Quantitative pharmacology approaches to inform treatment strategies against tuberculosis

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Chapter 5

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

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Abstract

Aim: Bedaquiline, pretomanid, and linezolid combination (BPaL) treatment against *Mycobacterium tuberculosis* is promising yet safety and adherence concerns exist that motivates exploration of alternative dosing regimens. We developed a mechanistic modeling 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 bodyweight, 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 400mg once daily (QD) 14-days followed by 200mg three times a week, linezolid 1200mg QD) and alternative dosing regimens (bedaquiline 200mg QD, linezolid 600mg QD).

Results: The framework adequately described the observed anti-bacterial 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 units (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.

Conclusion: 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.

Introduction

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 for the treatment of MDR-TB2,3. 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 myelosuppression4,5. Moreover, the unconventional, three times a week, bedaquiline dosing schedule leads to patient non-adherence which ultimately affects treatment efficacy and emergence of resistance6. To overcome these safety and adherence concerns associated with 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 QD7,8. The recently completed ZeNix study evaluating the suggested alternative bedaquiline and linezolid dosing demonstrated overall improved benefit-risk ratio following alternative, simplified and lower, bedaquiline and linezolid dosing regimen compared to approved dosing regimen8. Although the alternative linezolid dosing schedule was associated with overall improved benefit-risk ratio, slightly higher percentage (5%) of favorable outcome was reported at approved dosing compared to the alternative dosing. Additionally, 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 favorable 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 two months of therapy but 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 are 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 modeling 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 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.

Methods

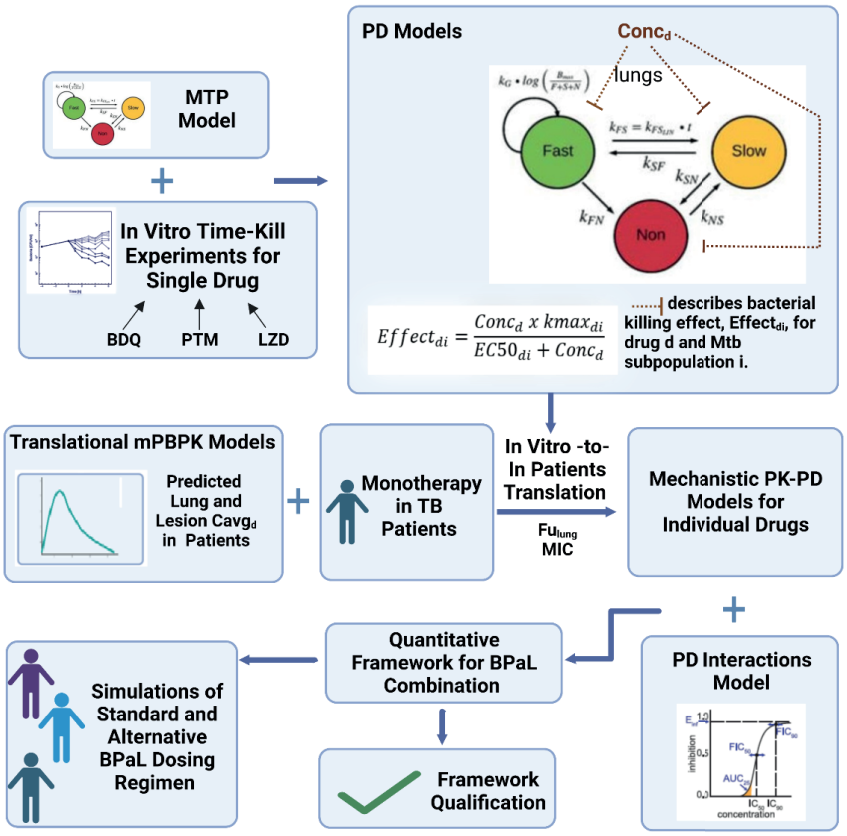
The development of the mechanistic PK-PD framework for BPaL combination treatments was performed in four main steps. We first fit the multi-state tuberculosis model to in vitro time-kill data for bedaquiline, pretomanid, and linezolid for fast- and slow-replicating subpopulations of Mtb separately. Then, 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 (CFU) 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 5.1**.

Mechanistic PD models

The published multi-state tuberculosis model which describes the growth dynamics of fast-, slow-, and non-replicating Mtb population 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 (Bmax), were estimated using the untreated control data. Next, drug effects for bedaquiline, pretomanid, and linezolid were separately estimated (S5.1). Linear and nonlinear drug-induced kill functions on fast-, slow-, and non-replicating Mtb populations were evaluated. As no data for slow-replicating bacteria were 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 vs. predictions plots, and plausibility and precision of the parameter estimates.

