Quantitative pharmacology approaches to inform treatment strategies against tuberculosis

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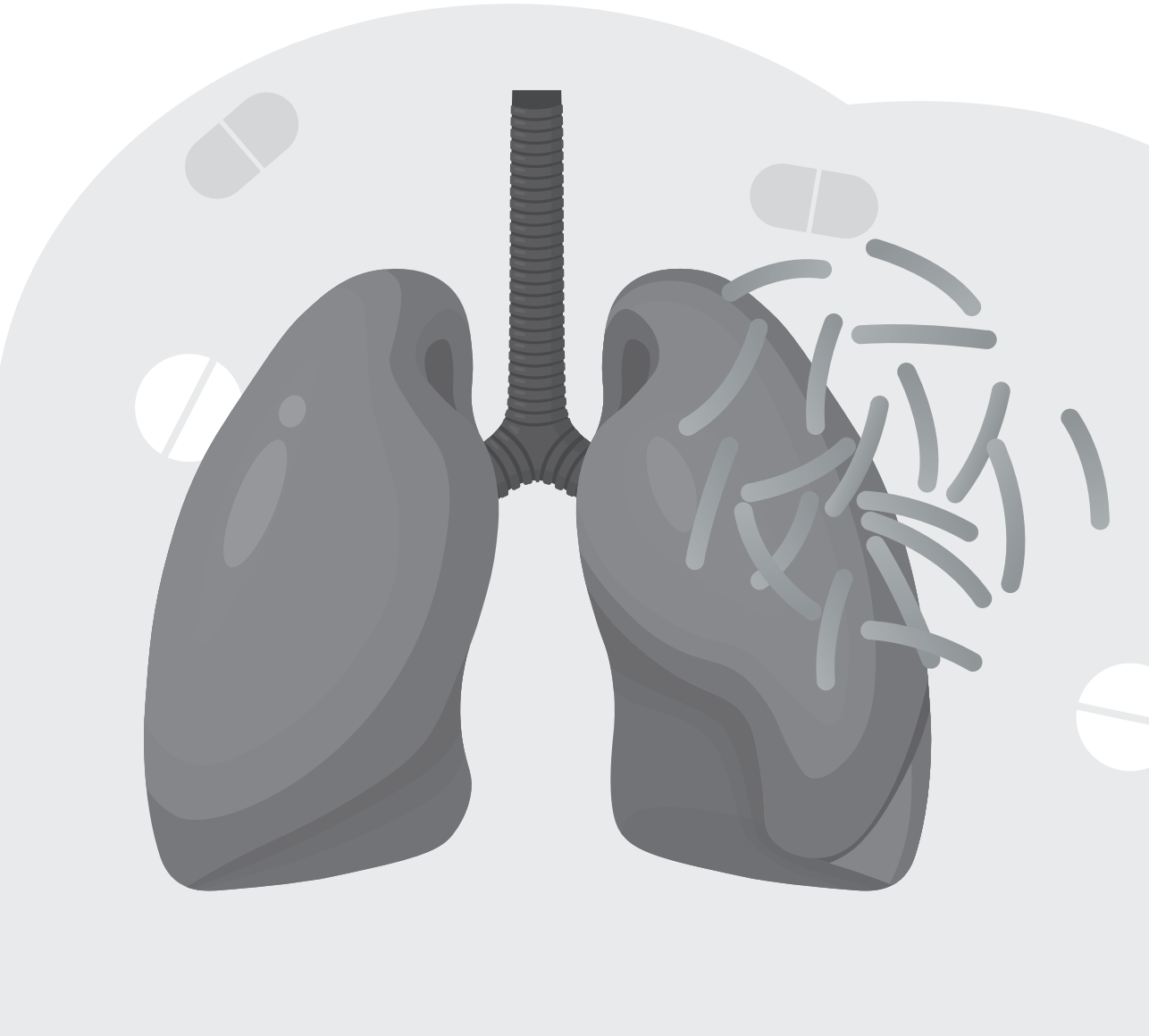
Section I.

