PROGRAMMATIC MANAGEMENT OF LATENT TUBERCULOSIS INFECTION

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EXECUTIVE SUMMARY

Background

Approximately 1.7 billion people, representing one-fourth of the world's population, are estimated to have latent tuberculosis infection (LTBI). Latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active tuberculosis. A person has latent tuberculosis if he or she is infected with the tuberculosis bacteria but does not have signs of active tuberculosis disease and does not feel ill. Disease may arise when the host immune system is no longer able to contain the pathogenic bacteria. The person is at 5-15% risk of developing active tuberculosis disease during his or her lifetime. A higher risk of falling ill is associated with those who have compromised immune systems, such as people living with HIV, children aged under 5 years who are household contacts of a confirmed case of pulmonary tuberculosis, malnutrition or diabetes, or people who use tobacco.

In accordance with WHO's recommendations, ending tuberculosis requires maintaining and strengthening current tuberculosis control priorities while increasing efforts to identify and treat latent tuberculosis infection among high-risk populations. Malaysia is a middle-income country with intermediate tuberculosis prevalence. To date, there is no prevalence data for latent tuberculosis infection in the general Malaysian population. There is no national system that collects data for LTBI. There also has not yet been a routine screening programme for LTBI among at risk populations in Malaysia. World Health Organization recommends that individual countries determine their own LTBI diagnostic criteria and tests based on local tuberculosis burden and country capacity. A national policy for LTBI management is currently under development and a tailored programmatic management that best suited our local tuberculosis epidemiology could be the key element to strengthen the effort for local tuberculosis control. This technology review was requested by Disease Control Division (TB/Leprosy Sector), Ministry of Health Malaysia to assess the evidence on programmatic management of LTBI in order to identify the optimal approach of its implementation into the national tuberculosis programme given the heterogenous spectrum of national determinants that will influence the decision making process.

Objective/Aim

The objective of this technology review was to evaluate the effectiveness, safety, cost-effectiveness, organisational issues, ethical considerations and social implications of the programmatic management of LTBI.

Results and conclusions

A total of 3751 records were identified through the Ovid interface and PubMed. Additional 13 articles were identified from references of retrieved articles. After removal of irrelevant and duplicate articles, 835 tittles were screened. After reading, appraising and applying the inclusion and exclusion criteria, 33 full text articles were included for qualitative synthesis, which one HTA, 25 systematic reviews (including four systematic reviews of economic evaluation studies), two economic evaluation studies, one cohort and four cross-sectional studies.

Efficacy/Effectiveness

Diagnostic tests for programmatic management of LTBI

There was good level of retrievable evidence to suggest that both TST and IGRA poorly predict the development of active TB (low PPV). Limited evidence had shown that neither test was preferred above the other when assessing progression to TB disease. Among non-BCG vaccinated population, both had similar sensitivity and high specificity to detect LTBI. However, TST displayed lower specificity compared to IGRA in BCG-vaccinated population.

Children

The predictive performance of TST 5mm and IGRA for progression to active TB were similar. Interferon gamma release assays performed better than TST 10mm in predicting the development of active TB. In detection of LTBI, IGRA appeared to outperform TST in low TB burden settings but not high TB burden settings, Interferon gamma release assays had reduced sensitivity and specificity in high TB burden settings. This type of effect modification could be explained by higher frequency of exposure to *M. tuberculosis*, different transmission dynamics, malnutrition, comorbidity, coinfection with HIV or helminthic infection.

Immunocompromised people

There was large variation in the performance of IGRAs compared with TST across different clinical subgroups. QFT-GIT and T-SPOT.TB performed better than TST 5 mm/10 mm in those undergoing haemodialysis and those with hepatitis C. In contrast, QFT-GIT performed significantly worse than TST 10mm in people with HIV/AIDS. Among transplant candidates, IGRAs were shown to be more sensitive and specific. For other clinical subgroups of immunocompromised people the evidence was inconclusive because of the high level of uncertainty around the statistically non-significant effect estimates.

Migrants

Among recently arrived people from countries with a high TB burden, there was no significant difference between the performance of IGRAs and the performance of TST in identifying LTBI.

Preventive Therapy

There was good level of retrievable evidence to suggest that in comparison to placebo, INH regimen of six months or 12 to 72 months, RMP regimen, RMP-INH regimen of 3 to 4 months, RMP-INH-PZA regimen and RMP-PZA regimen were shown to be efficacious in preventing the development active TB. A well tolerated, lesser side effects and shorter duration regimen was associated with better adherence and higher completion rate.

Safety

There was good level of retrievable evidence to suggest that regimens containing PZA had higher hepatotoxicity compared with six months of INH or 12 weeks of RPT-INH [pooled RR 4.59 (95%CI 2.14, 9.85)]. Serious adverse events were documented to be rare. However, RMP-PZA regimens were reported to have the highest risk for gastrointestinal adverse events, and RMP regimens were reported to have the highest risk for central nervous system adverse events.

Cost-effectiveness

Diagnostic test

- Evidence on screening of high risk populations identified the influence of TST and IGRA sensitivity and specificity, TB and LTBI prevalence, treatment effectiveness, duration and treatment costs on cost-effectiveness.
- Based on WTP threshold of USD100,000, from US and Canadian healthcare perspective;

  <u>Migrants</u>
  - The IGRA was found moderately cost-effective in adult migrants, while the TST was dominated by no screening.

  <u>Immunocompromised people</u>
  - Screening of people with HIV was strongly cost effective with a TST and moderately cost effective with an IGRA
  - Neither TST nor IGRA was cost effective for screening of LTBI in renal diseases and diabetic patients, however, the IGRA was found to be the most cost-effective test more often than the TST, if screening had to be performed for renal diseases patients and TST was found to be most cost effective for diabetic patients if screening was done.
  - All ICERs for other immunocompromising conditions were cost prohibitive, although the TST was found to be the most cost-effective test if screening had to occur.

