PROPORTION OF INCOMPLETE PREVENTIVE TREATMENT AND ITS ASSOCIATED FACTORS AMONG LATENT TUBERCULOSIS INFECTION PATIENTS IN SABAH

by

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LIST OF ABBREVIATIONS

Adj. OR	Adjusted Odd Ratio
Adj. RR	Adjusted Relative Risk
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CPG	Clinical Practice Guideline
df	Degrees of freedom
HBM	Health Belief Model
HCW	Healthcare Worker
HIV	Human Immunodeficiency Virus
IGRA	Interferon Gamma Release Assay
km^2	Square Kilometer
LTBI	Latent TB Infection
MCO	Movement Control Order
MTB	Mycobacterium Tuberculosis
OR	Odd Ratio
ROC	Receiver Operating Characteristic
RR	Relative Risk
SD	Standard Deviation
SDH	Social Determinats of Health
SPSS	Statistical Package for Social Science
TB	Tuberculosis
TST	Tuberculin Skin Test
UN	United Nations
WHO	World Health Organization

DECLARATION

I, Ahmad Firdaus bin Mohamed, hereby confirm that the content presented in this thesis is my original work. Any information obtained from external sources has been duly acknowledged and cited within the thesis.

ABSTRAK

KADAR RAWATAN PENCEGAHAN JANGKITAN TUBERKULOSIS PENDAM YANG TIDAK LENGKAP DAN FAKTOR-FAKTOR BERKAITANNYA DALAM KALANGAN PESAKIT JANGKITAN TUBERKULOSIS PENDAM DI SABAH.

Latar Belakang: Jangkitan Tuberkulosis Pendam *(LTBI)* adalah isu kesihatan awam yang utama; hampir satu pertiga daripada penduduk dunia dianggarkan mengalami *LTBI*. Sebilangan besar individu *LTBI* berkemungkinan akan menghidap penyakit tuberkulosis (TB) aktif, terutamanya dalam kalangan kumpulan yang kerap terdedah kepada bakteria *Mycobacterium tuberculosis* dan kurang daya tahan. Penyempurnaan rawatan pencegahan *LTBI* adalah penting untuk mencegah daripada menjadi penyakit TB aktif.

Objektif: Kajian ini bertujuan untuk mengenal pasti kadar rawatan pencegahan LTBI yang tidak lengkap dan faktor-faktor yang berkaitannya dalam kalangan pesakit jangkitan tuberkulosis pendam di Sabah, Malaysia.

Methodologi: Kajian ini menggunakan reka bentuk kajian kohort retrospektif menggunakan data sekunder dari rekod laporan LTBIS 401A Jabatan Kesihatan Negeri Sabah bagi tempoh empat tahun mulai Januari 2019 sehingga Julai 2022. Data dikumpul menggunakan proforma dan kemudian dipindahkan ke Microsoft Excel. Analisis dilakukan menggunakan SPSS versi 26. Analisis deskriptif dan kaedah regresi logistik berganda telah digunakan untuk menentukan faktor yang berkaitan dengan rawatan pencegahan *LTBI* yang tidak lengkap.

Keputusan: Sejumlah 895 pesakit *LTBI* telah dimasukkan dalam kajian ini. Kadar rawatan pencegahan *LTBI* yang tidak lengkap ialah 9.2%. Faktor yang dikaitkan secara signifikan dengan rawatan pencegahan yang tidak lengkap adalah pekerjaan bukan petugas kesihatan *(non-HCW)* (OR=4.21, 95% CI: 1.25, 14.22), penduduk di Bahagian Tawau (OR=2.00, 95% CI: 1.10, 3.65), dan pesakit *LTBI* yang tiada kontak dengan pesakit TB (OR=2.79, 95% CI: 1.42, 5.48).

Kesimpulan: Kadar rawatan pencegahan yang tidak lengkap dalam kalangan pesakit *LTBI* di Sabah adalah lebih rendah berbanding kajian lain yang diterbitkan sebelum ini. Intervensi yang disasarkan harus dibangunkan untuk menangani keperluan khusus kumpulan yang berkemungkinan lebih tinggi untuk tidak lengkap rawatan pencegahan *LTBI*. Hal ini termasuk menangani Penentu Sosial Kesihatan seperti meningkatkan ketercapaian sistem penjagaan kesihatan dan kecerunan sosial. Kajian prospektif harus dijalankan untuk menilai keberkesanan rawatan pencegahan *LTBI* ini.

Kata kunci: Jangkitan Tuberkulosis Pendam, tidak lengkap, rawatan pencegahan, Sabah, faktor berkaitan.

ABSTRACT

PROPORTION OF INCOMPLETE PREVENTIVE TREATMENT AND ITS ASSOCIATED FACTORS AMONG LATENT TUBERCULOSIS INFECTION PATIENTS IN SABAH.

Background: Latent tuberculosis infection (LTBI) is a major public health concern; almost a third of the world's population is estimated to have LTBI. A significant proportion of infected individuals progress to active tuberculosis (TB), especially among the frequently exposed and immunocompromised groups. Completion of LTBI preventive treatment is crucial to prevent progression to active TB.

Objective: This study aimed to identify the proportion of incomplete preventive treatment and its associated factors among LTBI patients in Sabah, Malaysia.

