populations. *J Antimicrob Chemother*. 2015;70(2):448-455. doi:10.1093/jac/dku415
33. van Heeswijk RPG, Dannemann B, Hoetelmans RMW. Bedaquiline: a review of human pharmacokinetics and drug–drug interactions. *J Antimicrob Chemother*. 2014;69(9):2310-2318. doi:10.1093/jac/dku171
34. Nguyen TVA, Anthony RM, Bañuls AL, Vu DH, Alffenaar JWC. Bedaquiline resistance: its emergence, mechanism, and prevention. *Clin Infect Dis*. 2018;66(10):1625-1630. doi:10.1093/cid/cix992
35. Tanneau L, Karlsson MO, Rosenkranz SL, et al. Assessing prolongation of the corrected QT interval with bedaquiline and delamanid coadministration to predict the cardiac safety of simplified dosing regimens. *Clin Pharmacol Ther*. 2022;112(4):873-881. doi:10.1002/cpt.2685
36. Evangelopoulos D, da Fonseca JD, Waddell SJ. Understanding antituberculosis drug efficacy: rethinking bacterial populations and how we model them. *Int J Infect Dis*. 2015;32:76-80. doi:10.1016/j.ijid.2014.11.028
37. Khoshnood S, Goudarzi M, Taki E, et al. Bedaquiline: current status and future perspectives. *J Glob Antimicrob Resist*. 2021;25:48-59. doi:10.1016/j.jgar.2021.02.017
38. Kim S, Yamada WM, Duncanson B, et al. Building optimal three-drug combination chemotherapy regimens to eradicate *Mycobacterium tuberculosis* in its slow-growth acid phase. *Antimicrob Agents Chemother*. 2021;65(10):e00693-e00621. doi:10.1128/AAC.00693-21
39. European Medicines Agency. Pretomanid FGK: PAR. 2020. https://www.ema.europa.eu/en/documents/assessment-report/pretomanid-fgk-epar-public-assessment-report_en.pdf. Accessed October 16, 2023.
40. Muliaditan M, Della PO. Bacterial growth dynamics and pharmacokinetic–pharmacodynamic relationships of rifampicin and bedaquiline in BALB/c mice. *Br J Pharmacol*. 2022;179(6):1251-1263. doi:10.1111/bph.15688
41. Sturkenboom MGG, Märtson AG, Svensson EM, et al. Population pharmacokinetics and Bayesian dose adjustment to advance TDM of anti-TB drugs. *Clin Pharmacokinet*. 2021;60(6):685-710. doi:10.1007/s40262-021-00997-0
42. Mockeliunas L, Keutzer L, Sturkenboom MGG, et al. Model-informed precision dosing of linezolid in patients with drug-resistant tuberculosis. *Pharmaceutics*. 2022;14(4):753. doi:10.3390/pharmaceutics14040753

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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