- The economic model for diagnostic tests showed that the best-available options (the most cost-effective strategies) from NHS UK perspective were:
  - In children: TST (≥5 mm) followed by IGRAs if negative
  - In immunocompromised people: IGRAs followed by TST (≥5 mm) if negative

- In the recently arrived population from high TB burden countries: TST alone (≥5 mm)

Preventive therapy

- Three months of weekly RPT-INH was more cost-effective than other WHO-recommended regimens or serial radiographic surveillance, from US and other comparable health system perspective at a WTP threshold of USD50,000 per QALY gained.
- Since RPT-INH-DOT prevented more incident cases of active TB, it was found to be more cost-effective than the same regimen when self-administered (RPT-INH -SAT). The cost-effectiveness of RPT-INH-DOT was strongly driven by treatment completion rates.

Organisational

Identification of target risk groups

- There was fair level of retrievable evidence to suggest that clinical risk groups had no increased risk of LTBI in comparison to general population except for candidates of anti-TNF alpha therapy. However, there was evidence of increased risk of progression to active TB in people with LTBI belonging to clinical risk groups.
- Based on limited evidence, it was found that migrants and close contacts of TB cases had an increased risk of being infected and progressing to active TB disease, depending on socioeconomic and epidemiological determinants.
- For healthcare workers, there was no increased risk of LTBI, but an increased risk of active TB of LTBI positive healthcare workers compared to the general population.
- Based on local published studies, the prevalence of LTBI among healthcare workers and prison employees were 10.6-46% and 81%, respectively. The risk factors for LTBI among healthcare workers were working in clinical areas, duration of employment more than five years, aged ≥ 35, close contacts, having chronic disease, working as a nurse and being male. While the increased risk among prison employees was associated with having worked in the correctional system for 12 months or more and smoking tobacco.

Determinants of LTBI treatment initiation, adherence and completion

- The progressive losses at all stages of the care cascade resulted in low completion rate of LTBI treatment.
- Factors associated with higher compliance rate were people with immune-compromising medical indications, female gender, being part of contact investigations, immigrant or refugee status and shorter LTBI treatment regimens with DOTS.
- Barriers from patients, providers and within the health system exacerbated nonadherence. The main patient-level barriers included fear or experience of adverse effects, the treatment regimen, lack of transportation to clinics, and lack of knowledge of LTBI. Provider-level barriers included insufficient prioritization of and resources for LTBI control in their setting and lack of coordination of LTBI care, while system-level barriers included a lack of prioritization of LTBI control by governments.

Interventions to improve LTBI treatment initiation, adherence and completion

- Incentives may have positive effects on adherence in the short term, particularly for marginalized populations such as drug users, recently released prisoners, and the homeless
- Cultural case management which included targeted and culturally appropriate programming that was focused on specific population was also found to be effective.
- Education approaches with innovative strategies for both LTBI patients and health care workers may improve adherence.

Training

- The administration and interpretation of the LTBI diagnostic tests requires adequate training for healthcare workers to guarantee the reliability of the results.
- Education and training of healthcare workers designed to increase the knowledge of TB/LTBI and raise awareness of the disease are important. It will help in informing and effectively treating TB patients, thereby contributing to the control of LTBI.

Ethical considerations

LTBI management is a preventive, rather than a curative measure, hence benefits for otherwise healthy people need to outweigh risks. In programmatic management of LTBI, both individual aspects and TB control through prevention of transmission should be considered. The policy development should address three distinctive characteristics of LTBI management; potentiality (the risk of future development of active disease and not the current risk), uncertainty (current limitations imposed by scientific and technological methodology, both diagnosis and treatment of LTBI) and vulnerability (poverty and social marginalisation). Testing for LTBI should be done with the intention of offering treatment when the screening is positive. Screening strategies must be accompanied by appropriate individual and community education to avoid unintended harm for tested individuals.

Social implication

Health-related quality of life

- There was no meaningful change in HRQOL among subjects treated for LTBI between time of diagnosis and treatment completion in comparison to subjects treated for TB disease or general population (no decrement detactable by either SF-36 or EQ-5D scores).
- However, three themes emerged for the mental health concerns; ambiguous threat, fear of being contagious and future uncertainties.

Recommendation

The tuberculin skin test (TST) and interferon gamma release assays (IGRA) or a combination of both tests may be used to diagnose LTBI. The choice of test should be based on target risk group and available resource. Screening of LTBI should consider availability of and accessibility to diagnostic tests, the intention to provide LTBI treatment (if appropriate), the implementation of interventions promoting the uptake and completion of LTBI screening procedures.

Provision of LTBI treatment should be using treatment regimens that are of shorter duration and lesser toxicity in order to promote adherence and enhance completion by different target groups. The selection of LTBI treatment regimen may be based on an individual risk assessment. The following regimens can be considered: isoniazid alone (for 6–9 months), rifampicin alone (for 3–4 months), isoniazid and rifapentine (for 3 months), isoniazid and rifampicin (for 3–4 months).

Methods

Electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1946 to December 15, 2019, EBM Reviews - Cochrane Central Register of Controlled Trials – November 2019, EBM Reviews - Cochrane Database of Systematic Reviews – 2005 to December 2019, EBM Reviews - Health Technology Assessment – 4th Quarter 2016, EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2016. Searches were also run in PubMed. Google was used to search for additional web-based materials and information. Grey literature and published guidelines and reports at the US Centres for Disease Control and Prevention (CDC), ECDC, WHO, and the International Union Against Tuberculosis and Lung Disease (IUATLD) were also searched. Additional articles were identified from reviewing the references of retrieved articles. No limits were applied. The search strategies used in the major databases are provided in Appendix 1. The searches were undertaken on 11 July 2019 and were updated on 17 December 2019 using the same strategies. Supplementary searches were undertaken between 11 July 2019 and 10 November 2019. Last search was conducted on 17 December 2019.