Methods: A retrospective record review was conducted among LTBI patients registered in the Sabah State Health Department's LTBIS 401A registry. This study utilized a retrospective cohort study design, using secondary data from the Sabah State Health Department's LTBIS 401A registry over four years, from January 2019 to July 2022. Data collection was conducted using a pre-designed proforma, and data were subsequently entered into a Microsoft Excel spreadsheet. Statistical analysis was performed using the SPSS version 26 software. Multiple logistic regression was used to determine the factors associated with incomplete LTBI preventive treatment.

Results: A total of 895 LTBI patients were included in the study. The overall proportion of incomplete LTBI preventive treatment was 9.2%. Factors that were significantly associated with the incomplete preventive treatment were non-HCW occupation (OR=4.21, 95% CI: 1.25, 14.22), residents of Tawau Division (OR=2.00,

95% CI: 1.10, 3.65), and LTBI patients without contact to TB patients (OR=2.79, 95% CI: 1.42, 5.48).

Conclusion: The proportion of incomplete preventive treatment among LTBI patients in Sabah was comparatively lower than in previously published studies. Targeted interventions should be developed to address the specific needs of the groups with higher odds of having incomplete LTBI preventive treatment. This includes tackling the Social Determinants of Health for example improving healthcare system accessibility and social gradient. Prospective studies should be conducted to evaluate these interventions' effectiveness in improving LTBI preventive treatment completion rates.

Keywords: Latent Tuberculosis Infection, incomplete, preventive treatment, Sabah, associated factor.

CHAPTER 1
INTRODUCTION

1.1 Background

1.1.1 Latent TB Infection and TB Disease

Latent Tuberculosis Infection (LTBI) is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active Tuberculosis (TB). TB infection is sometimes used interchangeably with LTBI, while active TB is synonymous with TB disease (WHO, 2020a). It is estimated that 1.7 billion people (about a quarter of the world population) were latently infected with *Mycobacterium tuberculosis* (Houben and Dodd, 2016). During their lifetime, the risk of LTBI progressing to active Tuberculosis disease is 5-10%, many within the first five years (WHO, 2020a). The outcome of *Mycobacterium Tuberculosis* (*MTB*) infection, whether it results in recovery, latency, or active disease, is influenced by a complex interplay of various factors, including the host, pathogen, and environment (CDC, 2012). Understanding these factors is crucial in determining the course of Tuberculosis (TB) infection and developing effective strategies for TB control.

Mycobacterium tuberculosis (MTB), the pathogen, is primarily transmitted through the air when a person with active TB disease coughs, sneezes, or speaks, releasing droplets containing the bacteria into the air. TB infection commonly begins in the lungs and is caused by inhaling a small particle that contains the tuberculosis bacterium. *MTB* has unique characteristics that enable it to evade the immune system and persist in the host for long periods. When the immune response cannot eliminate the bacteria, *MTB* can enter a state of latency, which remains dormant in the body

without causing active disease. Subsequently, the bacteria can reactivate under certain conditions and cause active TB disease.

The host refers to the individual infected with *MTB*. Factors such as the immune competence of the host can influence the progression of *MTB* infection. In most cases, a healthy host's immune response can control or eliminate the bacteria, resulting in recovery from the infection. However, conditions compromising the immune system, such as HIV infection, malnutrition, diabetes, cancer, organ transplant, and chronic renal disease, can increase the risk of progression from LTBI to active TB disease (Salgame *et al.*, 2015; WHO, 2020a). This can lead to the reactivation of the bacteria and the emergence of symptomatic TB disease.

The environment, including factors such as frequent exposure to *Mycobacterium tuberculosis* bacteria, living conditions, and access to healthcare, can also influence the outcome of TB infection. Individuals frequently exposed to *MTB*, such as healthcare workers (HCW) and those living in overcrowded or poorly ventilated environments, are at a higher risk of contracting TB than those who are not. Living conditions are also an important environmental factor that can impact the outcome of TB infection. Poor living conditions, such as inadequate housing, lack of sanitation, and poor nutrition, can weaken the immune system, making individuals more susceptible to TB infection and less able to fight it off once infected. Overcrowding and lack of ventilation in living spaces also increase the risk of TB transmission, as it is an airborne disease that spreads through the air when an infected person coughs or sneezes.

LTBI and TB disease are caused by multiple factors, making them complex diseases to understand. Rothman's Causal Pie Theory, which identifies multiple factors

contributing to a particular outcome, can summarize the various causes of LTBI and TB disease (CDC, 2012). To fully comprehend the complex nature of TB, it is crucial to not only examine the biological mechanisms by which *MTB* damages the human body but also take into account the impact of various social and economic factors on individuals. Consequently, many scholars recognize TB as a social disease due to the substantial influence of social determinants on TB transmission, incidence, and outcomes (WHO, 2010; Ali, 2014).

1.1.2 Diagnosis

Currently, there is no direct test available to diagnose LTBI. LTBI is identified through the presence of evidence of TB infection without active TB disease. This can be done by either Tuberculin Skin Test (TST) or Interferon-Gamma Release Assays (IGRA) after excluding active TB disease. This is based on both international and local guidelines (Ministry of Health Malaysia, 2021b; WHO, 2022e).

1.1.3 Burden of Tuberculosis

Globally, there were 10.6 million people diagnosed with active TB disease, with 1.6 million TB death in 2022 (WHO, 2023a). Of all diseases, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19 worldwide (WHO, 2022b). TB can affect people of all ages and is found in all countries. Fortunately, TB is both preventable and curable.