Introduction



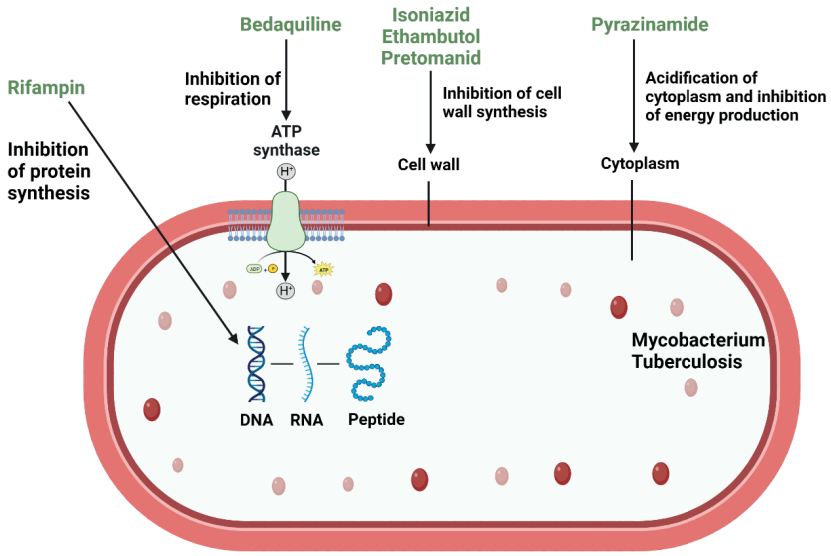
Chapter 1

Introduction and scope of the thesis

Tuberculosis treatment landscape

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb). TB is the oldest known infectious disease with the first documentation dating back to 3300 years ago although it is believed to be that Mtb existed even 70,000 years back[1]. The first isolation of Mtb by Dr. Robert Koch in 1882 marked a key step in the fight against Mtb. Today, more than 140 years later, Mtb infections are still associated with approximately 1.5 – 2 million deaths annually[2]. Initiation of TB infection occurs through the respiratory route by inhalation of aerosols containing Mtb bacteria. In the first few days, Mtb invades pulmonary alveoli of the host and alveolar resident macrophages will ingest Mtb via phagocytosis followed by induction of the host immune response against Mtb. The host immune response will lead to the formation of granulomas that contain Mtb bacilli, where Mtb may remain in a dormant state, also known as latent TB. If granulomas are unable to contain Mtb because they have multiplied significantly, an active TB infection can develop. Approximately 5-10% of individuals with latent TB develop active TB[3]. Individuals with a weakened immune response, i.e., patients with co-morbid conditions, such as HIV, diabetes, and patients taking immunosuppressants are at higher risk of developing active TB. Current first-line treatment of drug-sensitive TB includes a weight-based fixed-dose combination of four antibiotic agents, isoniazid, rifampin, pyrazinamide, and ethambutol. First discovered and developed in the 1960s through early 1970s, isoniazid and rifampin have been the most important drugs in the treatment of patients with TB[4]. Isoniazid is a potent bactericidal drug that inhibits mycolic acid synthesis leading to cell wall synthesis in Mtb **(Figure 1.1)**. Rifampin is also bactericidal against Mtb and inhibits Mtb ribonucleic acid (RNA) polymerase. Pyrazinamide and ethambutol add to the anti-bacterial activity of rifampin and isoniazid and act through Mtb plasma membrane disruption and inhibition of cell wall synthesis, respectively. Overall, this first-line combination treatment regimen results in a reasonable cure rate in patients with drug-sensitive TB; however, various challenges remain as discussed further **(Figure 1.2)**.