PROGRAMMATIC MANAGEMENT OF LATENT TUBERCULOSIS INFECTION

1. BACKGROUND

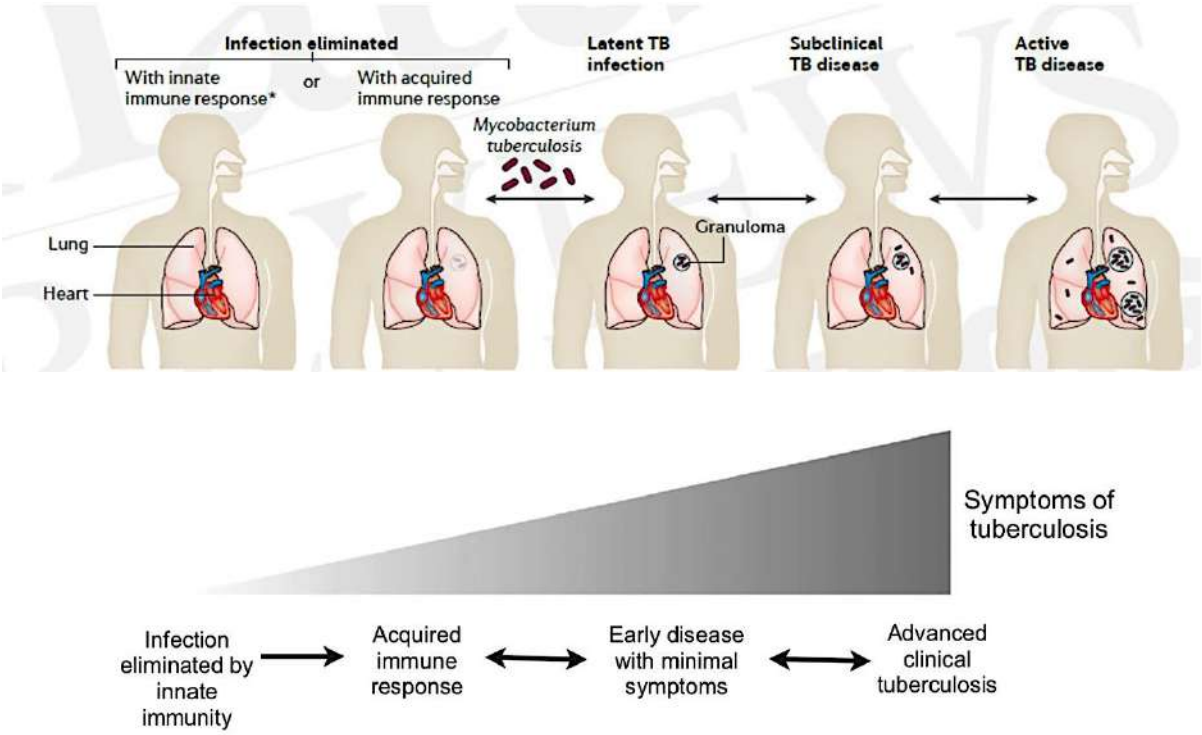
Tuberculosis, famously known throughout history by many names; 'Consumption', 'Great White Plaque', 'White Death', has been a scourge and one of the most feared diseases. Upholding its reputation as one of the most notorious serial killers of mankind, it evokes despair as well as horror of the condition and may have killed more people than any other microbial pathogen. Despite it is curable and preventable nowadays, tuberculosis continues to cause widespread public health concern. Tuberculosis is ranked in the top ten causes of death worldwide.[1] Ten million people were estimated to have developed tuberculosis in 2017 and 1.3 million died from the disease with additional 300,000 deaths from tuberculosis among HIV-positive people.[1] The 2017 facts and figures also reported an estimated one million children became sick with tuberculosis disease with 230 000 fatal cases (including children with HIV associated TB cases).[1] According to 2018 WHO Global Tuberculosis Report, the tuberculosis cases occured in every countries and all age groups. Nevertheless, national epidemic among countries varied widely. Majority of new tuberculosis cases occurred in the South-East Asia and Western Pacific regions (62% of new cases), followed by the African region (25% of new cases). Large percentage of cases (90%) were adults (aged ≥15 years) and 9% were people living with HIV (72% in Africa).[2] Based on WHO report, the provision of tuberculosis prevention, diagnostic and treatment services has received more than doubled the funding since 2006, however, continues to fail to reach its target on what is needed. Furthermore, the financial requirement for 2018 in 119 low and middle-income countries was an estimated US$10.4 billion with the receiving funding only managed to reach US$6.9 billion, leaving a gap of US$3.5 billion. The annual gap will widen to US$5.4 billion in 2020 and to at least US$6.1 billion in 2022 if there is no further increment in funding.[2]

The prolonged global neglect of tuberculosis disease has long ended with 1993 WHO's declaration of tuberculosis as global public health emergency. Despite efforts for global expansion of tuberculosis care and control, the rate of reduction of tuberculosis incidence has remained very slow, at approximately 2% per year.[2] The new post-2015 Global TB Strategy known as End TB Strategy 2016-2035 which was approved by the World Health Assembly in 2014 and the Sustainable Development Goals adopted by the United Nations General Assembly in 2015 have set ambitious targets to intensify action against tuberculosis epidemic. Ending the global tuberculosis epidemic by 2035 is the ultimate goal with accompanying milestones at year 2020 and 2025. In order to accomplish that, three targets need to be achieved: a 95% decline in TB mortality, a 90% reduction in TB incidence (down to less than 10 cases per 100,000 at global level) and 0% of tuberculosis affected households that experience catastrophic costs due to tuberculosis.[2, 3] These can only be possible if the incidence of tuberculosis is reduced at the accelerated rate of 10% per year and

the mortality rate is reduced to 6.5% by 2025.[4] Such levels will be achievable if the provision of tuberculosis control and care is within the context of progress towards universal health coverage (UHC), combined with multisectoral action to address the social and economic elements that drive tuberculosis epidemic.

Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis*.[1] It most commonly affects the lungs. The spreading of disease from human to human happens through inhalation of the germs which were expelled by infected person via the act of coughing, sneezing and spitting. The probability of transmission from one person to another depends upon several factors. These include the number of infectious droplets expelled by the carrier, the effectiveness of ventilation, the duration of exposure, the virulence of the *M. tuberculosis* strain and the level of immunity in the uninfected person.[5] People with active tuberculosis disease can infect 10–15 other people through close contact over the course of a year. Without proper treatment, on average 45% of HIV-negative people with tuberculosis and nearly all HIV-positive people with TB will die.[1] Infection occurs when the inhaled droplet nuclei containing tubercle bacilli reach the alveoli of the lungs. Within two to eight weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control. Starting from week eight onward, the person most likely tests positive for latent tuberculosis infection (LTBI). The progression from latent tuberculosis infection to tuberculosis disease occurs when the granuloma breaks open and the tuberculosis bacteria multiply, then the person becomes sick with tuberculosis disease and may be infectious. This progression can occur immediately after infection, many years later or not at all. When the tuberculosis escapes from granuloma and begins to destroy person's lungs, it is called pulmonary tuberculosis. Tuberculosis bacteria can also enter the bloodstream and travel to other parts of the body causing extrapulmonary tuberculosis.[6]

Latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active tuberculosis.[7] A person has latent tuberculosis if he or she is infected with the tuberculosis bacteria but does not have signs of active tuberculosis disease and does not feel ill. Disease may arise when the host immune system is no longer able to contain the pathogenic bacteria. In immunocompetent individuals, only a small minority of those with LTBI will develop symptomatic disease. Advanced imaging has suggested that tuberculosis infection outcomes represent a spectrum of immunological responses to the infecting mycobacteria. At one end of the spectrum, a person may completely clear all viable bacteria. At the other end, bacterial replication may result in fulminant active TB (sepsis) (Figure 1).[8]



G.J. Fox et al. / International Journal of Infectious Diseases 56 (2017)

Figure 1: The spectrum from latent tuberculosis infection to disease

Approximately 1.7 billion people, representing one-fourth of the world's population, are estimated to have LTBI.[2, 9] They are at risk of developing active tuberculosis disease during their lifetime. The lifetime risk of falling ill with tuberculosis is 5-15%.[2] A higher risk of falling ill is associated with those who have compromised immune systems, such as people living with HIV, children aged under 5 years who are household contacts of a confirmed case of pulmonary tuberculosis, malnutrition or diabetes, or people who use tobacco.[2, 8] Majority of people develop active tuberculosis disease following re-activation of latent tuberculosis infection within the first two to five years after initial infection.[10] An estimated 5-7% of new tuberculosis cases in low burden countries are due to transmission from individuals with reactivated LTBI, with most cases primarily affecting family members and close social contacts.[11] Individuals with LTBI are the reservoir of *Mycobacterium tuberculosis* in a population and as long as this reservoir exists, the elimination of tuberculosis will not be feasible. Major escalation in term of scope and scale of tuberculosis control must take into account scaling up management of LTBI. Based on this rationale, prevention of active tuberculosis disease by treatment of LTBI through programmatic management has become a critical component of the first pillar of the new post-2015 End TB Strategy.[7]

Malaysia has a population of 32 million, is a middle-income country with intermediate tuberculosis prevalence. The incidence rate of tuberculosis disease in Malaysia remained stagnant in the early 2000s. However, there was a gradual increase seen through 2002 - 2017 period and has reached 93 cases per 100,000 population in 2017.

The rate declined 1.3% in 2018 with an annual incidence rate of 78.6 per 100,000, recording a total of 25 837 cases compared to 26 168 cases in the previous year. The migrants accounted for 12.5% of active tuberculosis cases. An increment was observed in tuberculosis death rate, from 6.5 per 100,000 population in 2017 to 6.6 per 100,000 population in 2018. Sabah recorded the highest number of deaths with 376 cases.[12, 13]

The national programme for tuberculosis was started in 1961, in the midst of major tuberculosis epidemic in Malaysia. It was initiated as vertical programme then later reorganized to horizontal/integrated programme in 1994 following WHO's recommendation. Among the strategies implemented under the National Tuberculosis Control Programme include BCG vaccination programme (1961) and Observed Treatment Short Course (DOTS)(1984). During the early period of its implementation, the programme had massive success with tuberculosis control. There was a significant reduction in reported tuberculosis cases, from 350 cases per 100,000 population in 1961 to less than 100 cases per 100,000 population in the 1980s.[14] An approximately 3.6% reduction per year over 20 years period. However, since 1990 the rate of reduction of cases slowed down and became stagnant for a while before it slowly rising up again. The worsening of local tuberculosis burden is due to factors like multidrug-resistant tuberculosis (MDR-TB), HIV co-infection and migration.[15, 16] In order to intensify the nation fight against tuberculosis, the National Strategic Plan (NSP) for Tuberculosis (2011-2015) and (2016-2020) were developed with the later aiming to align the national tuberculosis response with the Regional Framework for Action on Implementation of the End Tuberculosis Strategy in the Western Pacific.[14, 17] In accordance with WHO's recommendations, ending tuberculosis requires maintaining and strengthening current tuberculosis control priorities while increasing efforts to identify and treat latent tuberculosis infection among high-risk populations. To date, there is no prevalence data for latent tuberculosis infection in the general Malaysian population. There is no national system that collects data for LTBI. There also has not yet been a routine screening programme for LTBI among at risk populations in Malaysia. World Health Organization recommends that individual countries determine their own LTBI diagnostic criteria and tests based on local tuberculosis burden and country capacity.[7] A national policy for LTBI management is currently under development and a tailored programmatic management that best suited our local tuberculosis epidemiology could be the key element to strengthen the effort for local tuberculosis control.