Malaysia is ranked as an upper-middle-income country with an upper-moderate TB disease burden (WHO, 2021c; The World Bank Group, 2022). In Malaysia, the burden of TB in 2022 was significant, with 25,391 reported cases of active TB disease (incidence rate of 77.8 per 100,000) and 2,572 TB-related deaths

(Monihuldin, 2023). However, as of now, there is no published data on LTBI prevalence in Malaysia (Ministry of Health Malaysia, 2020d).

At the sub-national level, Sabah is a state located in East Malaysia and economically less developed than the other states in West Malaysia. Sabah also has many legal and illegal immigrants from the Philippines and Indonesia who usually live in overcrowded settlements (Dollah *et al.*, 2016; Avoi and Liaw, 2021). The Philippines and Indonesia are the top 30 TB burden countries, with an incidence rate of 539 and 301 per 100,000 population, respectively (WHO, 2021c, 2022a). The state of Sabah persistently recorded the highest case of TB in Malaysia, with more than 5238 cases (incidence rate of 134.2 per 100,000) reported in 2019 (Department of Statistics Malaysia, 2022a). Furthermore, Dony *et al.* (2004) reported that immigrants contributed more than 24% of new cases detected since 1990. The TB mortality rate in Sabah alarmingly increases yearly (Avoi and Liaw, 2021). These findings highlight the concerning situation of TB in Sabah, which may be influenced by various factors such as economic development, immigration patterns, overcrowded living conditions, and the high burden of TB in neighbouring countries.

1.1.4 Impact of Covid-19 Pandemic on TB Control

While the dust is just settling from the Covid-19 pandemic, the impact of the pandemic on TB control worldwide is very alarming. There was a reduction of 1.4 million people who received TB treatment in 2020 compared to 2019 which may consequently increase the TB death to an extra 0.5 million deaths, reversing the TB control program back to where it was in 2010 (Glaziou, 2021; WHO, 2021a; Dass *et al.*, 2022). Based on the current situation, the TB battle is still far from over. Therefore, it is essential not to lose focus on TB.

1.1.5 LTBI Preventive Treatment

There are several regimens for treating both active TB disease and LTBI. The similarities of treatment for TB & LTBI are that they usually require a prolonged treatment period, from 1 month to 36 months. Apart from the long duration of treatment, there are other important issues that need to be considered. One such issue is the potential side effects of the medications used to treat TB and LTBI, such as hepatotoxicity (liver toxicity), which can pose risks to patients. Additionally, the emergence of drug resistance is a concern, as it can compromise the effectiveness of treatment and pose challenges in managing TB and LTBI patients. Access to treatment and availability of the required medications are also crucial considerations. They can impact the success of TB and LTBI treatment (Ministry of Health Malaysia, 2012a; WHO, 2020a, 2020b; Avoi and Liaw, 2021; WHO, 2022d).

To achieve the long-term goal of TB elimination, the WHO is pushing for more comprehensive preventive treatment of LTBI (United Nations, 2015; WHO, 2020a). In Malaysia, the Ministry of Health took steps to address LTBI by developing a pilot project in 2019 that utilised Interferon-Gamma Release Assays (IGRA) to detect LTBI, along with strengthening LTBI treatment and data management. The pilot project was subsequently implemented nationwide in August 2020, indicating the commitment of the Ministry of Health towards addressing LTBI as a part of TB elimination efforts in Malaysia (Ministry of Health Malaysia, 2020e). The latent Tuberculosis Information System (LTBIS) registry was established in 2020 following the implementation of Programmatic Screening of LTBI patients. It is a manual registry using Microsoft Excel, compiled monthly at the district, state, and national levels. Currently, it only includes the LTBI patients detected by the government health facility (Ministry of Health Malaysia, 2020b).

Incomplete preventive treatment of LTBI is important as it can lead to progression of TB infection to active TB disease. Furthermore, it also can attribute to increase risk of drug resistant *MTB* (Balcells et al., 2006). Hence, it is important to monitor the incomplete preventive treatment of LTBI to achieve the End TB strategy set by the WHO. In the context of the research being conducted, the outcomes of LTBI treatment will be studied, which may shed light on the effectiveness and challenges associated with treating individuals with latent TB infection.

1.2 Problem Statement

Sabah has the highest TB burden in Malaysia. The TB incidence rate in Sabah is double that of the national incidence rate (Goroh *et al.*, 2020; Department of Statistics Malaysia, 2022a). The disease burden is exacerbated by factors such as poverty, migration, and cross-border movement. The porous border with Indonesia and the Philippines might further aggravate the TB burden in Sabah (Dollah *et al.*, 2016). Among the strategies that will improve the TB burden is by implementing preventive treatment of LTBI.

In recent years, throughout the globe, several studies have explored factors associated with the incomplete preventive treatment of LTBI. However, since nationwide access to IGRA tests and programmatic screening of LTBI are relatively new to Malaysia, there is no prior research regarding LTBI preventive treatment completion in Malaysia.

The incomplete preventive treatment of LTBI is concerning as it can result in the progression of the infection to active TB, which poses a significant risk to public health. Programmatic screening and treatment of LTBI in high-risk groups are among

the priorities set by WHO in the End TB strategy. Hence studies that evaluate the factors associated with incomplete preventive treatment among LTBI patients become even more relevant.