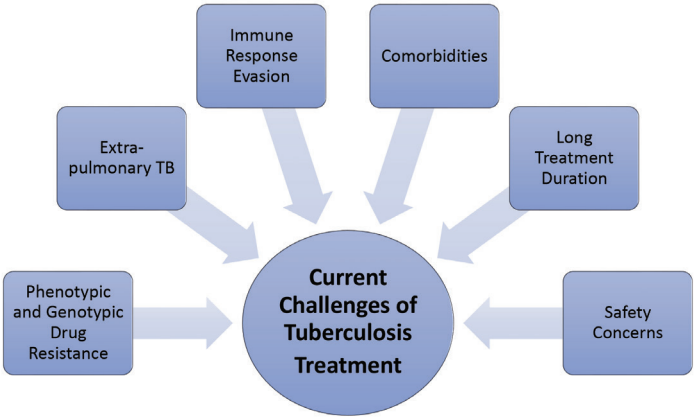
Figure 1.1 Mechanism of action of anti-tuberculosis drugs. Adapted based on Zumla et al., 2013[4]. Figure created with biorender.com.



Current challenges of tuberculosis therapeutics

Mtb has evolved and developed resistance mechanisms. The key mechanism of resistance development against antibiotics includes a subpopulation of Mtb, persisters, which are phenotypically resistant against the drugs without genetic mutations.[5,45,46] Factors contributing to Mtb developing phenotypic resistance against drugs include interruptions in treatment, suboptimal drug concentrations, and poor host immune response against Mtb. Over time, phenotypic resistance leads to the development of genetic mutations resulting in the proliferation and transmission of drug-resistant Mtb strains.[5,45,46] Various forms of drug-resistant TB exist, including, rifampin-resistant TB (RR-TB), rifampin- and isoniazid-resistant TB (known as multi-drug resistant TB (MDR-TB)), and extensive form of MDR-TB (XDR-TB) that is resistant to rifampin, isoniazid, and one or more additional anti-TB drugs. Together, drug-resistant TB constitutes 450,000 TB cases globally in 2021. As such, drug-resistant TB is a major global health challenge[6].

Figure 1.2 Current challenges against the treatment of tuberculosis.



Prior to availability of bedaquiline and other newer anti-TB drugs, standard regimens for MDR-TB included a combination of five or more drugs. These combination regimens against MDR-TB were associated with toxicity issues and had poor efficacy outcomes with approximately 20% cure rate only. Bedaquiline, the first newly approved anti-TB drug in 40 years, is a diarylquinoline and inhibits Mtb adenosine triphosphate synthesis to exert its bactericidal effect[7]. Bedaquiline-containing regimens have shown reasonable efficacy in MDR-TB patients[8,9]. Increased prevalence of RR-TB and MDR-TB cases and bedaquiline development was followed by a revival in anti-TB research leading to the development and approvals of nitroimidazoles, pretomanid and delamanid, in the last decade[10]. The new, all-oral, combination regimen of bedaquiline, pretomanid, and linezolid (BPaL) showed approximately 90% cure rate and is now endorsed by the WHO for the treatment of MDR-TB[11,12]. Additional drug combinations including these newer drugs are being evaluated for the treatment of various forms of drug-resistant TB[47-49].

TB primarily affects the lungs; however, Mtb may get disseminated into the lymphatics, distribute through systemic circulation, and infect other organs leading to extrapulmonary TB. Extrapulmonary TB is generally difficult to diagnose and treat. The most severe form of extrapulmonary TB is TB meningitis (TBM) affecting the central nervous system (CNS). TBM is associated with high morbidity and mortality with approximately half the patients suffering from severe neurologic disability or death[13]. Treatment of TB meningitis is especially challenging due to poor penetration of anti-TB drugs, especially rifampin, into CNS[14]. Standard treatment of TBM patients remains the same as the first-line treatment of pulmonary TB patients; however, high morbidity and mortality rates remain. As

such, the efficacy and safety of intensified dosing schedules are being evaluated for the treatment of patients with TBM. There has been an increasing trend in the prevalence of drug resistance amongst TBM patients[15–18]. Currently, no standard treatment recommendations for drug-resistant TBM, and treatment approaches are generally selected by treating physicians based on individual patient factors often including extensive treatment with more than 5 drugs. Safety concerns about extensive treatments and high mortality rate (69-100%) amongst drug-resistant TBM patients persist[15].