Figure 5.1 Overview of the BPaL Quantitative Framework Development Process. BDQ=bedaquiline, CFU=colony-forming unit of Mtb, Cavgd=daily average concentrations of drug d at the site of action of TB patients (bedaquiline, pretomanid, or linezolid), Concd=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.



Mechanistic PK-PD models

Sputum CFU data from bedaquiline, pretomanid, and linezolid early bactericidal activity (EBA) studies, i.e., clinical studies that evaluated monotherapy 14-day anti-Mtb effects, in pulmonary tuberculosis 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 to use in the simulations of anti-Mtb activities. The multistate tuberculosis pharmacometrics model, 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, i.e., CFU, simulations were performed according to the dosing schedules tested in the corresponding studies. CFU was calculated as sum of predicted fast- and slow-replicating Mtb population 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 5.1).**

Table 5.1 Parameter Estimates of Bedaquiline, Pretomanid, and Linezolid Semi-Mechanistic 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]
bdqm2-scaling	Bedaquiline to M2 antibacterial 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	

The Multi-state 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 Bmax = 6.5e+07 mL^{-1} were estimated by fitting the Multi-state tuberculosis model to combined log-phase Mtb growth data in absence of bedaquiline.; b Bmax = 8.25e+09 mL^{-1} was estimated by fitting the Multi-state tuberculosis model to combined log-phase Mtb growth data in absence of pretomanid.; [c] Linezolid hollow-fiber experiment showed no increase in Mtb load for the controls group for the duration of the study; therefore, linezolid controls data were best described by first-order natural death rates 0.542 day^{-1} and 0.275 day^{-1} for fast- and non-replicating bacteria, respectively.

BPaL quantitative framework

Clinical studies often measure anti-microbial activity using solid culture (CFU) or liquid culture time to positivity (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 sub-population 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 scaling parameter and plotting typical CFU predictions (S5.2). 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, multistate tuberculosis pharmacometrics model, and PD parameters were simulated in a similar manner as monotherapy simulations described above. Then, drug effect parameters, kmax and EC50, were adjusted for MIC by taking the ratio between the in-patient vs. in vitro MIC for each drug and multiplying it with the parameter value[29]. Bacterial growth simulations were generated for up to 150 days using the above-mentioned parameters. To qualify the quantitative framework, observed changes in microbiological measure, EBA-TTP from 0-14 day ($EBA\text{-}TTP_{0\text{-}14day}$) and 0-28 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 Bmax was set to match observed baseline median TTP in the study.

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 14days followed by 200 mg three times a week (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 14days 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 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.