1.3 Study Rationale

There has not been any previous research on the completion of LTBI preventive treatment in Malaysia, as the nationwide access to IGRA test and programmatic screening of LTBI are relatively recent developments. Given that this is a new area of research in Malaysia, there is a need for more studies to explore the factors influencing the incompletion of preventive treatment among individuals diagnosed with LTBI. This will help healthcare providers to understand the challenges and barriers to completing LTBI preventive treatment and develop strategies to improve the completion rate, which is essential to achieving the goal of TB elimination in Malaysia and globally.

By identifying the factors associated with the incomplete preventive treatment of LTBI, this study could help Sabah State Health Department to decide on targeted interventions to improve the completion rates of preventive treatment among LTBI patients in Sabah. This, in turn, could help reduce the burden of TB in the Sabah state. The research is also helpful for the Disease Control Division (TB/ Leprosy Sector) in the Ministry of Health Malaysia for future planning of LTBI management and, subsequently, to the global efforts to eliminate the disease.

1.4 Research Questions

The research questions are:

1. What is the proportion of incomplete preventive treatment among LTBI patients in Sabah?

2. What are the factors associated with incomplete preventive treatment among LTBI patients in Sabah?

1.5 Objectives

The general objective is to study the proportion of incomplete preventive treatment and its associated factors among LTBI patients in Sabah.

There are two specific objectives for this research:

1. To determine the proportion of incomplete preventive treatment among LTBI patients in Sabah; and

2. To determine the associated factors for incomplete preventive treatment among LTBI patients in Sabah.

CHAPTER 2
LITERATURE REVIEW

The literature search was done using online search engines and databases, including PubMed, Scopus, Google Scholar, WHO, and the Ministry of Health databases. Several search strategies were applied, including Boolean operators "AND" and" OR". The keywords used were Tuberculosis, TB, Latent TB Infection, LTBI, *Mycobacterium Tuberculosis*, prevention, treatment, treatment outcome, incomplete, and complication.

2.1 Overview of Latent TB Infection

2.1.1 Definition

Tuberculosis (TB) is an infectious disease due to *Mycobacterium tuberculosis* that has always been a massive challenge throughout human history. Humankind has been battling TB since ancient times (Zimmerman, 1979). Over the years, there have been some significant breakthroughs in the fight against TB, such as Robert Koch's isolation of *Mycobacterium Tuberculosis* in 1882 and the development of the first anti-tuberculous drugs (Barberis *et al.*, 2017). However, looking at the current TB burden worldwide, we are far from winning the battle against TB (WHO, 2023a).

TB primarily affects the lungs but can also affect other body parts. It is spread through the air when an infected person coughs, sneezes, or talks, and another person inhales the bacteria (CDC, 2016). It can be classified into two main forms: latent TB infection and TB disease. LTBI occurs when a person has been infected with *MTB* but does not have active TB disease, meaning they do not have symptoms and cannot

spread the infection to others. However, they may develop TB disease later in life if the bacteria become active (CDC, 2016). By definition, latent Tuberculosis Infection (LTBI) is a state of persistent immune response to stimulation by *Mycobacterium Tuberculosis* antigens without evidence of clinically manifested active TB. The term TB infection is occasionally used in place of LTBI (WHO, 2020a).

The United Nations introduced the Sustainable Developmental Goals in 2015. Among the target is to end the epidemic of Tuberculosis by the year 2030 (United Nations, 2015). Following that, the WHO introduced the End TB Strategy as a blueprint to achieve a global TB incidence of <100 per million by 2035 (WHO, 2015a). Subsequently, the WHO targets to eliminate TB by the year 2050, which is defined as a TB incidence rate of less than 1 case per million per year.

This target will only be achieved by a sustained decline in TB incidence, far more than what currently is achieved. The existing TB control measures, identifying and treating cases of active TB, and the practice of effective infection control are important and will need to be intensified. However, doing what we already do now will not achieve the TB elimination target. Models suggest that the additional strategy of treating those LTBI patients will be required to meet this elimination target (Esmail *et al.*, 2012).

2.1.2 Epidemiology

In 2022, globally, there were 10.6 million people diagnosed with active Tuberculosis (TB) disease, and 1.6 million TB-related deaths, as reported by the World Health Organization (WHO, 2023a). In Malaysia, the burden of TB in 2022 was significant, with 25,391 reported cases of active TB disease (incidence rate of 77.8 per 100,000) and 2,572 TB-related deaths (Monihuldin, 2023). For the burden of LTBI, the two

most cited studies on the estimate of global LTBI burden are by Dye *et al.* (1999) and Houben and Dodd (2016). Both studies estimated that about one-third to one-quarter of the world population were latently infected with TB. However, as of now, there is no published data on LTBI prevalence in Malaysia (Ministry of Health Malaysia, 2020d).

The state of Sabah persistently recorded the highest case of TB in Malaysia, with more than 5238 cases (incidence rate of 134.2 per 100,000) reported in 2019 (Department of Statistics Malaysia, 2022). The TB mortality rate in Sabah alarmingly increases yearly (Avoi and Liaw, 2021). These statistics underline the urgent need for effective TB prevention, detection, and treatment strategies, particularly in high-burden areas like Sabah, to reduce the burden of TB and prevent TB-related deaths.

