# FACTORS ASSOCIATED WITH NON-INITIATION OF TUBERCULOSIS PREVENTIVE TREATMENT AMONG LATENT TUBERCULOSIS INFECTION CASES IN NEGERI SEMBILAN FROM 2022-2024

## SANGGARY MARIMUTHU

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# FACTORS ASSOCIATED WITH NON-INITIATION OF TUBERCULOSIS PREVENTIVE TREATMENT AMONG LATENT TUBERCULOSIS INFECTION CASES IN NEGERI SEMBILAN FROM 2022-2024

by

**SANGGARY MARIMUTHU**

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# ACKNOWLEDGEMENTS

Lastly, to my dear mother, Rajeswary Thangarajoo, your endless love, prayers, and sacrifices have laid the foundation for all that I am and all that I have achieved. Your presence in my life is a blessing beyond words.

To everyone who has contributed, directly or indirectly, to the completion of this research, I extend my heartfelt gratitude.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AIDS | Acquired immunodeficiency syndrome |
| ART | Antiretroviral therapy |
| BCG | Bacille Calmette-Guérin |
| HCWs | Healthcare workers |
| HIV | Human Immunodeficiency virus |
| IGRAs | Interferon-gamma release assays |
| IPT | Isoniazid Preventive Therapy |
| LTBI | Latent tuberculosis infection |
| MPHIA | Malawi Population-Based HIV Impact Assessment |
| NTBR | National Tuberculosis Registry |
| PBMCs | Peripheral blood mononuclear cells |
| PLHIV | People living with HIV |
| PPD | Purified protein derivative |
| TB | Tuberculosis |
| TPT | Tuberculosis preventive treatment |
| TST | Tuberculin skin test |
| WHO | World Health Organisation |

# LIST OF SYMBOLS

| | |
|---|---|
| aOR | Adjusted odds ratio |
| OR | Odds ratio |
| % | Percentage |
| $P_0$ | Baseline proportion |
| α | Alpha |
| β | Beta |
| ≥ | Greater than and equal to |
| ≤ | Less than and equal to |
| > | Greater than |
| < | Less than |
| = | Equal to |
| * | Indicates a note or additional explanation at the bottom of the page (Asterisk) |

# FAKTOR-FAKTOR YANG BERKAITAN DENGAN TIDAK MEMULAKAN RAWATAN PENCEGAHAN TUBERKULOSIS DALAM KALANGAN KES JANGKITAN TUBERKULOSIS PENDAM DI NEGERI SEMBILAN DARI TAHUN 2022 HINGGA 2024

## ABSTRAK

**Latar belakang:** Rawatan pencegahan tuberkulosis (TPT) memainkan peranan penting dalam mengurangkan risiko perkembangan jangkitan tuberkulosis pendam (LTBI) kepada penyakit aktif. Walau bagaimanapun, faktor-faktor tidak memulakan rawatan TPT masih belum dianalisa sepenuhnya.

**Objektif:** Kajian ini bertujuan untuk menentukan kadar pengambilan rawatan TPT dan faktor-faktor yang berkaitan dengan tidak memulakan rawatan dalam kalangan kes LTBI di Negeri Sembilan bagi tempoh 2022 hingga 2024.

**Metodologi:** Kajian keratan rentas retrospektif ini melibatkan 757 kes LTBI yang dilaporkan di Negeri Sembilan antara Januari 2022 hingga Disember 2024. Data diperoleh daripada sistem NTBR dan dianalisis menggunakan SPSS. Analisis regresi logistik univariat dan multivariat telah dijalankan bagi mengenal pasti faktor-faktor yang berkaitan secara signifikan dengan tidak memulakan rawatan TPT.

**Keputusan:** Sebanyak 9.3% pesakit tidak memulakan rawatan TPT. Pekerjaan didapati sebagai faktor signifikan, di mana kumpulan "tidak bekerja golongan muda"

(yang terdiri daripada pelajar dan kanak-kanak bawah lima tahun) menunjukkan kebarangkalian lebih tinggi untuk tidak memulakan rawatan berbanding golongan profesional (aOR = 3.52; 95% CI: 1.35,9.16; p = 0.010). Daerah tempat tinggal juga mempengaruhi rawatan; pesakit dari daerah Tampin mempunyai lima kali ganda kebarangkalian untuk tidak memulakan rawatan berbanding mereka dari Seremban (aOR = 5.12; 95% CI: 2.59,10.11; p < 0.01), manakala pesakit dari Jempol menunjukkan kebarangkalian yang rendah terhadap penolakan rawatan (aOR = 0.10; 95% CI: 0.01,0.74; p = 0.024). Selain itu, pesakit bukan warganegara menunjukkan kebarangkalian lebih tinggi untuk tidak memulakan rawatan berbanding warganegara Malaysia (aOR = 3.83; 95% CI: 1.65,8.85; p = 0.020).

**Kesimpulan:** Faktor seperti pekerjaan, kewarganegaraan dan lokasi geografi didapati mempengaruhi keputusan pesakit untuk memulakan rawatan TPT. Kajian ini menekankan keperluan bagi pendekatan rawatan yang lebih berpusat, sistem susulan yang teguh, serta pendidikan kesihatan yang menyasarkan kumpulan berisiko tinggi seperti pesakit HIV, kontak rapat kes index TB, petugas kesihatan, OKT penjara dan penduduk rumah kebajikan warga emas.

**Kata Kunci:** Latent TB, TPT, faktor, tidak memulakan rawatan, Negeri Sembilan

# FACTORS ASSOCIATED WITH NON-INITIATION OF TUBERCULOSIS PREVENTIVE TREATMENT AMONG LATENT TUBERCULOSIS INFECTION CASES IN NEGERI SEMBILAN FROM 2022-2024

## ABSTRACT

**Background:** Tuberculosis Preventive Treatment (TPT) is essential in reducing the risk of progression from latent tuberculosis infection (LTBI) to active disease. However, the factors associated with the non-initiation of TPT have not been explored thoroughly.