This technology review was requested by Disease Control Division (TB/Leprosy Sector), Ministry of Health Malaysia to assess the evidence on programmatic management of LTBI in order to identify the optimal approach of its implementation into the national tuberculosis programme given the heterogenous spectrum of national determinants that will influence the decision making process.

2. OBJECTIVE / AIM

The objective of this technology review was to evaluate the effectiveness, safety, cost-effectiveness, organisational, ethical and social issues of the programmatic management of LTBI.

3. TECHNICAL FEATURES

3.1 Definition

Programmatic management of LTBI is defined as management of latent tuberculosis with input from different components responsible for tuberculosis prevention and control involving **specific risk groups** based on the **underlying epidemiology** and **burden of tuberculosis** and the **availability of resources**. These components include detection of individuals with LTBI, treatment, surveillance as well as monitoring and evaluation of the programme's performance.[7, 18]

3.2 Components of Programmatic Management of LTBI

a. Identification of groups at risk [7]

There are two broad categories of risk groups;

- **LTBI infection risk group** -people with an increased risk of LTBI but without an increased risk of progression to active tuberculosis.[19-21]
- **LTBI progression risk group** -people with LTBI who have a higher risk of progression to active tuberculosis compared to others with LTBI.[22-26]
- The groups are further divided into the following;
  - Clinical risk groups
  - Population risk groups
  - Vulnerable group
  - Occupational risk group

Based on WHO recommendation, in selecting at-risk populations for programmatic management of LTBI, consideration should be given to the epidemiology and pattern of transmission of tuberculosis in the country, so that treatment offers lasting protection.[7]

b. Diagnostic approach for LTBI detection [7]

The selection of diagnostic test(s) and the diagnostic algorithm most appropriate for each target group.

Currently, there is no gold standard diagnostic test for identification of LTBI. The available screening tests for LTBI provide an indirect assessment of the presence of LTBI by relying on a host's immunological response to tuberculosis antigens.[27] The tuberculin skin test (TST) and interferon gamma release assays (IGRA) or a combination of both tests can be used to diagnose LTBI. None of the these tests can accurately differentiate between people with LTBI and people with active TB, between recent and remote (> 2-5 years) LTBI or between cleared and persistent infection.[28]

c. Provision of LTBI treatment [7]

LTBI treatment aims to decrease the probability of progression to active tuberculosis but it may cause drug-related adverse events. When providing treatment at the individual level, careful consideration must be given to the risks and benefits.

d. Implementation of patient-centered strategies for service delivery[7]

Patient-centred case management that can be considered as part of an integrated strategy for LTBI treatment provision includes a combination of ;

- material incentives and enablers
- counselling and education
- peer-based support and culturally-sensible approaches

e. Effective health education and communication with target groups and healthcare providers. [7]

Comprehensive educational approach is designed to increase awareness about the importance of detecting and treating LTBI among specific target groups (policymakers, healthcare workers, medical students, community workers, risk groups and general population).

d. Programme monitoring and evaluation [7]

Reporting and monitoring procedures need to be in place in order to measure the effect and appropriateness of programmatic management of LTBI. The following measures should be taken into consideration to ensure effective monitoring and evaluation system.

- Development of appropriate recording and reporting tools
- Proper recording and reporting from both the private and public sectors
- Measurement of standardised or clear defined performance indicators (Table 1)

- Performing regular programme monitoring to enable an overall assessment of programme implementation in order to inform decision-making for programme implementation.
- Monitoring and evaluation systems that are aligned with national patient monitoring and surveillance systems
- National procedures that are preferably aligned with global and regional monitoring and evaluation frameworks, to allow inter-country comparability.
- The use of electronic case-based monitoring to facilitate recording and reporting for LTBI management.

Table 1 : Monitoring and evaluation indicators for programmatic management of LTBI recommended by WHO [7]

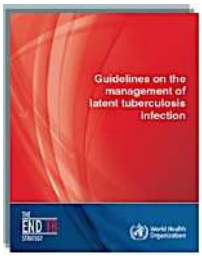
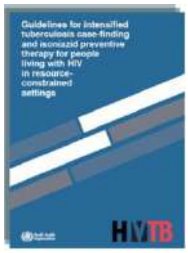
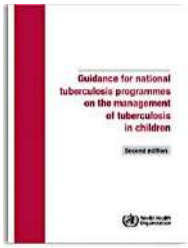
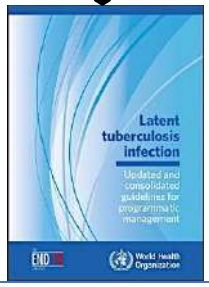
	CORE GLOBAL AND NATIONAL INDICATORS
1	Proportion of children < 5 years who are household contacts of TB cases (according to national guidelines) who have completed investigations for TB
2	Proportion of children < 5 years old who are household contacts of TB cases (according to national guidelines) who are eligible for TB preventive treatment who have started treatment
3	Proportion of eligible people living with HIV, newly enrolled in HIV care and started on TB preventive treatment
	CORE NATIONAL INDICATORS
4	Proportion of eligible individuals in at-risk populations (as defined by national guidelines) tested for LTBI infection
5	Proportion of individuals in at-risk populations (according to national guidelines) with a positive LTBI test who are eligible for TB preventive treatment and who have started treatment
6	Proportion of eligible individuals in at-risk populations (according to national guidelines) with a positive LTBI test who started TB preventive treatment and completed the course
7	Proportion of eligible people living with HIV who completed a course of TB preventive treatment
8	Proportion of children < 5 years who are household contacts of TB cases (according to national guidelines) who have completed a course of TB preventive treatment
	OPTIONAL INDICATOR
9	TB incidence rate in at-risk populations (as defined by national guidelines)