2.1.3 Impact of the Covid-19 Pandemic on TB Control

The COVID-19 pandemic has significantly impacted global Tuberculosis (TB) control efforts, and the aftermath is cause for alarm. In 2020, there was a reduction of 1.4 million people who received TB treatment compared to 2019, which could potentially result in an additional 0.5 million TB deaths, effectively setting back TB control programs to levels seen in 2010 (Glaziou, 2021; WHO, 2021a; Dass *et al.*, 2022). This reduction in TB treatment and the potential increase in TB-related deaths due to the impact of the COVID-19 pandemic underscores the ongoing challenges in the fight against TB. Consequently, it is imperative to maintain our attention and commitment to addressing TB.

The implications of the pandemic on TB control highlight the need to continue prioritising and implementing effective TB prevention, detection, and treatment strategies to mitigate the negative impact on TB control programs and prevent further

loss of lives to this persistent infectious disease. It is imperative to maintain vigilance and concerted efforts toward TB control, even as the world grapples with the ongoing challenges of the COVID-19 pandemic.

The three-delays model is a well-known framework used to understand the various factors contributing to delays in accessing and receiving appropriate healthcare for a particular condition, such as Tuberculosis (TB). In the context of the COVID-19 pandemic, these delays may have played a significant role in the decline in TB treatment uptake observed in 2020 compared to the previous year (Di Gennaro *et al.*, 2021).

The first delay, which involves the delay in seeking treatment, may have been driven by fear and concerns about contracting COVID-19. During the pandemic, there was widespread fear of visiting healthcare facilities due to the risk of exposure to the virus. This led to hesitancy in seeking medical care, despite having TB symptoms. This fear may have resulted in individuals delaying or avoiding seeking TB treatment, which could harm their health outcomes.

The second delay, related to accessing treatment centres, may have been exacerbated by the implementation of movement control orders or lockdowns in many countries during the COVID-19 pandemic. These restrictions may have limited the mobility of individuals and disrupted the functioning of healthcare facilities, making it challenging for people to access TB treatment centres. This could have resulted in delays in seeking and receiving timely TB care, leading to adverse outcomes.

The third delay, which involves the delay in diagnosis and treatment, may have been influenced by the strain on healthcare resources during the pandemic. The overwhelming demand for healthcare services, including COVID-19 management,

may have strained the capacity of healthcare systems, resulting in delays in diagnosing TB and initiating timely treatment. During the pandemic, healthcare resources had been redistributed more towards managing Covid-19 illness. This lead to limited availability of resources, such as diagnostic tests, medications, and healthcare personnel, which may have further contributed to TB diagnosis and treatment delays.

These delays in seeking treatment, accessing treatment centres, and receiving timely diagnosis and treatment may have had a negative impact on TB outcomes. Delayed initiation of TB treatment can lead to disease progression, increased severity of symptoms, and potentially increased TB-related deaths.

2.1.4 Diagnosis / Test Available

As of now, there is no direct test that can measure LTBI. Three main immune-based approaches are currently used for the identification of LTBI. They are the tuberculin skin test (TST), interferon-gamma release assay (IGRA), and *Mycobacterium Tuberculosis* antigen-based skin tests (TBSTs). All three methods represent indirect markers of *MTB* exposure and indicate a cellular immune response to *MTB.* Studies have shown that both TST and IGRA have low predictive value for progression from infection to active TB (Pai and Behr, 2016). For TBSTs, it is the latest method, which was recently endorsed as LTBI diagnostic method by the WHO in 2022 (WHO, 2022c).

2.1.5 LTBI Preventive Treatment

LTBI comprises a reservoir for the new disease and ongoing *MTB* transmission within communities, thereby perpetuating the disease cycle at a population level. The ability to accurately and efficiently identify those with LTBI at the most significant risk of

progression and provide targeted preventive therapy is essential for achieving TB eradication globally, given that one-third of the world's population is latently infected with TB (Dye *et al.*, 1999; Salgame *et al.*, 2015; Cohen *et al.*, 2019).

Taking preventive treatment can prevent the reactivation of TB. As LTBI preventive treatment has associated risks and costs, it should be targeted to those at the highest risk of progressing to active TB disease who will benefit the most (WHO, 2020a). It is essential to focus the treatment of latent tuberculosis infection (LTBI) on the individuals at the highest risk of developing active TB to ensure cost-effectiveness and minimise the risk of adverse treatment reactions. WHO recommends systematic testing and treatment for high-risk groups for developing active TB. These include household and close contacts of confirmed PTB, PLHIV, patients receiving anti-TNF treatment, dialysis patients, those preparing for organ/hematological transplant, and patients with silicosis. Meanwhile, certain groups, including healthcare workers, immigrants from high TB-burden countries, prisoners, illicit drug users, and homeless people, may be considered for LTBI testing and treatment (WHO, 2020a; Ministry of Health Malaysia, 2021a; WHO, 2021b).

2.1.6 Treatment options for latent tuberculosis infection

Several preventive treatment options are available for people with latent tuberculosis infection (LTBI). These treatment regimens include six or nine months of daily Isoniazid monotherapy (6H or 9H), four months of daily Rifampicin (4R), three months of daily Rifampicin plus Isoniazid (3HR), three months of weekly Rifapentine plus Isoniazid (3HP), one month of daily Rifapentine plus Isoniazid (1HP), and six months of daily Levofloxacin. The selection of a specific treatment regimen depends on various factors such as the availability of the drugs, the age group of the patient,

comorbidities, drug tolerance, and drug-resistance status of the index case, among others (WHO, 2020a; Ministry of Health Malaysia, 2021a). New evidence suggested shorter regimes such as 1HP, 3HP, 3 HR, and 4R have almost similar efficacy and adverse medication reaction development, with some regimes even having better costeffectiveness (Trajman *et al.*, 2010; Haley, 2017; McClintock *et al.*, 2017; Ronald *et al.*, 2020).