**Objective:** This study aimed to determine the proportion of LTBI patients who did not initiate TPT and to identify factors associated with non-initiation in Negeri Sembilan between 2022 and 2024.

**Methodology:** A retrospective cross-sectional study was conducted involving 757 LTBI cases reported from January 2022 to December 2024. Data were extracted from the National Tuberculosis Registry system using a universal sampling method and analysed with SPSS software. Univariable and multivariable logistic regression analyses were performed to determine the factors significantly associated with non-initiation of TPT.

**Results:** Overall, 9.3% of patients did not initiate TPT. Occupation emerged as a significant predictor; the "unemployed young" group (comprising students and

children under five) had significantly higher odds of non-initiation compared to professionals (aOR = 3.52; 95% CI: 1.35,9.16; p = 0.010). The district of residence was also influential, with patients from Tampin having five times the odds of not initiating TPT compared to those from Seremban (aOR = 5.12; 95% CI: 2.59,10.11; p < 0.01), while residence in Jempol had lower odds (aOR = 0.10; 95% CI: 0.01,0.74; p = 0.024). In addition, foreign nationals were significantly more likely not to initiate treatment compared to Malaysian citizens (aOR = 3.83; 95% CI:1.65,8.85; p = 0.020).

**Conclusion:** Occupation, nationality, and geographical location significantly influence the initiation of TPT among LTBI patients in Negeri Sembilan. These findings highlight the importance of centralised LTBI care, robust follow-up mechanisms, and tailored health education efforts to improve treatment uptake especially among high-risk group such as people living with HIV (PLHIV), contact of TB index cases, healthcare worker, prisoners and residents of nursing home.

**Keywords:** Latent TB, TPT, factors, non-initiation, Negeri Sembilan

# CHAPTER 1: INTRODUCTION

## 1.1 Epidemiology of Latent Tuberculosis

Latent tuberculosis infection (LTBI) is a critical global health issue, affecting approximately one-quarter of the world's population, or about 1.7 billion individuals. People with LTBI harbour the *Mycobacterium tuberculosis* bacteria without showing symptoms of active disease, yet they carry a 5-10% lifetime risk of progressing to active tuberculosis (TB) if left untreated. This risk is particularly high within the first two years post-infection and is further amplified among high-risk groups such as people with HIV/AIDS, individuals with diabetes, and those undergoing immunosuppressive treatments (Bar-Meir *et al.*, 2021; Harries *et al.*, 2020). Addressing LTBI is thus essential to TB prevention and forms a cornerstone of the WHO's End TB Strategy, which envisions a 90% reduction in TB incidence by 2030.

Figure 1.1 illustrates the regional distribution of active TB cases as of 2019, highlighting high-burden countries and regions based on WHO classification. South-East Asia accounted for the highest proportion (44%) of global TB cases, followed by Africa (24%) and the Western Pacific (18%) (Oxford Immunotec, 2019). Furthermore, Figure 1.2 illustrates that approximately one-quarter of the global population is infected with LTBI. Of these, 10–15% are estimated to progress to active tuberculosis disease over their lifetime, emphasizing the significance of LTBI as a reservoir for TB transmission (Pan American Health Organization, 2020).
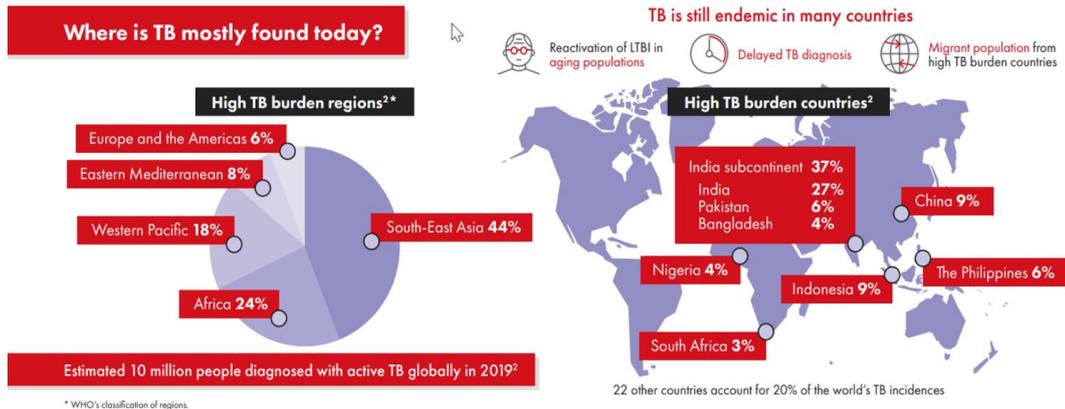
**Figure 1.1: Global Distribution of Tuberculosis Burden and High TB Burden Countries (Oxford Immunotec, 2019)**
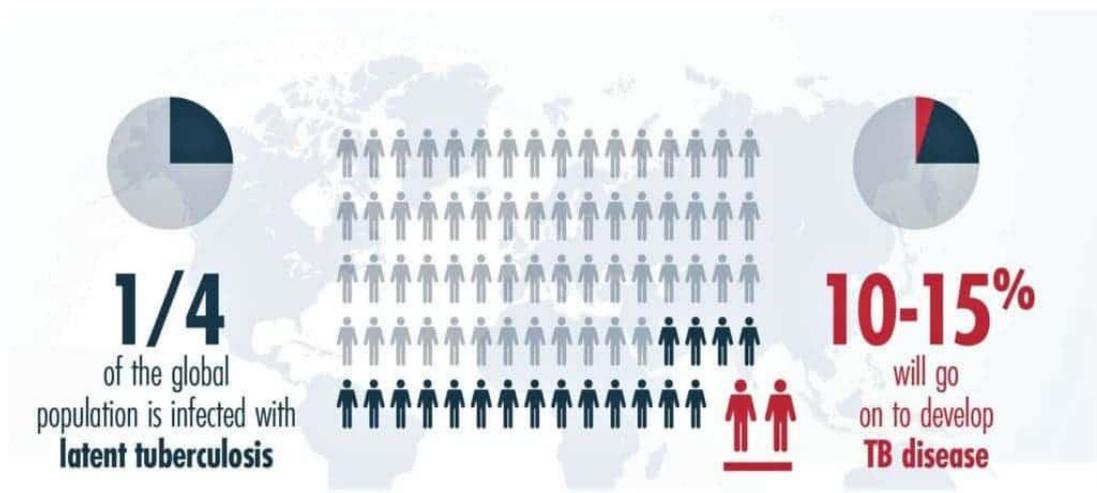