Software

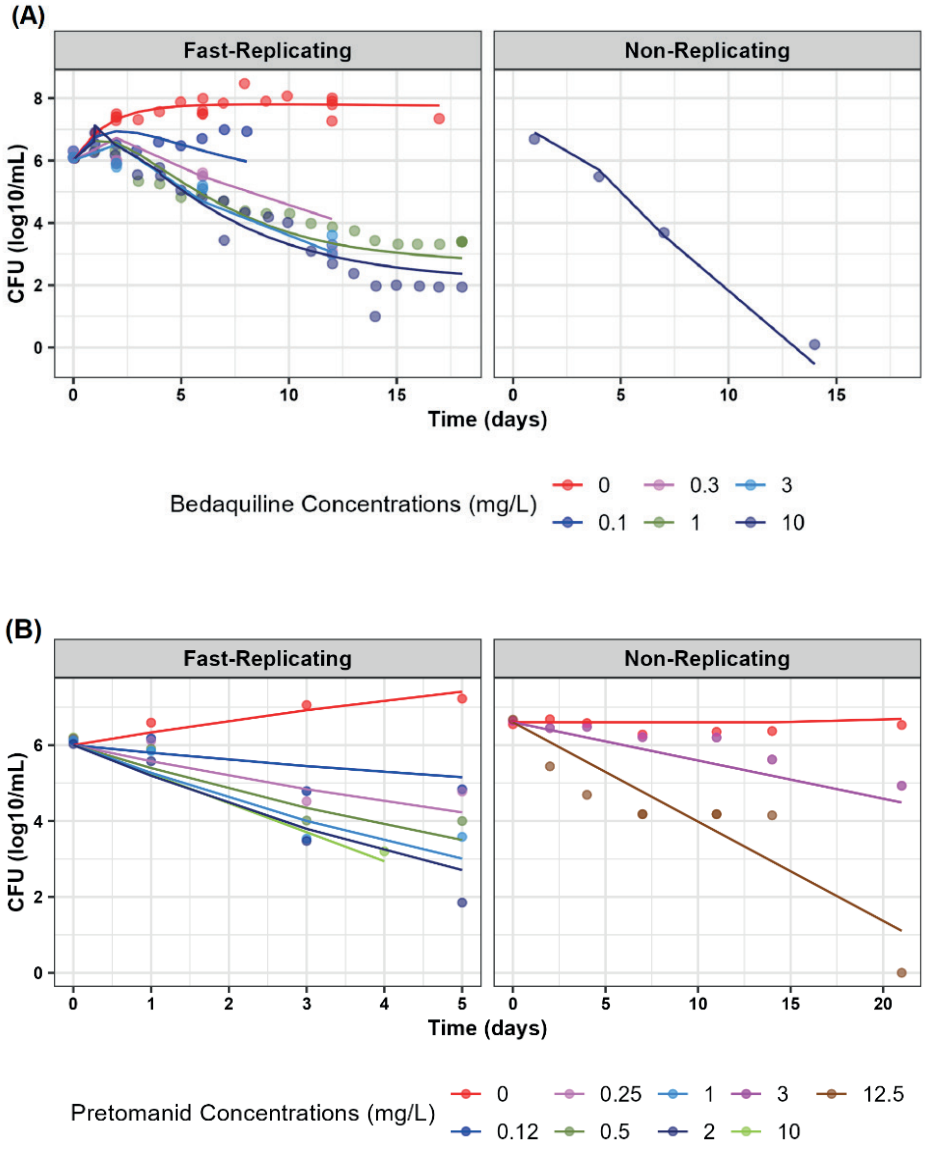
All analyses were conducted in R (R for Windows, v4.1, https://www.r-project.org/) using RStudio (RStudio, v1-554, www.rstudio.com/). Data management and plotting were performed using the tidyverse package. Parameter optimization and model simulations were conducted using nlmixr and RxODE packages.

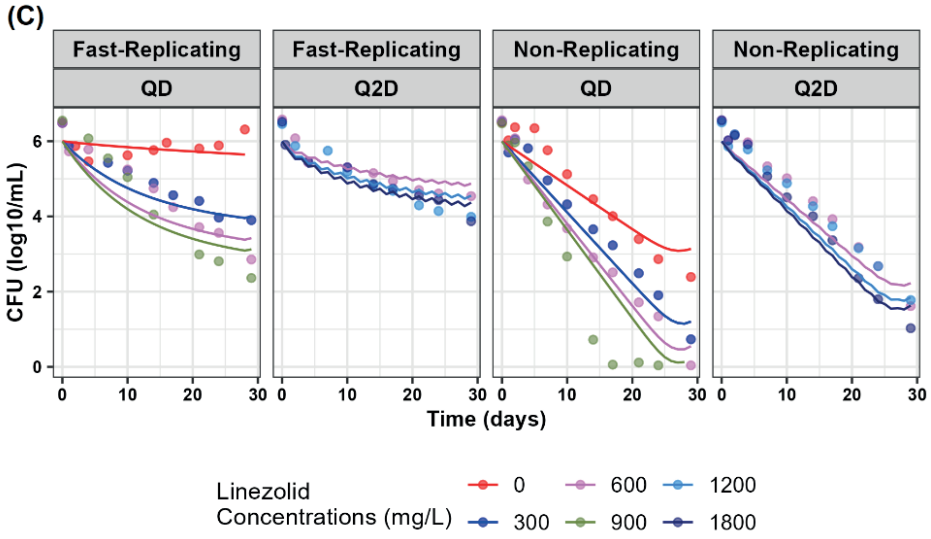
Results

Development of mechanistic pd models for in vitro time-kill data

The multi-state tuberculosis 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 controls data. Estimation of both kG and Bmax for bedaquiline experiments, and only Bmax for pretomanid experiments best described the in vitro control data. Estimation of kG for pretomanid controls 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-fiber 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].

Figure 5.2 Model fitting of the semi-mechanistic 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.





The non-linear model with separate drug-induced effects for each drug on fast-replicating and non-replicating Mtb provided improved fits than the linear models for all three drugs. No data for slow-replicating bacteria was available. Parameterization of drug effects was attempted separately for slow- and non-replicating Mtb population using a multi-state tuberculosis 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 population. 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 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 5.1)**. Overall, the models described the available data reasonably well **(Figure 5.2)**.

