Improving treatment outcomes of tuberculosis

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CHAPTER 1

GENERAL INTRODUCTION

Tuberculosis (TB) remains a continuous global problem. TB, an infectious disease caused by *Mycobacterium tuberculosis* (*M.tb*), is an ancient disease that was described about 70,000 years ago.(1) The pathogen can easily transmit from a TB patient to healthy people by air transmission. Nowadays, TB has spread worldwide owing to its ability to establish a latent infection, the capability of long persistence in the host,(2) and variations in its sensitivity to antibiotics.(3)

Global burden of tuberculosis disease

Nowadays, TB is one of the top 10 causes of death.(4) The World Health Organization (WHO) estimated that 10 million people developed TB and 1.3 million patients died because of TB in 2017.(4) A global report estimated that a large proportion of the world population has a latent TB infection (an existing *M.tb* with no evidence of clinically manifest active tuberculosis).(4) In approximately 10% of the population infected with latent TB, active TB disease will develop during the lifetime.(4) As a consequence, an active TB status is associated with disease transmission and substantial morbidity, which is even more problematic in the case of drug-resistant tuberculosis (DR-TB).

Drug-resistant tuberculosis (DR-TB) is a resistance of *M.tb* to one or more anti-tuberculosis drugs. The resistance patterns can be classified into mono-, poly-, rifampicin-, multidrug- and extensive drug-resistance.(5) Mono-resistant TB is defined as resistance to one first-line anti-TB drug only, while poly-resistant TB is resistance to more than one first-line anti-TB drugs other than isoniazid and rifampicin.(5) The more extensive patterns of drug resistance are multi-drug resistant TB (MDR-TB) and extensive drug-resistant TB (XDR-TB). MDR-TB is defined as resistance to at least both of the most potent anti-TB drugs (isoniazid and rifampicin), while XDR-TB is resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin) in addition to multidrug resistance.(5) As one of the most potent TB drugs, rifampicin resistance has been a great concern in TB treatment. Hence, the resistance of rifampicin has been included in the classification of DR-TB as rifampicin resistant-TB (RR-TB). Considering sensitivity to the anti-tuberculosis drugs, RR-TB is defined as resistance to rifampicin, with or without resistance to other anti-TB drugs, including any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR.(5)

The WHO identified 558,000 people who developed RR-TB and among this group, 82% had MDR-TB.(4) MDR-TB was reported responsible for about a quarter of all deaths caused by antimicrobial-resistant infections(6) and contributed to an estimated 14% of TB deaths worldwide.(4) If it comes to the treatment of MDR-TB, such patients should take multiple drugs and the drug treatment can be up to 24 months.(7) Combination of prolonged therapy, drug toxicities and cost burden, explain why MDR-TB patients have more frequent sub-

optimal outcomes than DS-TB or mono-resistant TB,(4,8) with an overall low success rate for treatment of MDR-TB of 55%.(4)

The global target for TB elimination 2035: low versus high burden TB countries

The WHO has divided all countries into two general categories of TB countries, i.e. low and high burden countries. TB low burden countries are the countries with TB incidence below 10 per 100,000 population,(9) while high burden countries are the countries with the highest absolute number of estimated incident cases and those with the most severe burden in terms of incidence rate per capita.(10) Although the quantitative burden level is different among low and high burden countries, the global target defined by the WHO is to achieve a global incidence rate of TB below 10 per 100,000 population by the year 2035.(11)

To achieve the strict targets, the WHO initiated a global strategy for TB prevention, care and control. The program, called the END-TB strategy, includes three main pillars, i.e., 1) integrated, patient-centered care and prevention, 2) strong policies and supportive systems, and 3) intensified research and innovation.(11) To respond to the global target, the specific target set in the low burden TB countries is to reduce the TB incidence to below 1 case per 100,000 population in 2035.(12) This challenging goal was followed up by the low burden TB countries. As an example, the Netherlands, a country with a total population of 17 million inhabitants in 2017, committed to reducing the TB case burden from 5.9 cases per 100,000 population in 2016 (13) to below 1 case per 100,000 population by 2035.(14) As an example for the high burden countries, Indonesia with a total estimated population of 264 million people, set a target from 254 cases per 100,000 population in 2017 (15) to 10 cases per 100,000 population by 2035.(16) More intensified research and health programs and policies are hence needed to achieve such strict targets within the coming 15 years.

Therapeutic failure is an essential problem for controlling drug-resistant tuberculosis

The mechanism of development of DR-TB can be classified into two main pathways: 1) primary drug-resistance which occurs when resistant strains are transmitted into a new host, and 2) secondary or acquired drug resistance which occurs through the acquisition of drug resistance mutations to one or more drugs.(17–19) Increasing the risk of primary drug resistance is higher in areas with a high prevalence of DR-TB. The transmission can be enhanced by environmental conditions such as crowding, poor ventilation and lack of infection control. On the other hand, secondary/acquired DR-TB is more affected by the low quality of drug treatment such as non-adherence to drugs and low drug exposure due to adverse drug reaction, drug interaction or inadequately dose.(5)

A history of previous TB treatment is one of the main risk factors for MDR-TB.(20) This evidence indicates that MDR-TB can be caused by secondary drug-resistance due to unsuccessful treatment from a prior treatment. A global report estimated that 3.5% of all

new TB cases had MDR or RR-TB, while 18% of previously treated cases had MDR or RR-TB in 2017.(4) The report provides evidence that unsuccessful TB treatment in the first episode of disease should be a concern for controlling DR-TB.