**Figure 1.2: Global Prevalence of Latent Tuberculosis Infection and Risk of Progression to Active TB Disease (Pan American Health Organization, 2020)**

**1.2 Transmission of Tuberculosis**

The progression of tuberculosis begins when *M. tuberculosis* is inhaled, leading to initial bacterial replication and spread, followed by the host's immune response that contains the bacteria. This results in a clinically silent state known as LTBI, which is characterized by the continued presence of viable bacteria under immune control, without symptoms of active disease.

Figure 1.3 displays a schematic diagram of latent tuberculosis infection and its mechanism. LTBI is a balance between immunity of host and invasiveness of *M. tuberculosis*; any tilt would upset the balance (A) (Gong and Wu, 2021). The *M. tuberculosis* excreted from patients with active TB is inhaled by healthy people through airborne transmission and recognized and phagocytized by antigen-presenting cells such as macrophages, neutrophils, natural killer cells, and B lymphocytes (B). Then, neutrophils release cytokines to activate and recruit T lymphocytes to gather at the place where *M. tuberculosis* invades to form granulomas (B). If the host immunity is strong, *M. tuberculosis* will be cleared by immune cells and the host recovers; If the host immunity is weak, *M. tuberculosis* will reproduce in the granulomatous tissue and breaks through the granulomatous restriction to cause active TB; If the immunity of host and invasiveness of *M. tuberculosis* is balanced, the host will be latently infected (A,B).
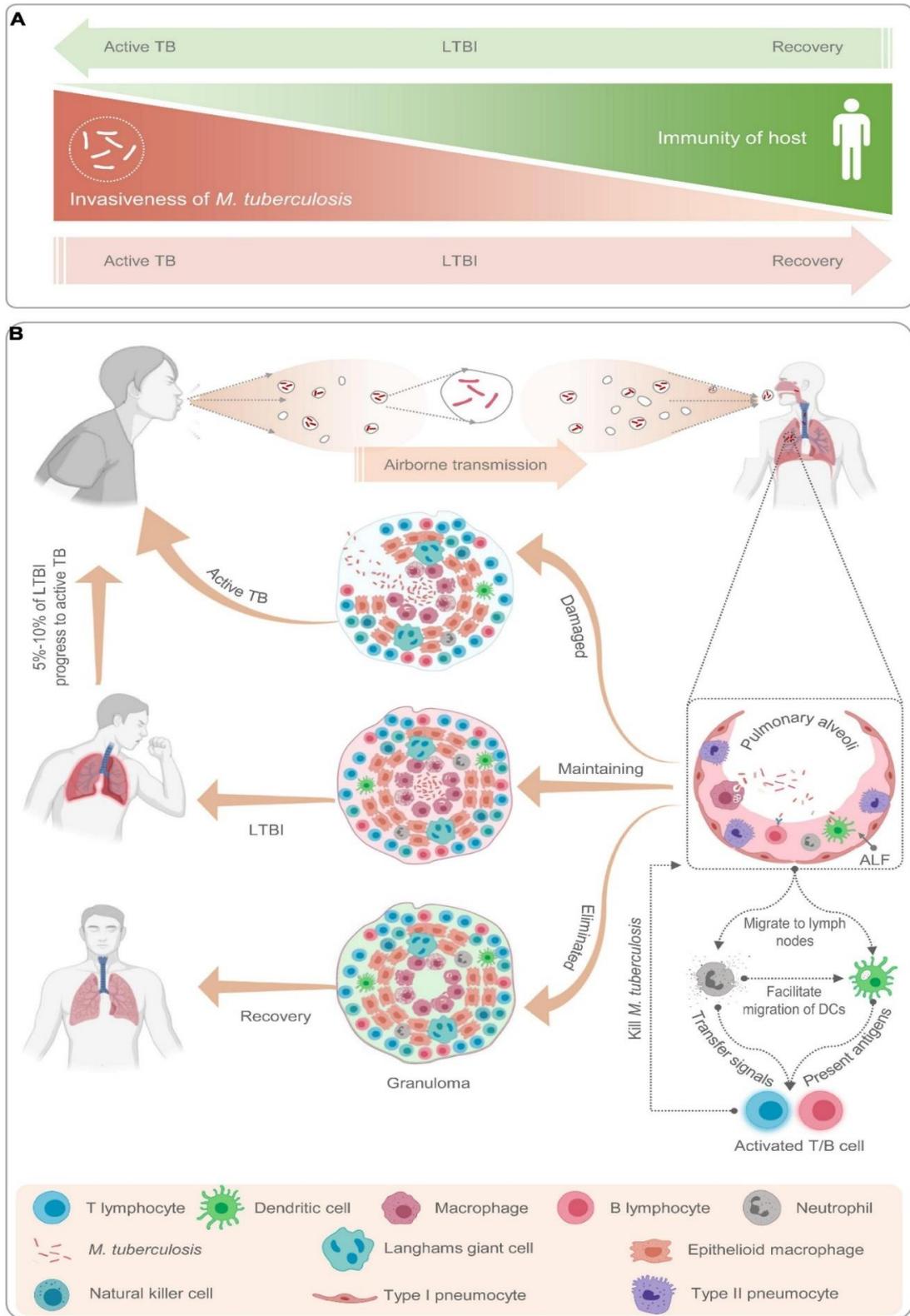
**Figure 1.3: Schematic diagram of latent tuberculosis infection and its mechanism (Gong and Wu, 2021)**

**1.3 Screening and treatments**

The primary objective of testing for LTB is to identify individuals who are at heightened risk of progressing to active TB, as these individuals are most likely to benefit from preventive treatment, also referred to as prophylaxis. Testing should be selectively offered to individuals for whom treatment would be considered if the result is positive, thereby ensuring clinical value and minimizing unnecessary interventions. Generally, LTBI testing is warranted when there is a significant likelihood of recent infection such as in close contacts of active TB cases or when the individual's immune capacity to control latent infection is compromised. High-risk groups include young children exposed to TB, individuals living with HIV, and those experiencing immunosuppression due to medical therapies or chronic conditions like uncontrolled diabetes.