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 (S5.1). 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 over-predicted the anti-Mtb activity of bedaquiline. As bedaquiline strongly binds to plasma proteins and is widely distributed in tissues, a lung tissue binding factor parameter was introduced and estimated to be 0.01[33] **(Table 5.1)**. The final model described the median 14-day EBA data for bedaquiline at various doses well **(Figure 5.3)**. The lung tissue binding factor of 1 and 0.29 for pretomanid and linezolid, respectively described the median EBA data for both drugs well[27]. The simulations confirmed that the developed framework predicts the central tendency in bedaquiline, pretomanid, and linezolid EBA in TB patients separately well. The framework was deemed reliable for the evaluation of the next steps of the analysis, i.e., to simulate anti-Mtb activity following treatment with BPaL combination in MDR-TB patients.

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 antibacterial activity following BPaL combination therapy (**Table 5.2**, S5.3). Median (95% 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 5.4)**. Overall, this modeling framework was deemed appropriate to simulate anti-Mtb activity following approved and alternative BPaL dosing regimens.

Figure 5.3 Evaluation of the Bedaquiline, Pretomanid, and Linezolid semi-mechanistic PK-PD models using early bactericidal activity studies data from pulmonary Tuberculosis 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, i.e., panel 1 represents a group that received 200 mg on day 1 and 100 mg on day 2 onwards. Lines represent median.

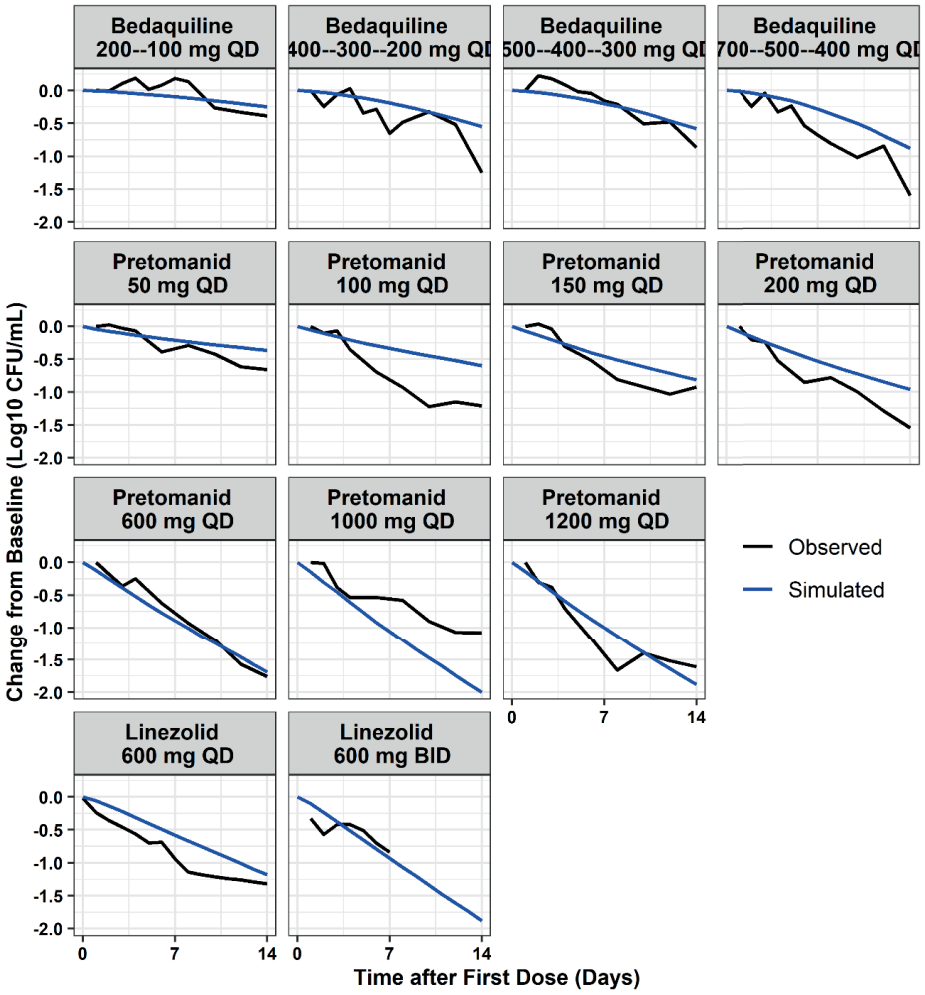


Table 5.2 Observed and predicted early bactericidal activity as measured by time to culture positivity (EBA-TTP) (1/day) following Bedaquiline, Pretomanid, and Linezolid combination therapy.