3.3 WHO Key Recommendations For Programmatic Management LTBI [7, 29]

- The programmatic management of LTBI should consider the underlying epidemiology of tuberculosis, the burden of LTBI among risk groups, the availability of national policies and surveillance as well as effective health service delivery system and resources. Hence, it requires establishing national policies and legal frameworks, as well as close collaboration and harmonisation across the different services.
- The risk of progression is highest in young children, the immunosuppressed and shortly after infection. Therefore, these individuals should be targeted for LTBI screening and treatment. In most cases, this would lead to an "**intention to test is intention to treat**" approach, with an exception for close contacts of multidrug-resistant TB cases, in which testing may be used to inform "**watchful waiting**".
- WHO recommends the management of LTBI among at risk populations in upper-middle and high-income countries with **low tuberculosis burden** (estimated annual tuberculosis incidence rate of $<$ 100 per 100,000 population).[29] In these countries, systematic LTBI testing and treatment is strongly recommended for a wider range of clinical risk groups: patients with silicosis, patients initiating anti-tumour necrosis factor (TNF) treatment, patients on dialysis, and patients preparing for organ and haematological transplantation.
- WHO also recommends the management of LTBI for people living with HIV[30] and for children under five years who are household contacts of people with pulmonary tuberculosis[31] in all settings including those with a **high tuberculosis burden** (estimated annual tuberculosis incidence rate of ≥ 100 per 100,000 population).
- WHO conditionally recommends systematic testing and treatment of LTBI should be considered for prisoners, health workers, immigrants from high tuberculosis burden countries, homeless persons and illicit drug users.

The cut-off point for defining a country as having a low or a high tuberculosis burden was set by consensus of the previous Guideline Development Group (GDG). The two-prong policy based global approach according to WHO recommendations for management of LTBI are presented in Table 2.

Table 2: WHO Recommendations For Management of LTBI Based On Category of Countries

	High-income & upper-middle income countries with an estimated TB incidence rate <100 per 100,000 population (low TB burden)	Resource-limited and and other high and middle-income countries with an estimated TB incidence rate ≥ 100 per 100,000 population (high TB burden)
Indicated at risk population	▪ People living with HIV ▪ Adults & children who are house contacts of PTB cases ▪ Clinical indications: patients with silicosis; patients initiating anti-TNF treatment; patients on dialysis; patients preparing for organ or haematological transplantation	▪ People living with HIV ▪ Children aged < 5 years who are household contacts of a pulmonary TB case
Testing algorithm	▪ Exclude active TB using TB investigations according to national guidelines ▪ A positive IGRA or TST result is required to diagnose LTBI	▪ Exclude active TB using TB investigations according to national guidelines ▪ An LTBI test is not required prior to LTBI treatment, but is encouraged for people living with HIV ▪ IGRA should not replace TST
Treatment options	▪ 6 months daily isoniazid ▪ 9 months daily isoniazid ▪ 3 months weekly rifapentine plus isoniazid ▪ 3-4 months daily isoniazid plus rifampicin ▪ 3-4 months daily rifampicin	▪ 6 months daily isoniazid
WHO Guidelines	 Guidelines on the management of latent tuberculosis infection	 Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings  Guidance for national tuberculosis programmes on the management of tuberculosis in children  Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries 

TB – tuberculosis, PTB – pulmonary tuberculosis

4. METHODS

4.1 Searching

Electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1946 to December 15, 2019, EBM Reviews - Cochrane Central Register of Controlled Trials – November 2019, EBM Reviews - Cochrane Database of Systematic Reviews – 2005 to December 2019, EBM Reviews - Health Technology Assessment – 4th Quarter 2016, EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2016. Searches were also run in PubMed. Google was used to search for additional web-based materials and information. Grey literature and published guidelines and reports at the US Centres for Disease Control and Prevention (CDC), ECDC, WHO, and the International Union Against Tuberculosis and Lung Disease (IUATLD) were also searched. Additional articles were identified from reviewing the references of retrieved articles. No limits were applied. The search strategies used in the major databases are provided in Appendix 1. The searches were undertaken on 11 July 2019 and were updated on 17 December 2019 using the same strategies. Supplementary searches were undertaken between 11 July 2019 and 10 November 2019. Last search was conducted on 17 December 2019.