Conversely, routine screening in populations with low risk of progression to active disease is discouraged, as the diagnostic yield is low, and the potential harms of treatment may outweigh its benefits. This consideration is particularly relevant in high TB burden settings, where the possibility of reinfection is considerable and the negative predictive value of LTBI screening is diminished. In children, however, the risk-benefit balance of LTBI testing and treatment is generally more favourable compared to adults.

It is important to note that there is no definitive diagnostic test for LTBI. Current diagnostic tools are indirect and rely on detecting an immune response indicative of sensitization to TB antigens. The two widely accepted methods for identifying LTBI are the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs). Both tests measure cell-mediated immunity specifically the memory

T-cell response but neither can reliably differentiate LTBI from active TB disease (Pai *et al.*, 2014).

Figure 1.4 illustrates the procedures for the three main diagnostic tests for latent tuberculosis infection (Shah and Dorman, 2021). The tuberculin skin test involves intradermal inoculation of purified protein derivative (PPD) and reading the induration diameter after 48–72 hours. The T-SPOT.TB IGRA requires isolation and incubation of peripheral blood mononuclear cells (PBMCs) with Mycobacterium tuberculosis antigens, followed by spot enumeration. The QuantiFERON-TB Gold Plus assay uses whole blood stimulation with TB antigens and ELISA-based quantification of interferon-gamma levels.

Meanwhile, Figure 1.5 outlines the thresholds for a positive TST result according to the risk profile of the individual (Ministry of Health Malaysia, 2021). A reaction of ≥5 mm is considered positive for people living with HIV (PLHIV), organ transplant recipients, and other immunosuppressed individuals. A threshold of ≥10 mm applies to other high-risk groups such as healthcare workers and children, while ≥15 mm is considered positive for individuals from countries with low TB incidence.
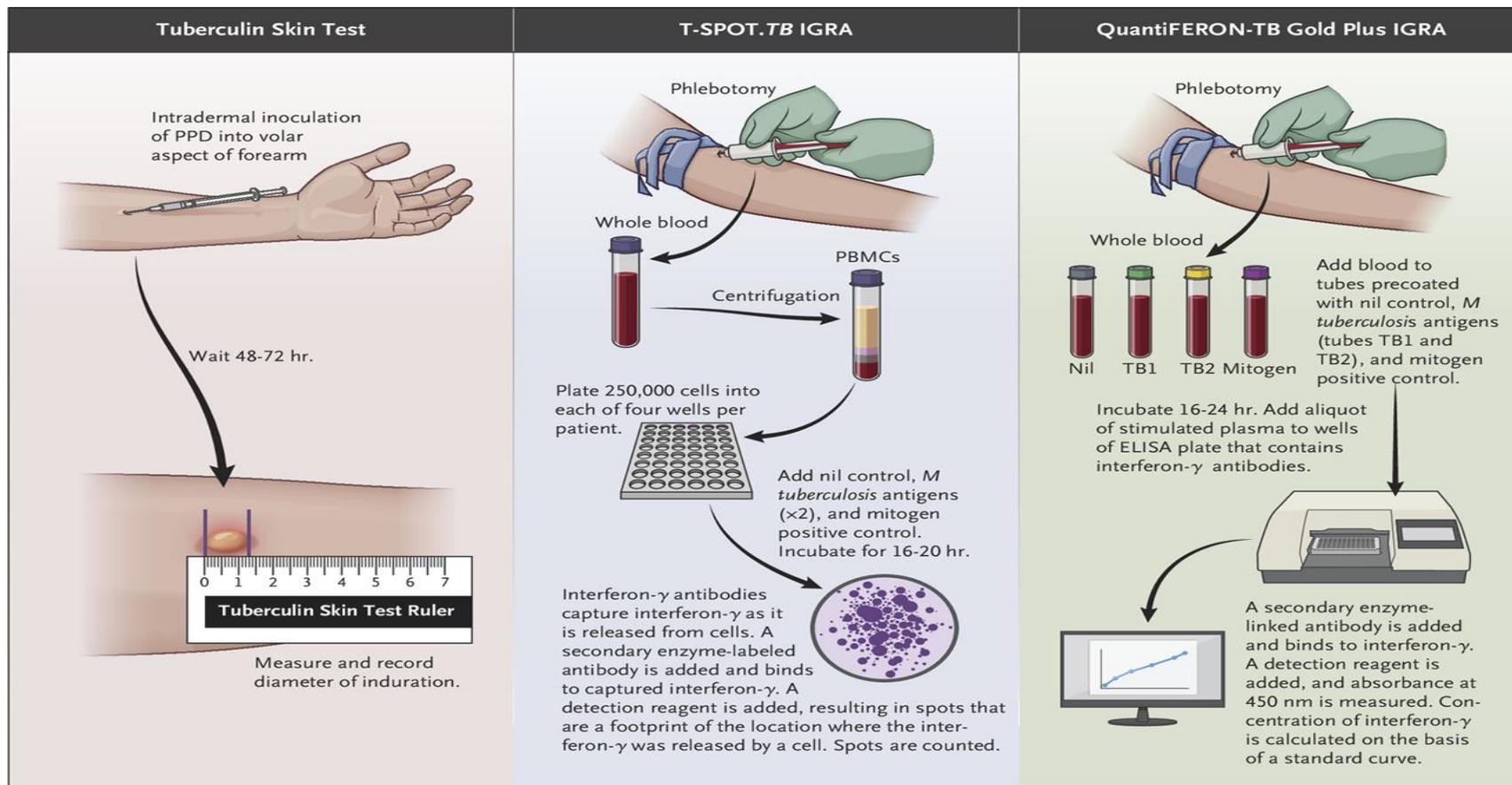
**Figure 1.4: Comparative Overview of Diagnostic Tests for Latent Tuberculosis Infection (Shah and Dorman, 2021)**