2.1.7 The magnitude of incomplete LTBI preventive treatment

LTBI preventive treatment completion has been a topic of interest in recent years, especially in developed countries since the introduction of Interferon Gamma Release Assay (IGRA) for LTBI diagnosis in 2001. It is important to monitor LTBI preventive treatment completion, especially in high-risk populations, to reduce the incidence of active TB disease and improve overall TB control efforts. Various studies have been conducted to determine the proportion of incomplete LTBI preventive treatment in different regions.

Chang *et al.* (2014) conducted a study in California county, US, among LTBI patients aged 18 years old and less. The proportion of incomplete LTBI preventive treatment was 21.5%. Fiske *et al.* (2014) conducted a study in nine health departments in the US and Canada among patients aged 15 years old and older. They found that 39% of the study subject did not complete their LTBI preventive treatment. Another study in 30 clinics among all LTBI patients in US and Canada by Hirsch-Moverman *et al.* (2015) found that 53.4% of the study subject did not complete their LTBI preventive treatment. Also, in the US, Stockbridge *et al.* (2018) conducted a study among LTBI patients covered by Optum Clinformatics® Data Mart insurance company and found that 53.8% did not complete LTBI preventive treatment.

Meanwhile, Iqbal *et al.* (2021) conducted a similar study among LTBI patients covered by the IBM Watson Health MarketScan insurance company and found that 50.1% did not complete LTBI preventive treatment.

In South Korea, a study was conducted among LTBI patients aged 65 years old and older in five university hospitals by Noh *et al.* (2019). They found that the proportion of incomplete LTBI preventive treatment was 16.9%. The majority of the incomplete treatment was due to a loss of follow-up. Chung *et al.* (2020) conducted a study among LTBI patients among HCW in a university hospital in South Korea. The proportion of incomplete LTBI preventive treatment was found at 37.7%, with the most frequent reason was hepatotoxicity. In Japan, Kawatsu *et al.* (2017) conducted a study among all notified LTBI patients who initiated treatment throughout the whole country. They found that the incomplete LTBI preventive treatment proportion was 28.1%. The most frequent cause for incomplete LTBI preventive treatment was due to the development of the adverse reaction. Meanwhile, in Taiwan, Feng *et al.* (2020) conducted a study among all LTBI patients in 8 referral medical centres in Taiwan. They found that 18.2% of the study subject had incomplete LTBI preventive treatment.

The lowest proportion of incomplete treatment was observed in Norway, with 9% (Schein *et al.*, 2018). The study was conducted among all LTBI patients throughout Norway. The magnitude of incomplete LTBI preventive treatment is widely varied between studies. This might be due to the methodology heterogeneity found in all studies. Nonetheless, the magnitude of the incomplete LTBI preventive treatment is huge, even in developed countries.

2.1.8 LTBI treatment completion rates in Malaysia and Sabah

Following the pilot project, unpublished data from the Malaysian Ministry of Health revealed that 20.6% of the individuals screened were positive for LTBI. Moreover, only 60.3% were given preventive treatment (Ministry of Health Malaysia, 2021b). However, no published LTBI treatment-related study conducted in Malaysia was discovered during the literature search.

2.2 Risk factors for Incomplete LTBI Preventive Treatment

Several studies have been conducted to determine the factors associated with incomplete preventive treatment. Many of these were conducted in developed countries, especially after IGRA was introduced as a method to diagnose LTBI. These studies are important as they can give insight into how to plan for a targeted approach to improve the outcome of LTBI preventive treatment.

2.2.1 Age

Some studies have identified an association between incomplete LTBI preventive treatment and age, but these studies did not treat age as a numerical variable. The results of these studies are heterogenous, as they identified different age groups as being associated with incomplete preventive treatment. The findings are heterogenous, with different studies finding different age groups associated with incomplete preventive treatment. Chang *et al.* (2014) did a study among children and adolescent LTBI patients. They found that the age group of 15-18 years old was associated with incomplete treatment (Adj. OR: 2.00, 95% CI: 1.30—3.00). 2 other studies in Japan and Taiwan found that the age groups of ≥ 65 years old (Adj. OR: 1.27, 95% CI : 1.10–1.47) and > 80 years old (Adj. OR: 4.96, 95% CI: 1.50–16.41) were associated with

incomplete LTBI preventive treatment (Kawatsu *et al.*, 2017; Feng *et al.*, 2020). The authors suggested that this might be most likely due to adverse events, including death, which were higher in the older age group. However, this contradicts a study in the US (Iqbal *et al.*, 2021) which found that the age group of <65 years old (Adj. OR: 1.40, 95% CI: 1.20-1.60) was associated with incomplete treatment.

2.2.2 Gender

The risk of not completing treatment was higher among females supported by a US study with Adj. OR:1.10, 95% CI: 1.04-1.20) (Iqbal *et al.*, 2021). Hirsch-Moverman *et al.* (2015) also stated that the female gender was associated with treatment incompletion. The researcher suggested this might be due to the higher treatment adverse effects in the female gender. Pettit *et al.* (2013) also found that the female gender was significantly (Adj. RR: 1.67, 95% CI: 1.32-2.10) associated with incomplete LTBI preventive treatment. Similarly, the authors found that the female gender was at increased risk of discontinuing LTBI preventive treatment due to adverse effects.