Mtb has developed several mechanisms to evade host immune-mediated eradiation to allow its survival and virulence in the host, such as inhibition of autophagy and apoptosis, inhibition of antigen presentation, inducing changes in host transcriptomics and cytokine balance, development of resistance against anti-Mtb treatment, etc. Understanding the mechanistic details of host-pathogen interactions is essential to develop new treatment approaches against Mtb. Comorbidities, especially human immunodeficiency virus (HIV) infections or type II diabetes mellitus, are associated with higher morbidity and mortality in TB patients due to their immunosuppressive nature[19,20]. HIV co-infection has also been associated with decreased exposures to several key anti-TB drugs[21–23]. Treatment of the comorbidities further increases the likelihood of drug-drug interactions[24]. Additional studies are needed to develop treatment and patient management plans for TB patients with comorbidities[25]. Current treatment duration ranges from 6 to 9 months for the majority of patients, with some patients, especially with MDR-TB and XDR-TB, requiring treatment up to 18 to 24 months[11]. Such long treatment duration leads to safety issues, increased economic burden, and treatment adherence issues, and significantly affects patients' quality of life[26]. Several studies have evaluated potential shorter combination treatment regimens but have yielded variable results[26,27,50]. It has been suggested that the required duration of TB treatment is highly dependent on various patient and disease factors. Overall, further evaluations are needed to develop innovative, shorter, efficacious, and safer treatment optimization approaches against pulmonary, extra-pulmonary, drug-sensitive, drug-resistant Mtb infections.

Quantitative pharmacology approaches for anti-tuberculosis therapeutics

The current challenges in the fight against Mtb infections call for innovative drug development and treatment approaches. Quantitative pharmacology combines concepts from biology, pharmacology, mathematics, statistics, and data science to inform drug development and treatment decisions across various therapeutic areas, including TB[28,29]. Various quantitative approaches, ranging from population pharmacokinetic (PopPK) and population pharmacokinetic-pharmacodynamic (PopPKPD) modeling to quantitative systems pharmacology (QSP) approaches, have been employed to streamline and optimize anti-TB drug development and treatment approaches[30–32]. Extensive work using PopPK and PopPKPD approaches for anti-TB therapeutics has been performed to date[33–36]. These models allowed thorough characterization of PK and PD of various anti-TB drugs using rich clinical trial data. Population models have enabled the exploration and identification of the roles of covariates, i.e., intrinsic and extrinsic factors, on PK and PD of anti-TB drugs. Such models have played a key role in determining dosing regimens for many anti-TB drugs. Semi-mechanistic models including target site compartments allowed the quantification of biodistribution of several anti-TB drugs into lungs and TB lesions in lungs[37–39]. Semi-mechanistic multi-state tuberculosis pharmacometrics (MTP) models describing dynamics of fast-, slow-, and non-replicating Mtb populations have been developed utilizing in vitro, mouse, and clinical data[30,32]. Such models allowed predictions of drug effects on the sub-population of Mtb rifampin[35,40]. The MTP model combined with PD models have been used to translate treatment effects from preclinical experiments to patients. The MTP model combined with PD interaction models to estimate optimal doses of individual drugs in combination therapy have been evaluated[41]. Physiologically-based pharmacokinetic (PBPK) models of anti-TB have been developed to perform drug metabolism and drug-drug interaction evaluations[42,43]. Extended PBPK models including multi-compartment lungs have also been developed to further understand the target site distribution of drugs[44]. QSP models of capturing the dynamics of bacterial and key immune response markers following Mtb infections have also been developed and combined with PK-PD models of first-line anti-TB drugs to explore the impact of immune effects on treatment outcomes[31]. These examples highlight how quantitative pharmacology has influenced the development and optimization of anti-TB therapeutics. However, several key challenges still persist, for example, translation of PK and efficacy from preclinical to patients, emergence of drug resistance, long treatment duration, poor treatment outcome in some patients especially with drug-resistant TB, extrapulmonary TB, and/or comorbidities, safety and adherence concerns, etc. **(Figure 1.2)**. Due to the

multifaceted nature of TB disease and the current challenges in its treatment, there is a necessity for increased efforts utilizing quantitative pharmacology approaches. These efforts can play a crucial role in the development of treatment strategies that are both more effective and safer.