4.2 Study Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion Criteria

Population/ Problem	Latent tuberculosis infection (LTBI)
Interventions	Programmatic management of LTBI ▪ Identification of at-risk population ▪ Diagnostic approach for LTBI detection; - Mantoux test/tuberculin skin test (TST) - Interferon gamma release assays (IGRAs); 2 types: i. QuantiFERON®-TB Gold-in-Tube (QFT-GIT) [old version QuantiFERON® -TB Gold(QFT-G)] ii.T-SPOT.TB ▪ Provision of LTBI treatment ▪ Implementation strategies; patient-centred management for service deliver, communication

	and health education with target groups and healthcare providers ▪ Programme monitoring and evaluation
Comparators	No comparator or Existing national TB control programme
Outcomes	i. Efficacy/effectiveness <u>Main outcomes</u> ▪ reduction in active TB cases ▪ reduction in active TB mortality ▪ reduction in transmission to others <u>Specific outcomes</u> ▪ performance of diagnostic tests - predictive values for IGRAs and TST for progression to active TB - degree of association of IGRA and TST results with previous exposure to MTB (defined by proximity, duration or dose-response gradient) - specificity IGRAs and TST in healthy populations - concordance/discordance between IGRAs and TST ▪ efficacy of treatment - ability to reduce the probability of progression to active TB - adherence and completion of treatment by different target groups ii. Safety ▪ frequency and severity of drug-related adverse events iii. Economic implication (cost, cost-effectiveness) iv. Organisational issues ▪ resources utilisation ▪ training requirement ▪ service delivery - accessibility of target risk groups to LTBI screening (case detection and contact investigation) and treatment - feasibility for mandatory screening and intention to provide treatment (if appropriate) to target groups - best approach for clinical monitoring of adverse events - interventions to improve screening and treatment uptake and completion

	- potential integration into existing health programmes ▪ barriers for programmatic management v. Ethical and legal implications ▪ ethical challenges ▪ existing legislation and potential changes needed vi. Social ▪ patient preferences ▪ acceptability ▪ knowledge and perception ▪ quality of life
Study designs	Health Technology Assessment (HTA), Systematic Review (SR), Randomised Controlled Trial (RCT), Non-randomised controlled trial, Cohort study, Case-control study, Cross-sectional study, Economic Evaluation
	English full text articles

Exclusion Criteria

Study design	Studies conducted in animals, narrative reviews, case series or case report
	Non English full text articles

Data were extracted from the full text articles and summarised in evidence table as in Appendix 2.

5.0 RESULTS AND DISCUSSION

5.1 Search results

A total of 3751 records were identified through the Ovid interface and PubMed. Additional 13 articles were identified from references of retrieved articles. After removal of irrelevant and duplicate articles, 835 tittles were screened. Of these, 94 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria, 33 full text articles were included for qualitative synthesis. A total of 61 full text articles were excluded due to irrelevant study design (n=6), already included in the selected systematic reviews (31), irrelevant population (n=8) and irrelevant outcome measure(s) (n=16). The 33 full text articles comprised of one HTA, 25 systematic reviews (including four systematic reviews of economic evaluation studies), two economic evaluation studies, one cohort and four cross-sectional studies. The selection of studies is showed in Figure 2.

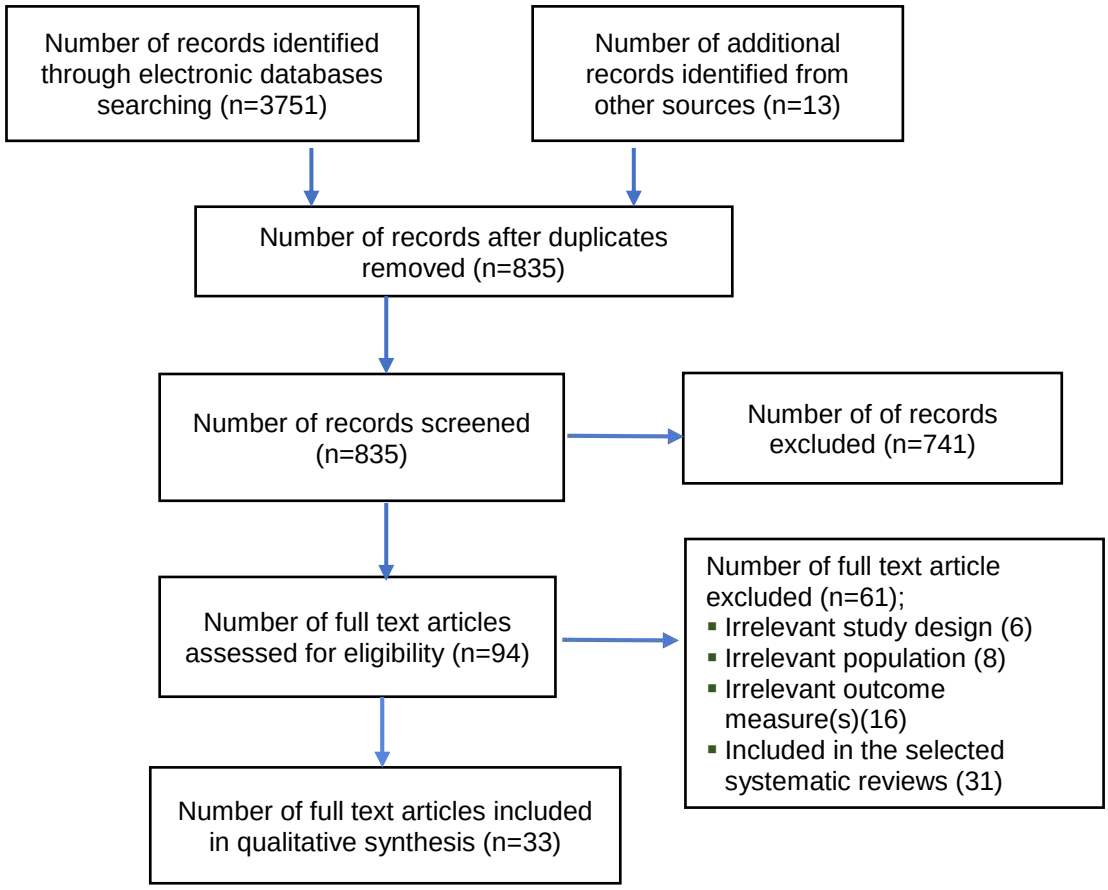


Figure 2: Flow chart of study selection

Assessment of risk of bias in included studies

Risk of bias was assessed using Critical Appraisal Skills Programme (CASP) checklist for Systematic Review (SR) and Economic Evaluation studies. For RCT, risk of bias for each study was assessed using the Cochrane Collaboration's tool for assessing risk of bias (Higgin 2011).[32] These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates YES (low risk of bias)
?	Indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

The results of risk of bias of included studies are summarised in Figure 3 and 4. The SRs displayed low risk of bias while the cohort study was associated with moderate risk bias. Systematic reviews of economic evaluation studies were not included in the risk of bias assessment.