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)

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 **(Figure 5.4, Figure 5.5)**. 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 $CFUmL^{-1}$ = 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 correlated with CFU clearance (combined fast- and slow-replicating Mtb). Median time to <1 non-replicating Mtb mL^{-1} was predicted to be additional 15 days from the CFU clearance state **(Figure 5.4)**. No clear correlation was predicted in time to Mtb clearance and individual MIC following BPaL combination therapy at the approved regimen (S5.4).

Figure 5.4 Spaghetti plots of anti-Mtb activity simulations using the 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, three times a week=three times a week. Dashed line 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 additional 15 days from the CFU clearance state.

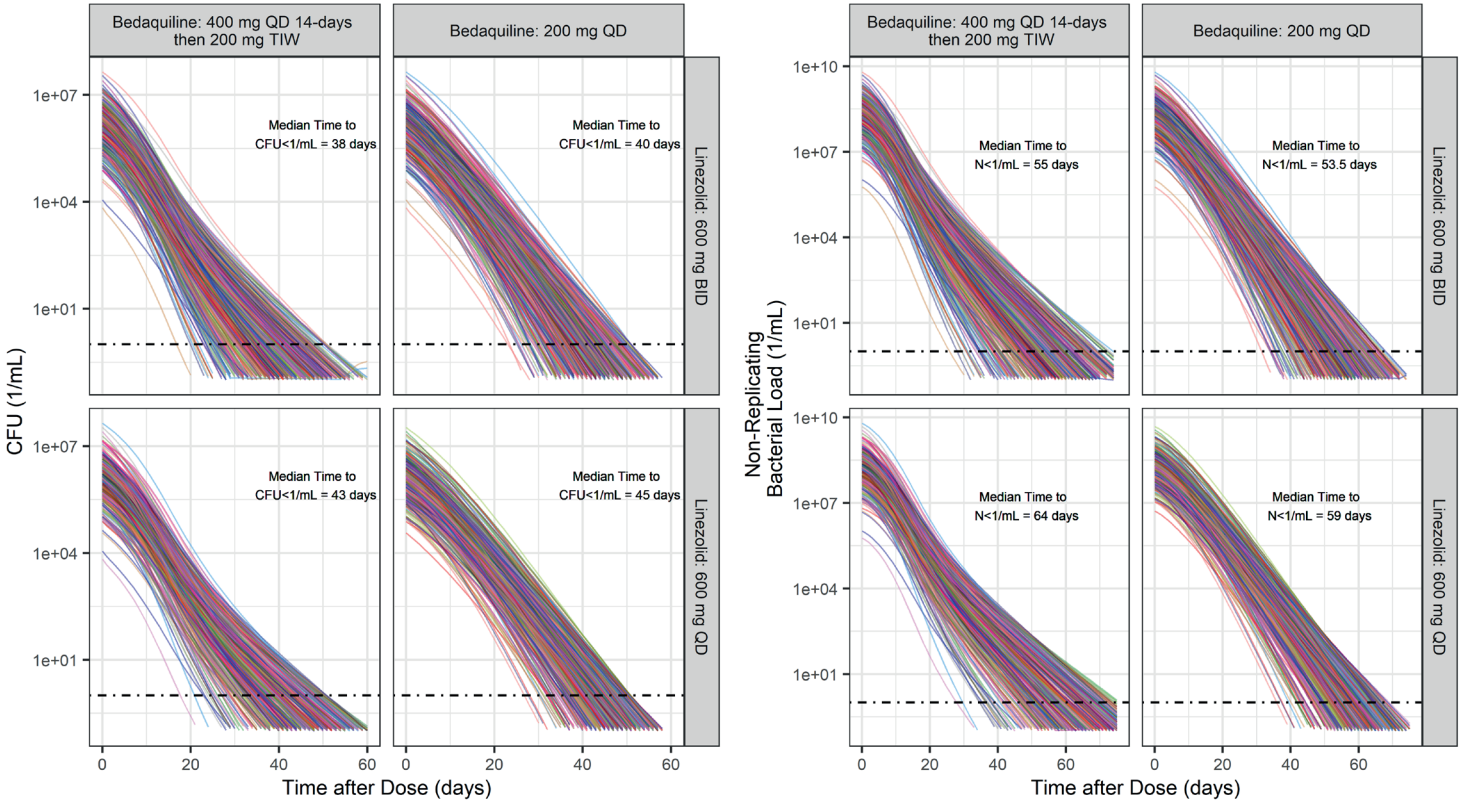
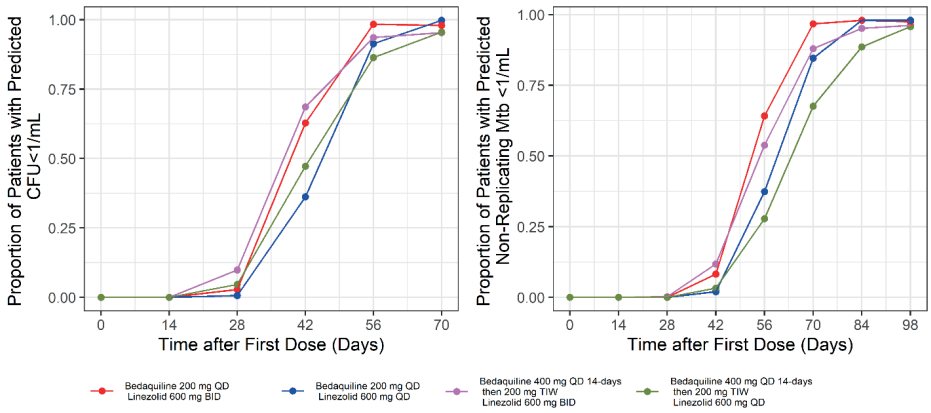