| Positive (TST) reaction | At-risk groups |
|---|---|
| ≥5 mm | • PLHIV<br>• Organ transplant recipients<br>• Persons who are immunosuppressed for other reasons (e.g. those taking the equivalent of >15 mg/day prednisolone for ≥1 month or taking anti-TNF treatment) |
| ≥10 mm | • All other high risk individuals including healthcare workers and children (except newborns and infants <3 months) |
| ≥15 mm | • Individuals from countries with low incidence of TB |

**Figure 1.5: Interpretation of Positive Tuberculin Skin Test (TST) Reaction Based on Risk Group (Ministry of Health Malaysia, 2021)**

Research indicates that 5% to 15% of individuals with LTBI may develop active tuberculosis during their lifetime, with the risk being significantly higher among immunocompromised individuals. Hence, individuals with LTBI are considered the reservoir for future active tuberculosis cases within the population (Getahun *et al.*, 2015). The importance of preventing TB through LTBI treatment has gained momentum in recent years, with a focus on scaling up TPT coverage among at-risk groups. Treating individuals with LTBI has been shown to reduce the likelihood of progressing to active tuberculosis by approximately 60% to 90%, thereby helping to curb further transmission. While the effectiveness of treatment in preventing active TB is a key consideration when selecting a regimen, it should not be the sole factor guiding decision-making. The primary aim is to lower the patient's risk of disease activation and to interrupt transmission at the community level. Additional critical factors include the expected treatment uptake rate referring to how many eligible individuals begin treatment and completion rate, which measures how many complete the prescribed course. Given that LTBI therapy is typically administered to individuals who are otherwise healthy, minimizing adverse effects is essential. Moreover, it is important to assess the cost-effectiveness of each regimen in comparison with other public health interventions.

Figure 1.6 summarises for the treatment of LTBI in adults (Ministry of Health Malaysia, 2021). Preferred first-line regimens include 3HR (daily isoniazid and rifampicin for 3 months) or 3HP (weekly isoniazid and rifapentine for 3 months), unless contraindicated. Alternative regimens such as 4R (daily rifampicin for 4 months), 6H or 9H (daily isoniazid for 6 or 9 months), and 1HP (daily isoniazid and rifapentine for 1 month) are considered based on individual tolerance and contraindications.

**Recommendation 22**

- In the treatment of all adults with latent tuberculosis infection (LTBI):
  - 3HR or 3HP* regimens should be the first-line regimen unless contraindicated
  - 4R may be used for patients who cannot tolerate or who are contraindicated for INH-based regimens
  - 6H or 9H may be used for patients who cannot tolerate or who are contraindicated for rifamycin-based regimens
  - 1HP* may be considered for HIV-positive adults

3HR=three months daily isoniazid and rifampicin, 3HP=three months weekly isoniazid and rifapentine, 4R=four months daily rifampicin, 6H=six months daily isoniazid, 9H=nine months daily isoniazid, 1HP=one month daily isoniazid and rifapentine

*rifapentine is not yet available in Malaysia

- The use of 3HR/3HP/4R:
  - is contraindicated in patients receiving protease inhibitor-based antiretroviral therapy
  - requires dose adjustment of dolutegravir and raltegravir

**Figure 1.6: Recommended Regimens for LTBI in adults (Ministry of Health Malaysia, 2021)**

**1.4 Problem statement**

TPT ideally needs to be widely accepted and implemented among all individuals with LTBI to effectively halt the progression to active TB. Despite the introduction of TPT in recent years, the burden of TB in Malaysia remains high, with a reported incidence of 97 cases per 100,000 population in 2021, highlighting the urgency of effective intervention strategies. The uptake and success of the TPT program have not been thoroughly explored, and there remains a significant knowledge gap regarding the factors that influence treatment initiation and adherence. In particular, understanding the reasons behind non-initiation of TPT is essential to inform targeted efforts to enhance treatment coverage, improve program outcomes, and contribute to national and global TB elimination goals.

Several barriers, ranging from individual factors to broader social and health system related issues, continue to impede treatment initiation and completion. Research has shown that awareness of LTBI and TPT benefits is particularly low among healthcare workers, despite the higher TB risk associated with their work environment (Plans-Rubió *et al.*, 2024). Educational interventions among healthcare workers increased LTBI treatment acceptance, underscoring the importance of healthcare education in improving TPT adherence (Bar-Meir *et al.*, 2021).

Beyond healthcare settings, broader socioeconomic and demographic factors also affect TPT adherence. In Catalonia, Spain, a study revealed that men, immigrants, and those exposed to TB in workplaces or schools were less likely to adhere to LTBI treatment regimens (Plans-Rubió *et al.*, 2024). Similar findings in high TB-burden countries indicate that structural barriers, including limited healthcare access and low health literacy, contribute significantly to treatment non-adherence. Addressing these barriers requires a patient-centred approach that considers the diverse needs and

challenges faced by individuals in different regions and demographic contexts (Harries *et al.*, 2020). Guidelines released by the National Tuberculosis Controllers Association in collaboration with the CDC emphasize the need for targeted interventions to improve TPT uptake, especially in regions with limited healthcare (Centers for Disease Control and Prevention, 2020). The risk of TB reactivation among those with LTBI is heightened in certain populations, including the elderly, immunocompromised individuals, and migrants from high TB-burden countries. These groups, along with healthcare workers, close contacts of active TB cases, and individuals with underlying health conditions, are prioritized for LTBI screening and treatment (Oxford Immunotec, 2019).