2.2.3 Immigration Status

Immigrants also have been found to have a higher risk of incomplete LTBI preventive treatment (Adj. OR: 1.14, 95% CI: 1.02–1.28), as seen by a study in Japan (Kawatsu *et al.*, 2017). The study found that many immigrants were lost to follow-up or self-terminated from the treatment. This might be due to cultural and linguistic barriers among the immigrants, as suggested by the researchers. The study highlights the need for targeted interventions and culturally sensitive approaches to increase completion rates among immigrant patients, who may face unique challenges in accessing and adhering to LTBI preventive treatment.

2.2.4 Ethnicity

A study in the US found that certain ethnic group was associated with a higher risk of treatment incompletion (Chang *et al.*, 2014). The non-Hispanic ethnicity was associated with treatment incompletion (Adj. OR: 2.00, 95% CI: 1.30—3.00) compared to the Hispanic race. The authors suggested that this might be attributed to cultural differences and openness to treatment compared to the Hispanic ethnicity.

2.2.5 Residential Region

In the US, the residential region was associated with higher treatment incompletion. The article by Iqbal *et al.* (2021) found that the residential region of LTBI patients in the US was significantly associated with higher treatment incompletion. Specifically, those living in the Northeast or South Census regions had a higher risk (Adj. OR: 1.20, 95% CI: 1.10-1.30) of incomplete treatment. The authors however did not explain further why residential region had significant association with treatment incompletion.

2.2.6 Income

Several studies have found that lower income and low socioeconomic status are associated with incomplete LTBI preventive treatment for Tuberculosis. A study conducted in Brazil by Silva *et al.* (2016) found that an income of ≤ USD 117 was a risk factor for treatment incompletion (Adj. OR: 11.20, 95% CI: 2.50–50.60). Similarly, a study conducted in the US by (Sandul *et al.*, 2017) found that a history of homelessness during the 12 months before treatment initiation was associated with incomplete treatment (Adj. OR: 1.72, 95% CI: 1.25–2.39) . It is agreed worldwide that poverty is the major contributory factor for homelessness (Johnsen and Watts, 2014).

2.2.7 Access to healthcare

Silva *et al.* (2016) conducted a study in Brazil and found that the cost of transportation to reach healthcare facilities was associated with incomplete LTBI preventive treatment. In particular, they found that a higher transport cost (≥ USD 4.70) was associated with treatment incompletion (Adj. OR: 3.70, 95% CI: 1.00–14.2).

2.2.8 Occupation

According to Kawatsu *et al.* (2017), healthcare workers (HCW) in Japan were found to be at risk for incomplete treatment of LTBI (Adj. OR: 1.44, 95% CI: 1.24–1.69), which is somewhat ironic given their expertise in the field. The authors suggested that this may be due to healthcare workers being more aware of potential adverse events associated with the treatment, which may lead to a reluctance to complete the full course.

2.2.9 Lifestyle

Sandul *et al.* (2017) conducted a study in the US and found that a history of incarceration within the past 12 months before treatment initiation was associated with treatment incompletion (Adj. OR: 1.43, 95% CI: 1.08–1.89). On the other hand, de Aguiar *et al.* (2022) found that illicit drug use was a risk factor for treatment incompletion in Brazil (Adj. OR: 23.33, 95% CI: 1.83-296.10).

2.2.10 Peer Factor

A study conducted in Brazil found that non-completion treatment by index case (Adj. OR: 16.97, 95% CI: 3.63-79.24) was associated with incomplete LTBI preventive treatment (de Aguiar *et al.*, 2022). In this study, the researchers defined the index case

as the person diagnosed with active TB and identified as the transmission source to other people. The study revealed that if the index case did not complete their treatment for active TB, there was a higher likelihood of incomplete LTBI preventive treatment among their contacts who were diagnosed with LTBI.

2.2.11 Clinical and Treatment Factors

The study by Feng *et al.* (2020) conducted in Taiwan found that two factors, namely severe adverse reactions (adj. OR: 6.15, 95% CI: 3.18–11.89) and longer treatment duration (Adj. OR: 4.47, 95% CI: 1.29–15.52), were associated with a higher risk of incomplete preventive treatment for LTBI. In the US, Chang *et al.* (2014) found that hepatotoxicity was associated with incomplete LTBI preventive treatment (Adj. OR: 24.60, 95% CI: 10.50—62.80). Similarly, another research in South Korea by Chung *et al.* (2020) also found that hepatotoxicity was associated with incomplete LTBI preventive treatment (Adj. OR: 7.99, 95% CI: 3.05–20.94). Hepatotoxicity is when the liver is damaged due to exposure to drugs or other toxins. Patients experiencing hepatotoxicity may need to discontinue the medication or take a lower dose, which could lead to incomplete treatment. In addition, a study conducted by Ronald *et al.* (2020) in Canada revealed that completion rates for LTBI preventive treatment were particularly low among patients with comorbidities, particularly those treated with rifampin. The study also reported a lower risk of severe hepatotoxicity among patients treated with rifampin than those treated with isoniazid.