Figure 5.5 Predicted proportions of patients with CFU and non-replicating Mtb < 1 mL^{-1}. Comparable proportions of patients were predicted to achieve Mtb clearance following bedaquiline QD dosing vs. bedaquiline approved dosing. Similarly, comparable proportions of patients were predicted to achieve Mtb clearance following linezolid QD dosing vs. linezolid approved dosing.



Discussion

In this work, we developed a quantitative framework for the BPaL combination that included key components that play 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, bedaquiline alternative dosing, 200 mg QD for 9 weeks followed by 100 mg QD has been proposed. Prior analyses predicted comparable safety concerns associated with bedaquiline alternative 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 favorable outcomes following BPaL including 1200 mg QD 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 but some MDR-TB patients.

Our modeling 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 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 period after the CFU-negative state and its impact on tolerance, resistance, or relapse rate can be beneficial[36].

We assumed that M2 target site exposures driven maximum kill rate for all three Mtb subpopulations is 5-fold lower than that of bedaquiline[33]. Observed plasma M2-bedaquiline exposures ratio has been reported to be 0.25-0.32[33]. Based on our translational mPBPK model, plasma, lungs, and lesion M2-bedaquiline exposures 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 literature[31]. Previously, mixed results have been reported for 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 literature. Such data are often not measured, and simpler bacterial growth models with two Mtb populations have been developed using murine experimental data[40]. Since our model was calibrated using multi-state tuberculosis model construct and parameterization and in vitro data from fast-replicating and slow-replicating Mtb experiments, our parameter estimates and thus simulations capture relative contributions of treatment on the killing of each Mtb subpopulations (S5.5). 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 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.

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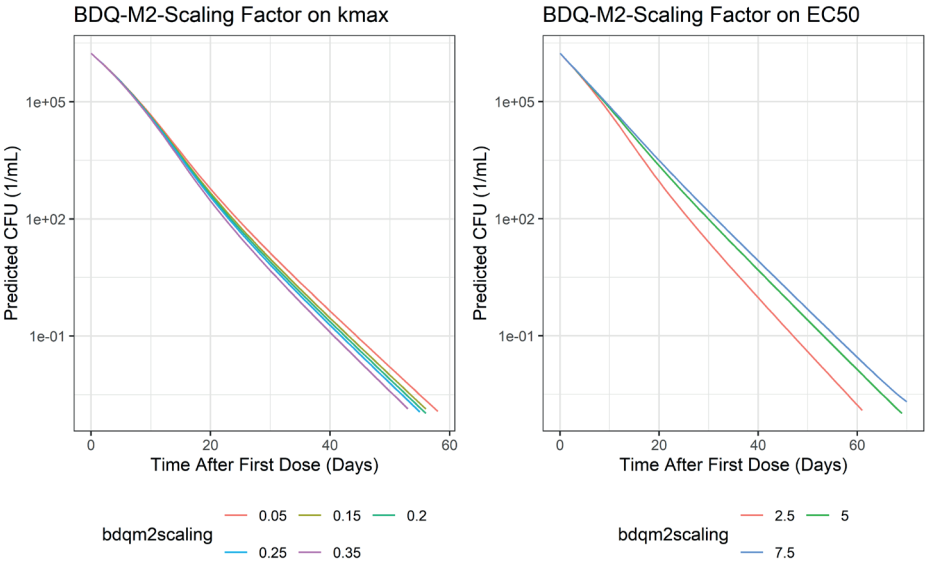
Supplementary Materials