## 1.5 Research rationale

Acquiring a comprehensive understanding of TPT is crucial as it serves as a key intervention to halt the progression of LTBI to active tuberculosis. This aligns with global health initiatives, particularly the WHO End TB Strategy, which aims to eliminate the TB epidemic by 2035, and with Sustainable Development Goal (SDG) 3"Good Health and Well-being" which targets ending the global TB epidemic by 2030. In Malaysia, these goals underscore the importance of public awareness, education, and preventive measures as part of national TB control strategies. Furthermore, understanding the factors and barriers contributing to the non-initiation of TPT, such as socioeconomic challenges, healthcare access issues, and knowledge gaps, is essential. Identifying these barriers can support the development of targeted and effective interventions to improve treatment uptake, adherence, and ultimately reduce TB incidence and transmission.

**1.6 Research question**

- What is the proportion of non-initiation of TPT among LTBI cases from 2022-2024 in Negeri Sembilan?

- What are factors associated with non-initiation of TPT among LTBI cases from 2022-2024 in Negeri Sembilan?

**1.7 Research objective**

General objective:

To study the proportion of non-initiation of TB Preventive Treatment and the factors contributing to non-initiation of TPT among LTBI cases from 2022-2024 in Negeri Sembilan

Specific objective:

(1) To determine the proportion of non-initiation of TPT among indicated LTBI cases from 2022- 2024 in Negeri Sembilan

(2) To determine factors associated with non-initiation of TPT among indicated LTBI cases from 2022-2024 in Negeri Sembilan

**1.8 Research hypothesis**

Hypothesis: There are significant association between the study factors with TPT non-initiation from 2022-2024 in Negeri Sembilan

# CHAPTER 2: LITERATURE REVIEW

## 2.1 Epidemiology of LTBI

A pivotal global modelling study by Houben and Dodd (2016) re-estimated the burden of LTBI and reported that approximately 1.7 billion people which is equivalent to 23.0% of the global population were latently infected with Mycobacterium tuberculosis in 2014. This updated figure challenges the long-held estimate of "one-third" of the world's population and highlights significant regional disparities, with nearly 80% of LTBI cases concentrated in the WHO South-East Asia, Western Pacific, and Africa regions. The study also estimated that around 56 million individuals had been recently infected (within the past two years), representing a group at heightened risk of developing active TB, of which approximately 11% harboured isoniazid-resistant strains. Children under 15 years accounted for 6% of LTBI cases globally, with higher proportions in Africa (13%). Importantly, even if TB transmission had ceased entirely after 2014, projections indicated that 11% of the global population would remain infected in 2035 and 6% in 2050 levels far above the thresholds required to achieve End TB Strategy elimination targets. These findings underscore the critical importance of aggressive global strategies to identify and treat LTBI, particularly in high-burden regions and high-risk subgroups (Houben and Dodd, 2016).

LTBI remains a significant public health concern in Malaysia, with varying prevalence rates across different populations. Among healthcare workers, the prevalence of LTBI has been estimated at 10.6%, underscoring the increased risk due to occupational exposure (Rafiza *et al.*, 2011). In contrast, the prevalence is lower among diabetic patients, reported at 4.8% in Terengganu (Husain *et al.*, 2023). However, certain vulnerable groups, such as refugee children, exhibit higher

prevalence rates, with 12.8% affected, highlighting substantial risks within these populations (Wong and Lee, 2020).

## 2.2 Proportion of non-initiation of TPT among LTBI cases

There is a notable proportion of individuals who do not initiate TPT after being indicated for it, pointing to barriers that hinder effective management and control of LTBI in Malaysia. Addressing the non-initiation of TPT is essential to reducing the risk of LTBI progressing to active TB, especially within high-risk groups. Similar challenges are evident globally. For instance, in Iqaluit, Nunavut (2012–2016), out of 439 individuals diagnosed with LTBI, only 328 (74.7%) were offered treatment, and just 246 (56.0%) initiated it. This reflects a 44% non-initiation rate among all diagnosed and 25% among those offered therapy (Pease *et al.*, 2019). Besides that, in a Korean study involving healthcare workers diagnosed with LTBI, only 43.7% initiated treatment, with non-initiation rate of LTBI treatment among healthcare workers was 56.3% linked to factors such as liver disease, long employment duration, and physician status (Lee *et al.*, 2019). These findings underscore the importance of addressing context-specific barriers to TPT initiation to ensure effective LTBI control strategies, both in Malaysia and globally.

## 2.3 Factors associated with non-initiation of TPT among LTBI

Non-initiation of LTBI treatment is influenced by a range of factors, including age, educational background, occupation, healthcare worker or non-healthcare worker, sex, comorbidities, nationality, ethnicity, HIV status, residential area (district), and treatment centre or provider characteristics.

### 2.3.1 Age

Age plays a significant role in treatment adherence and non-initiation of LTBI treatment. A Spanish study found that individuals over 65 were considerably less likely to begin LTBI treatment, with a non-initiation rate of 39.3%, compared to just 7% among younger contacts. This discrepancy may stem from concerns about age-related drug toxicity and a shorter life expectancy, which might reduce the perceived urgency of preventive treatment. Although age is associated with reduced initiation, the study suggests that age alone should not be a limiting factor, as the preventive benefits of LTBI treatment remain substantial for older adults (Gullón Blanco *et al.*, 2023).

In South Korea, Noh *et al.* (2019) found that among older patients, factors such as age, IGRA results, and the presence of comorbidities influenced treatment completion. The study suggests that older adults may face physical and psychological barriers, necessitating tailored interventions that address age-specific challenges. However, a study in Catalonia, Spain, reported that younger individuals were less likely to initiate treatment, indicating the need for age-sensitive approaches to encourage adherence in both younger and older demographics (Plans-Rubió *et al.*, 2024).