Scope of the thesis

The main objective of this thesis was to employ different quantitative pharmacology approaches to evaluate treatment optimization strategies for anti-TB therapeutics. In section II and III, we demonstrated applications of modeling and simulations to optimize treatment of first-line anti-TB therapeutics and newer anti-TB therapeutics, respectively by accounting for target site exposures, patient covariates, translational aspects, etc. In section IV, we discuss the utilization of QSP modeling to guide the development of host-directed therapies against Mtb infections. Lastly, in section V, we discuss a summary of our quantitative pharmacology analyses and discuss future perspectives to help eradicate TB. In Section II, we focus on quantitative pharmacology approaches for first-line anti-TB therapeutics, ethambutol, rifampin, and isoniazid. In **Chapter 2**, PopPK analysis of ethambutol in TB patients co-infected with HIV was performed. Covariate analysis was performed to evaluate the impact of HIV infection on the PK of ethambutol in pulmonary TB patients. PK target attainment simulations were performed to recommend alternative ethambutol dosing in TB patients co-infected with HIV. In **Chapter 3**, a whole-body PBPK modeling approach was used to evaluate the role of patient pharmacogenetic variability in determining the site of action target attainment in TBM patients. Rifampin and isoniazid PBPK models that included SLCO1B1 and NAT2 effects on exposures respectively were developed and validated using available cerebrospinal-fluid (CSF) concentrations from TB patients. Simulations were conducted to evaluate the combined effects of pharmacogenetic and Mtb minimum inhibitory concentrations (MIC) variability on target attainment at the site of action, brain, in TBM patients. In Section III, we focused on applying quantitative pharmacology approaches for newer anti-TB treatment regimens, including bedaquiline and pretomanid. In **Chapter 4**, bedaquiline and pretomanid translational mPBPK models were developed to predict site-of-action exposures and the probability of target attainment in TB patients. The probability of target attainment was calculated by comparing predicted target-site concentrations with minimal bactericidal concentrations (MBC) reported in the literature. In **Chapter 5**, a mechanistic framework was developed for a new combination regimen, bedaquiline, pretomanid, and linezolid (BPaL). The framework included key components that play a role in the overall response to the

therapy, such as patient body weight, TB lesion volume, target-site drug exposures, and individual patient and drug MICs. Simulations were conducted to predict anti-bacterial activity following BPaL current and alternative dosing strategies in virtual drug-resistant TB patients. In **Chapter 6**, a whole-body PBPK model with a CNS compartment was developed for bedaquiline and its active metabolite, M2, using bedaquiline and M2 PK data from plasma and CSF of TB patients. Simulations were conducted to predict target site drug concentrations to evaluate the feasibility of bedaquiline-containing regimens as a treatment option for MDR-TBM patients. In Section IV, we discuss innovative treatment approaches of host-directed therapies (HDT) for the treatment of TB. In **Chapter 7**, we review key host-pathogen interaction mechanisms as the basis of HDTs against Mtb. We introduce the components and utility of QSP approaches to support the identification and optimization of host-directed treatment targets, to facilitate preclinical to human translation, and to design combination treatment strategies including host-directed therapies. In **Chapter 8**, we developed a quantitative systems pharmacology (QSP) framework to evaluate the effects of metformin-associated autophagy induction in combination with first-line anti-TB therapy in patients. Simulations were conducted for adjunctive HDT therapy with metformin in newly diagnosed TB patients. In Section V, we discuss a summary of the evaluations and discuss future perspectives in utilizing quantitative pharmacology approaches for optimization of treatment approaches for TB therapeutics to eradicate TB.

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