2.3 Conceptual Framework

Figure 2.1 shows the conceptual framework of the factors associated with incomplete LTBI preventive treatment among latent TB cases. Based on the literature review, many factors are associated with incomplete LTBI preventive treatment. Since our study is based on secondary data, ten variables included were gender, age, nationality, ethnicity, occupational sector, residential region, contact with TB case status, comorbidities, adverse medication reaction, treatment regime, and incomplete LTBI preventive treatment status as the outcome of the study. Those marked with (*) were factors not included in this study due to the limitation of available data.

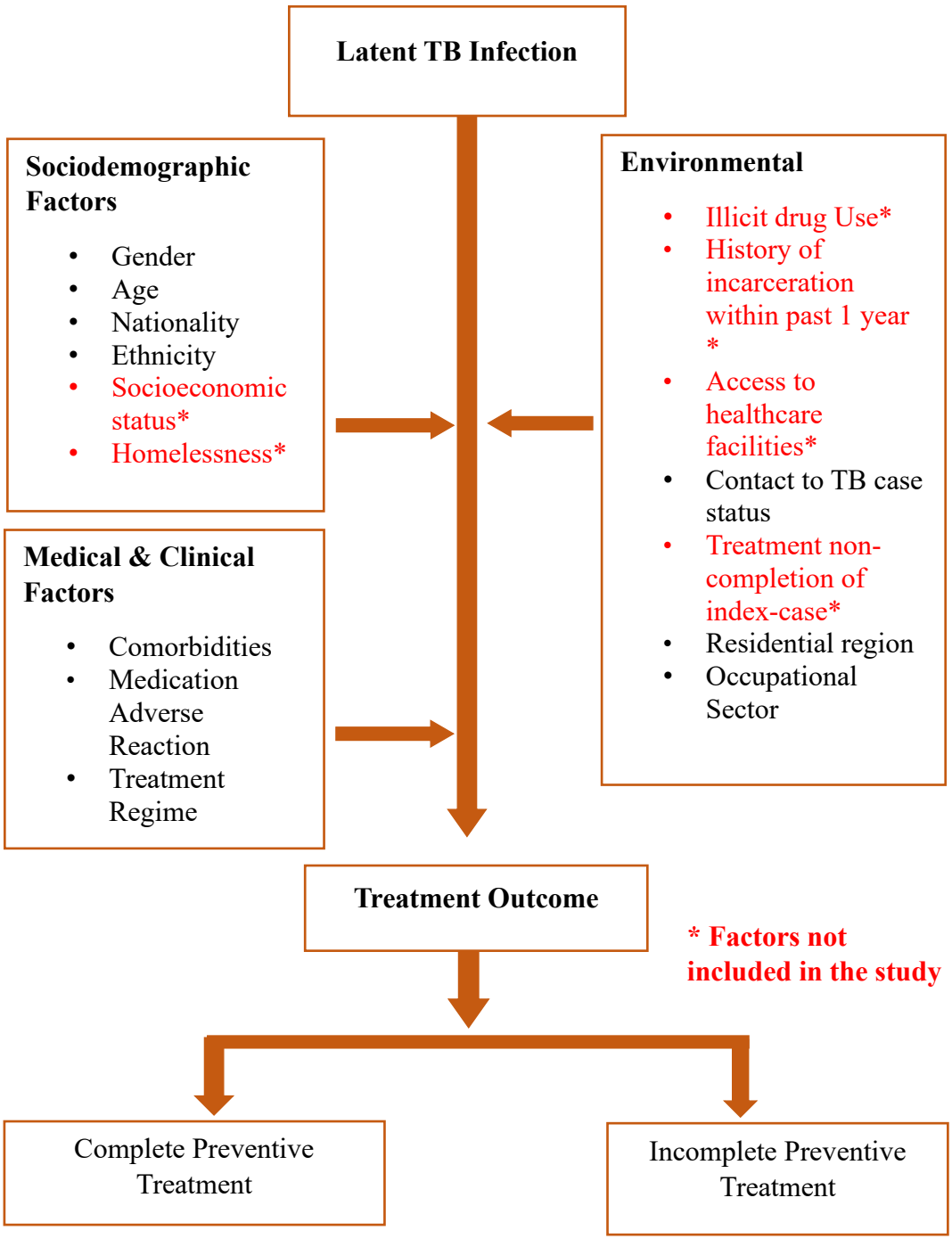

Figure 2.1: Conceptual framework of factors associated with incomplete preventive treatment among latent TB patients

CHAPTER 3
METHODOLOGY

3.1 Study Design

The study used a retrospective record review with a cohort design to identify factors associated with incomplete preventive treatment among LTBI patients. The data were obtained from the LTBIS 401A registry of Sabah State Health Department's Latent TB Information System.

3.2 Study Period

This study was conducted for six months, from 1st January 2023 until 30th June 2023.

3.3 Study Area

The study was conducted in Sabah, involving all districts. It is located at the north of Borneo Island and geographically separated from West Malaysia by the South China Sea. Internationally, Sabah shares borders with the Philippines and Indonesia. Sabah is the second largest state in Malaysia, after Sarawak. The land area covers 73,904 square kilometer. About 3.9 million people live in Sabah, with almost 30% being immigrants (Department of Statistics Malaysia, 2022e). Sabah, comprises five administrative divisions, which are further divided into 27 districts (Department of Statistics Malaysia, 2022c). The five divisions are West Coast Division, Tawau Division, Sandakan Division, Kudat Division, and Interior Division. In 2017, three sectors contributed about 89.9% of the Sabah's economy with the largest contribution came from the services sector (39.9%), mining and quarrying (31.3%) and agriculture