Besides TB case-finding, improving the rational use of anti-TB drugs has been an essential part of DR-TB control. Several studies have reported acquired drug-resistance due to therapeutic failures of TB treatment.(21–25) A study also demonstrated that TB patients with acquired drug resistance were at significantly increased risk for poor treatment outcome.(26) The global TB problem will become even more complicated when the trend of DR-TB transmission is shifting from acquired drug resistance to primary drug resistance. A dynamic modeling study in India showed that there is a predicted significant increasing transmission trend of primary drug-resistance from 15% in 2012 to 85% in 2032.(27) Therefore, emerging problems associated with TB drug treatment management should be primarily controlled to avoid the development of both primary and secondary DR-TB.

Antimicrobial stewardship program in TB disease

Antimicrobial stewardship is defined as "a coherent set of activities which promotes using antimicrobials in ways that ensure sustainable access to effective therapy for all who need them".(28) The primary goal is to optimize clinical outcomes and minimize unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms and the emergence of resistance.(29) An effective program should be designed based on setting priorities.(30) Engagement of multiple actors such as health care providers, government, patients, and society are also needed to enhance the benefits of an antimicrobial stewardship program.(28)

Although the terminology of antimicrobial stewardship is uncommonly used in the research and management of TB disease, the principles are still very relevant to achieve the global target of TB elimination in 2035. Activities related to treatment supervision can be part of antimicrobial stewardship programs for controlling DR-TB. Scientific knowledge of anti-TB drug use is needed to determine priority areas and plans for intervention.(31) The development of an effective program requires a more personalized approach that takes into account the heterogeneity in terms of patient characteristics across geographical areas and health care systems. In the development of intervention programs, it should be explored which high-risk groups of patients should be targeted for therapeutic failures. Furthermore, since treatment adherence is widely known as the main problem in TB disease, it should be explored who should be monitored and which intervention strategies should be developed to maintain good treatment adherence. Therefore, a comprehensive picture of unsuccessful treatment risks, treatment barriers and treatment non-adherence in TB disease should be obtained for developing an effective strategy to improve treatment outcome and control TB, notably DR-TB.

Unfortunately, comprehensive information on the current situation of high-risk groups for therapeutic failure and drug-related problems in TB disease is lacking. The controversial information is due to the differences in designs and settings of previous studies as well as the absence of more recent data, which is essential given the rapidly changing TB epidemiology. Updated studies and novel strategies are required for developing effective antimicrobial stewardship programs in TB disease. Therefore, this thesis attempted to provide a scientific knowledge base on the essential aspects to improve treatment outcomes of TB patients in the near future.

Thesis objectives and outlines

In this thesis, we aim to research both low and high TB endemic settings with the Netherlands as a low burden TB country and Indonesia as a high burden TB country. The empirical research will apply drug utilization and pharmacoepidemiological approaches to support potentially effective strategies to improve treatment outcomes as part of drug resistance control in TB disease. The specific objectives of this thesis can be listed as follows:

1. To analyze high-risk groups for therapeutic failure among TB patients.
2. To analyze potential interventions to improve treatment adherence in TB patients.
3. To analyze treatment barriers and potential strategies for successful TB treatment.

In **Chapter 2**, we aim to identify risk factors for MDR-TB as a fundamental part of this thesis. We will present a global systematic review and meta-analysis study that will identify patients' and geographical characteristics that are associated with the development of MDR-TB.

Since acquired drug-resistant TB can develop after the therapeutic failure of drug-susceptible TB (DS-TB), predictors for unsuccessful TB treatment among DS-TB patients are studied in **Chapter 3.** Using a nationwide TB database from the Netherlands, a low TB incidence country, we aim to identify the incidence, high-risk groups and predictors for unsuccessful TB treatment outcomes in an adult DS-TB population.

In **Chapter 4,** the current situation of the high-risk DR-TB patients in the Netherlands is investigated. We will present the prevalence of different types of DR-TB cases and the characteristics of patients who were lost to follow-up for the treatment outcome. To gain more insights in the treatment outcomes, we will determine the incidence, high-risk groups and predictors for poor outcome of TB treatment among all types of DR-TB patients also including MDR-TB patients.

In **Chapter 5**, we will systematically review measures of adherence and persistence to multiple medications using a pharmacoepidemiological approach. Since there is a lack of

studies in adherence to TB medications using real-world prescription databases, an example of cardio-metabolic medications that represent chronic diseases treated with multiple medications will be studied in this chapter. This review will implicitly provide scientific considerations for measuring adherence in TB disease using a prescription database.

Another TB drug adherence topic is continued in **Chapter 6.** This chapter will describe current studies on the impact of interventions to improve TB treatment adherence. In this chapter, we will also discuss several strategies to conduct valid intervention studies on TB treatment adherence.

In **Chapter 7**, we investigate treatment barriers among TB patients in a high burden TB setting. A qualitative study will be performed to determine treatment barriers from the patient perspective. In this chapter, we will discuss potential strategies to improve successful treatment among TB disease in Indonesia.

Finally, **Chapter 8** will describe an overview, general discussion, implication and future perspectives related to the findings of the studies presented in this thesis.

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