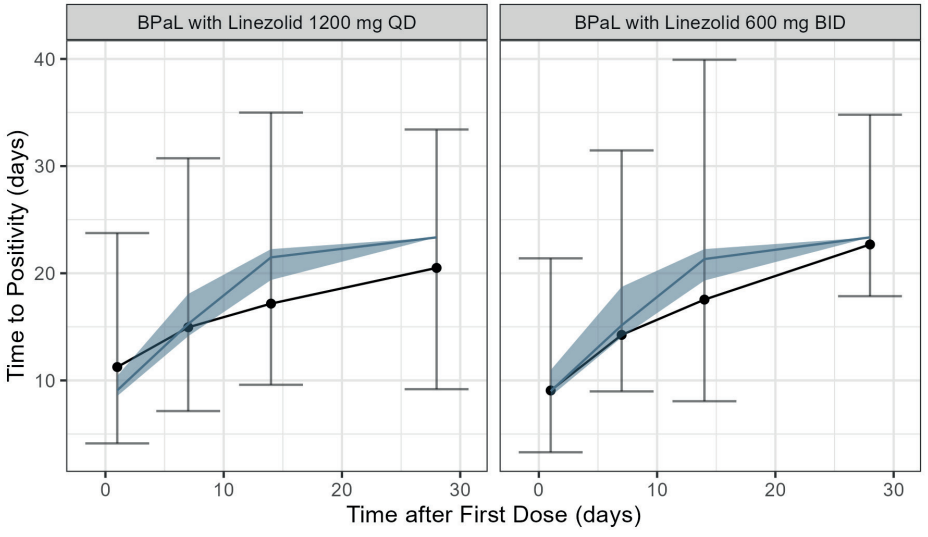
S5.1. Summary of the time course data used for the analysis

Drug Name	Details	Source
Digitized In Vitro Anti-Mtb Activity Data from Literature		
Bedaquiline	Mtb cultures in log-growth conditions were treated with either control or bedaquiline at 0.3- or 3- mg/L. Longitudinal bacterial load data were collected.	[1]
	Longitudinal bacterial load data were collected for log-phase and non-replicating Mtb cultures in presence of bedaquiline 10 mg/L.	[2]
	Mtb cultures in log-growth conditions were treated with either control or bedaquiline at 0.1-, 1- or 10- mg/L. Longitudinal bacterial load data were collected.	[3]
Pretomanid	Mtb cultures in log-growth conditions were treated with either control or pretomanid 0.12-, 0.25-, 0.5-, 1- or 2- mg/L. Longitudinal bacterial load data were collected.	[4]
	Mtb cultures in log-growth conditions were treated with either control or pretomanid 10 mg/L. Longitudinal bacterial load data were collected.	[5]
	Longitudinal bacterial load data were collected for non-replicating Mtb cultures in presence of control or 3- and 12.5- mg/L.	[6]
Linezolid	Mtb in log-growth and non-replicating conditions in a hollow-fiber infection model were treated with control or linezolid at 300-, 600-, 900-, 1200-, or 1800- mg dose once daily or every other day. Longitudinal bacterial load data were collected.	[7]
Monotherapy Anti-Bacterial Activity Data		
Bedaquiline	This was a Phase 1 clinical trial that evaluated 14-day bacterial load data from pulmonary TB patients who were either treated with first-line TB therapy or bedaquiline at various doses for 14 days QD. Individual, longitudinal CFU data were obtained from the TB-Pacts database.	Clinical Trial: NCT01215110
Pretomanid	This was a Phase 2 clinical trial that evaluated 14-day bacterial load data from pulmonary TB patients who were either treated with first-line TB therapy or pretomanid at various doses for 14 days QD. Individual, longitudinal CFU data were obtained from the TB-Pacts database.	[8] Clinical Trials: NCT00944021 and NCT00567840
Linezolid	This study evaluated the anti-Mtb activity of linezolid in pulmonary TB patients at either 600 mg QD or 600 mg BID doses. Median profiles were digitized from the publication.	[9]
BPaL Combination Therapy Data		
Bedaquiline, Pretomanid, and Linezolid Combination	This was a phase 3 clinical trial that evaluated the efficacy and safety of the BPaL combination regimen in MDR-TB patients. Individual, longitudinal time to liquid culture positivity data were obtained from the TB-Pacts database.	[10] Clinical Trial: NCT02333799