A study in Brazil identified age as a significant factor in the non-completion of the LTBI treatment cascade. Older patients were at a higher risk of treatment loss, particularly in initial stages, suggesting age-related barriers such as comorbidities or reduced mobility may impact adherence. Despite this, all active TB cases identified during the follow-up occurred among younger individuals, underscoring the need for targeted interventions across different age groups to improve LTBI treatment outcomes (Araujo *et al.*, 2020).

In a Canadian study, each five-year increase in age corresponded to a 6% higher risk of non-initiation, potentially due to concerns over treatment side effects or pre-existing health conditions that complicate treatment adherence. This association emphasizes the need for age-specific approaches in promoting LTBI treatment, such as tailored education on the importance of prevention for older adults and careful management of adverse effects to improve initiation rates (Sullivan *et al.*, 2021).

**2.3.2 Education**

Educational background affects patients' understanding and acceptance of LTBI treatment. In a study of Chinese college students, Yuan *et al.* (2023) reported that a lower educational level was associated with treatment refusal, likely due to misconceptions about TB and the preventive treatment. This finding emphasizes the need for targeted educational interventions that address gaps in understanding, particularly in settings where health literacy may impact treatment decisions.

Another study in China as well highlights that lower parental education levels were significantly associated with a higher likelihood of abandoning TPT among students. Specifically, students whose parents had an education level below technical secondary school were more than twice as likely to discontinue treatment. This association suggests that parents with higher education may better understand the benefits of TPT, thereby encouraging adherence. Improving awareness and educational support for families with lower educational backgrounds may help mitigate this risk factor and enhance treatment uptake (Huang *et al.*, 2018). Followed by another study in China found that education significantly influenced the acceptance of TPT among high school and college students who were contacts of tuberculosis patients. Students with a higher level of knowledge about TB transmission and

treatment were more likely to accept TPT, with those knowledgeable about TB policy being nearly three times as likely to agree to preventive treatment. The findings suggest that targeted TB education efforts, particularly focused on transmission and prevention, can improve TPT uptake, highlighting the critical role of educational interventions in increasing awareness and willingness to initiate treatment (Yang *et al.*, 2018).

### 2.3.3 Healthcare worker/ non-healthcare worker

Healthcare workers' attitudes and practices strongly impact patient decisions regarding LTBI treatment. In Malaysia, Manoharan *et al.* (2023) highlighted that primary healthcare workers' uncertainties around treatment necessity, time constraints, and apprehensions about side effects were significant barriers to treatment uptake. Addressing these concerns through education and support for healthcare workers could foster a more encouraging environment for patients.

Sinnathamby *et al.* (2021) in Singapore identified effective communication by healthcare providers as a critical component for improving patient adherence to LTBI treatment among paediatric cases, underscoring the need for clear provider-patient communication. A study on healthcare workers (HCWs) found that TPT acceptance rates were notably low, with only 16% of those diagnosed with LTBI agreeing to treatment. Key factors for nonacceptance included ambiguous medical recommendations, prior Bacille Calmette-Guérin (BCG) vaccination (which some HCWs believed provided protection or caused false positive results), and concerns about side effects. Additionally, HCWs who did not recall a clear discussion about the importance of LTBI treatment with their caregivers were less likely to accept TPT, highlighting the role of effective communication in influencing treatment decisions.

Improved educational efforts focused on LTBI risks and the benefits of preventive treatment could enhance uptake among HCWs (Bar-Meir *et al.*, 2021).

Another study in South Korea highlighted that HCWs often perceive LTBI as a low-risk condition, viewing it as "not a big deal," which undermines their motivation to initiate treatment. Additionally, factors such as busy work schedules, concerns about side effects, and the inconvenience of long-term medication regimens further contribute to non-initiation. The study suggests that targeted interventions to educate HCWs on the risks of LTBI and the benefits of preventive treatment, along with support for managing side effects and treatment convenience, could improve TPT uptake among HCWs (Yang *et al.*, 2023).

A study in the United States revealed that only 41.1% of HCWs accepted TPT, with acceptance rates particularly low among physicians and researchers. Concerns about treatment side effects, especially from isoniazid, scepticism regarding LTBI risk, and a perception of low necessity for preventive care were common barriers. These findings highlight the need for targeted educational strategies that emphasize the importance and safety of LTBI treatment to increase acceptance among HCWs (Swift *et al.*, 2020).

**2.3.4 Sex**

Studies also highlight sex as a factor influencing LTBI treatment initiation. Research indicates that male gender is a significant factor associated with non-adherence to TB preventive treatment for LTBI. In a study conducted in Catalonia, Spain, male contacts were found to have a 1.75 times higher likelihood of non-adherence compared to female contacts (Plans-Rubió *et al.*, 2024). This disparity may stem from various socio-behavioural and occupational factors. For instance, men often face more work-

related time constraints, which can interfere with consistent healthcare engagement and adherence to long-term medication regimens. Additionally, men may perceive a lower personal health risk, leading to reduced motivation to initiate or complete preventive treatment. Social expectations and roles may also influence this gender difference, as men might be less likely to seek preventive healthcare unless symptoms are present.

### 2.3.5 Comorbidity

The presence of comorbidities also contributes to a lower likelihood of LTBI treatment initiation. Individuals with additional health conditions had a 29.8% non-initiation rate, significantly higher than the 7.6% rate among those without comorbidities. The added complexity of managing multiple health issues, alongside concerns about potential drug interactions and side effects, may discourage both patients and healthcare providers from pursuing preventive treatment. These findings highlight the need for personalized approaches that address the specific concerns of individuals with comorbidities to enhance LTBI treatment uptake (Gullón Blanco *et al.*, 2023). In another study, Noh *et al.* (2019) found that elderly patients with comorbid conditions faced additional barriers to completing treatment, as complex health needs often required balancing multiple medications and managing side effects. These findings suggest that healthcare providers should consider a patient's full health profile when discussing LTBI treatment options.