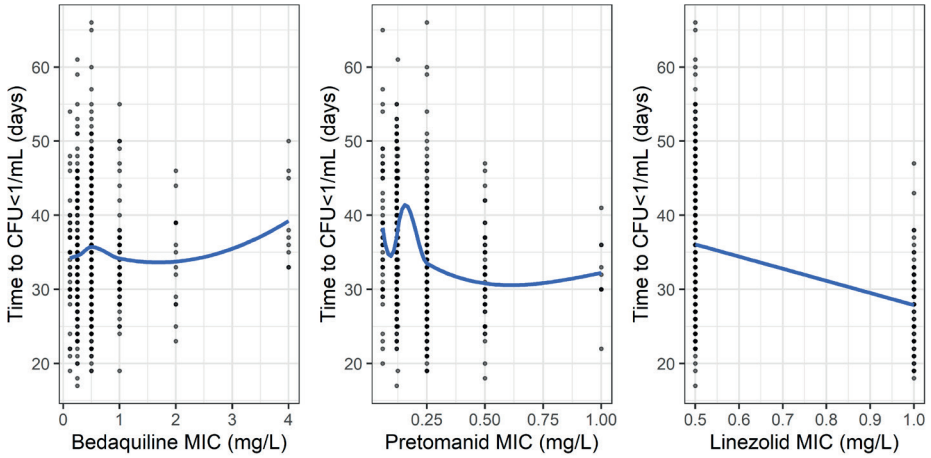
S5.2. Impact of bedaquiline – M2 effect scaling factor on kmax and EC50 of fast-, slow-, and non-replicating Mtb. Sensitivity analysis was conducted to evaluate the impact of bedaquiline M2 effect scaling parameter (bdqm2scaling). The impact of bdqm2scaling factor on the predicted CFU following the approved BPaL dosing was evaluated by varying the parameter by a range of values and applying on kmax and EC50 one at a time. Overall, the parameter bdqm2scaling was not predicted to significantly affect overall CFU predictions.



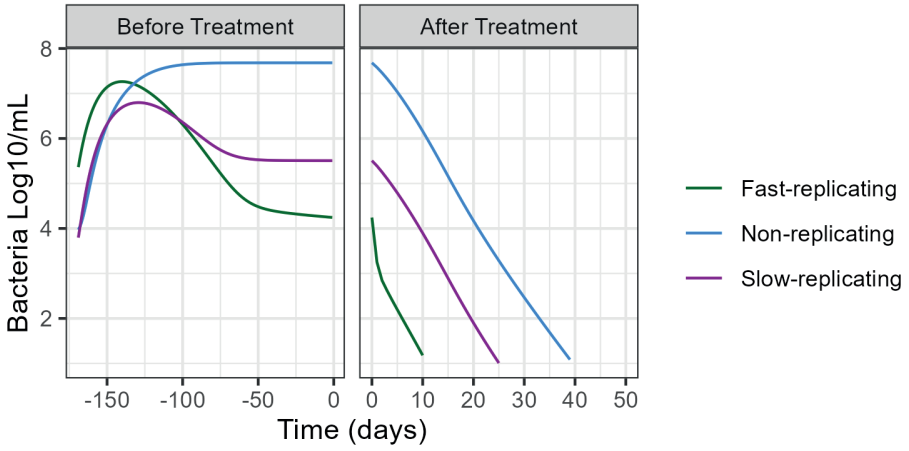
S5.3. Observed vs. Predicted $TTP_{0\text{-}14days}$ Following BPaL Combination at the Approved Dosing. Black point and error bars represent median and 95% confidence interval from the Nix-TB study[10]. Blue line and ribbon present median and 95% prediction interval.



S5.4. Predicted time to Mtb clearance vs. Mtb susceptibility for each drug following BPaL combination at standard dosing regimen. Colony-forming units (CFU) represent total fast- and slow-multiplying Mtb, MIC=minimum inhibitory concentration.



S5.5. Typical patient predictions from the BPaL quantitative framework before and after standard BPaL dosing regimen.



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