### 2.3.6 Nationality

Nationality and cultural background play a significant role in LTBI treatment initiation, especially in immigrant populations. Nguyen Truax *et al.* (2020) explored

this factor among Vietnamese immigrants in Southern California and found that cultural concerns regarding medication side effects, transportation issues, and scheduling conflicts served as major barriers. Similarly, in Catalonia, reported that foreign nationality was a significant predictor of non-adherence, with immigrant patients facing additional socio-cultural challenges that affect their treatment decisions. Immigrants, particularly those from high TB-burden countries, also exhibit lower rates of TPT uptake and completion. Factors such as language barriers, limited healthcare access, and cultural beliefs about TB significantly impact adherence to preventive treatment. Many immigrants may also hold misconceptions about TPT or prioritize other immediate healthcare needs, which can lead to lower initiation and completion rates. Addressing these barriers through culturally sensitive education, community support, and improved healthcare access is essential to enhance TPT adherence in immigrant populations (Swift *et al.*, 2020).

### 2.3.7 Healthcare facilities

The characteristics and practices of treatment centres and healthcare providers also shape patients' decisions. A study in Cambodia found that the healthcare facility types significantly influenced non-completion rates for TPT. Individuals who began TPT at referral hospitals were nearly twice as likely to discontinue treatment compared to those who initiated it at local health centres, with an adjusted odds ratio of 1.95. This difference may be due to referral hospitals' focus on complex cases, potentially limiting resources dedicated to preventive care management. In contrast, health centres, often more accessible and integrated within local communities, provided easier follow-up and support for patients. This suggests that decentralizing TPT

initiation to health centres could enhance adherence by reducing logistical and accessibility barriers (An and Khun, 2024).

In Cambodia, individuals who began treatment at referral hospitals were almost twice as likely to discontinue compared to those starting at local health centres. This trend may be due to accessibility challenges or a lack of resources in larger, busier hospitals, which might deprioritize preventive care management. Decentralizing LTBI services to community health centres could improve treatment adherence by making follow-up more convenient and accessible for patients (An and Khun, 2024).

Huang *et al.* (2018) conducted a cross-sectional study in Guangzhou, China, during a school TB outbreak and found that healthcare provider advice significantly influenced treatment adherence. Similarly, Manoharan *et al.* (2023) highlighted the importance of the doctor-patient relationship in Selangor, Malaysia, noting that strong, trust-based relationships between patients and providers could improve treatment uptake. Provider communication, support structures, and consistent patient follow-up emerge as essential components in addressing barriers to LTBI treatment.

**2.3.8 Ethnicity**

Ethnicity has been identified as an associated factor for TPT uptake, with disparities in adherence observed among different ethnic groups. A study in the United States highlighted that ethnicity significantly influenced the discontinuation rates of TPT. Hispanic/Latino ethnicity was associated with a higher risk of discontinuing the 3HP regimen, with a hazard ratio of 1.80. This increased risk could be influenced by socio-cultural factors or challenges such as language barriers, limited access to culturally sensitive care, or misconceptions about the treatment. Addressing these factors with tailored educational support and culturally competent healthcare services may improve

treatment completion rates among Hispanic/Latino individuals (Asare-Baah *et al.*, 2024).

**2.3.9 HIV status**

HIV status has emerged as a crucial factor influencing the uptake of TPT, with multiple studies identifying it as a determinant in whether individuals initiate or complete TPT regimens. The first study by (Maokola *et al.*, 2021) examined factors affecting the uptake of Isoniazid Preventive Therapy (IPT) among people living with HIV (PLHIV) in Tanzania from 2012 to 2016. It found that only 14.4% of the cohort initiated IPT, highlighting an association between HIV status and low initiation rates of TB preventive treatment. While certain demographic factors, such as female sex and clinical factors like WHO stage II, were linked with increased IPT uptake, being on antiretroviral therapy (ART) was associated with decreased IPT initiation (aOR = 0.67). The study underscored the critical need for strategies to address barriers to IPT implementation among PLHIV to mitigate TB risks in high-burden settings (Maokola *et al.*, 2021). However, a second study by (Musaazi *et al.*, 2023) reviewed TPT uptake among PLHIV in Uganda, assessing the impact of a 100-day accelerated campaign in 2019 noted initially uptake was under 25% but surged to over 60% post-campaign, illustrating the campaign's effectiveness. HIV positive status emerged as a factor linked to non-initiation, with notable challenges like drug stockouts and patient adherence issues. These findings point to the need for sustained TPT supply and health worker engagement to improve TPT rates among PLHIV in Uganda (Musaazi *et al.*, 2023).

**2.3.10 District**

Factors such as urban and rural settings play a crucial role in influencing the initiation of TPT. Typically, urban environments offer enhanced access to healthcare services, better transportation options, increased awareness, and improved healthcare infrastructure, all of which facilitate higher initiation and adherence rates. Conversely, individuals in rural settings often face significant barriers, including limited healthcare facilities, geographical isolation, inadequate health awareness, and transportation difficulties, resulting in lower initiation rates of preventive therapies.

According to the Malawi Population-Based HIV Impact Assessment (MPHIA) 2020–2021 survey, a significant disparity was observed between urban and rural settings concerning TPT initiation (Gunde *et al.*, 2024). The survey highlighted those urban dwellers had a higher proportion (30.3%) of TPT initiation compared to individuals residing in rural areas (23.3%). Furthermore, initiation rates were notably higher in major urban centres such as Lilongwe (10.9%) and Blantyre (12.9%). This underscores the critical influence of living in urban areas, likely attributed to the superior availability and accessibility of healthcare services in these regions. The study's findings emphasize the need to address healthcare access inequalities by strengthening rural health services and infrastructure, thereby promoting equitable initiation and adherence to TPT across diverse geographical locations.

According to another study conducted in rural South African primary healthcare clinics, TPT initiation rates were notably low (57.8%) among eligible individuals (Chandra *et al.*, 2022). This low initiation was primarily attributed to structural factors such as staffing shortages, limited integration of HIV/TB services, and gaps in healthcare worker knowledge factors commonly exacerbated in rural settings. Addressing these structural barriers through targeted interventions, including