Assessment for Systematic Review Using Critical Appraisal Skills Programme (CASP) Checklist

Criteria assessed **EFFECTIVENESS:**	Author look for appropriate paper?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
WHO (2015)[33]	+	+	+	+
Auguste P et al. (2016)[34] (2019)[35]	+	+	+	+
Greenaway C et al. (2018)[35]	+	+	+	+
Nasiri MJ et al. (2019)[36]	+	+	+	+
Zenner D et al. (2017)[37]	+	+	+	+
Sharma et al. (2013)[38]	+	+	+	+
SAFETY				
Pease C et al. (2018)[39]	+	+	+	+
Stagg et al. (2014)[40]	+	+	+	+
ORGANISATIONAL ISSUES				
Campbell JR et al. (2016)[48]	+	+	+	+
Campbell JR et al. (2015)[49]	+	+	+	+
Campbell et al. (2015)[50]	+	+	+	+
Fox et al. (2013)[51]	+	+	+	+
Kotila S et al. (2016)[52]	+	+	+	+
Schepisi et al. (2015) [53]	+	+	+	+
Patra J et al. (2015) [54]	+	+	+	+
Freeman et al.[55]	+	+	+	+
Alsdurf et al. (2016)[60]	+	+	+	+
Sandgren et al. (2016)[61]	+	+	+	+
Stuurman et al. (2016)[62]	+	+	+	+
Liu Y et al. (2018)[63]	+	+	+	+
SOCIAL IMPLICATION				
Bauer M et al. (2013)[69]	+	+	+	+

Figure 3: Summary of risk of bias assessment for systematic review

Assessment for Cohort Studies Using Critical Appraisal Skills Programme (CASP) Checklist

Criteria assessed SOCIAL IMPLICATION	Selection of cohort	Exposure accurately measured	Outcome accurately measured	Confounding factors	Follow-up of subjects
Bauer M et al. (2015)[70]	+	+	+	?	+

Figure 4: Summary of risk of bias assessment for Cohort Studies

5.2 Effectiveness

5.2.1 Performance of diagnostic test

A commissioned systematic review by WHO (2014) [33 level 1] was conducted to compare TB incidence following a positive test result versus a negative test result of TST and IGRA. Twenty-nine studies were included in the review. Majority (65%) of the studies were prospective cohort studies and reported from high- or upper middle-income countries with a TB prevalence <100 per 100 000 population (72%). The majority of studies (about 50%) reported to have followed up their study participants for an average of 20-35 months. The TST and IGRA were compared to each other in the same study population (head-to-head analysis). The pooled estimate risk ratio (RR) was 2.58 (95% CI 1.72, 3.88) for TST and 4.94 (95%CI 1.79,13.65) for IGRA. Three prospectively followed cohorts reported on the predictive utility of the TST versus IGRA for progression to active tuberculosis amongst immunocompromised patients [pooled RR 2.96 (0.38, 23.18)] for TST and 5.95 (0.57, 62.05) for IGRA. Based on risk of progression to active TB among amongst TB case-contacts, the pooled RR for TST was 2.3 (95%CI 1.76, 3.70) and for IGRA was 5.96 (95%CI 0.57, 62.05). It was reported that the observed differences in the effect estimates may be due to differences in study population rather than reflecting true differences between the tests. The authors concluded that there was little evidence that either the TST or IGRA test should be preferred above the other when assessing progression to TB disease.[33] level 1

A systematic review and meta-analysis conducted by Auguste P et al. (2016), aimed to compare two types of IGRAs QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and T-SPOT.TB with TST for identification of LTBI, by predicting progression to a diagnosis of active TB and previous TB exposure in three subgroups: children, immunocompromised people and those recently arrived from countries with high TB burden.[34 level 1] The pooled data had shown that there were only small percentages of those with positive results progressed to active TB across all studied populations, regardless of type of screening used (Table 3).

In their updated meta-analysis, Auguste et al.(2019) developed a bivariate Bayesian modelling framework to derive separately the sensitivity and specificity of TST and IGRA tests for identifying LTBI by predicting its progression to active TB in children, in immunocompromised individuals and in recent migrants (<5 years) from high TB incidence countries (≥40 cases per 100 000 population). In children population, the pooled estimates showed that TST (5mm) had the highest sensitivity [0.79, 95% Credible Interval (CrI) 0.55, 0.95] for predicting progression to active TB, and that TST (15mm) had the highest specificity (0.94, 95%CrI 0.79, 1.00). QFT-GIT had pooled sensitivity and specificity of respectively 0.67 (95%CrI 0.35, 0.90) and 0.73 (95%CrI 0.36, 0.93). No studies compared T-SPOT.TB with TST in the child population. In the immunocompromised population, the pooled estimates showed that IGRAs in general had a higher sensitivity for predicting progression to active TB than TST. QFT-GIT had the highest sensitivity [0.51 (95%CrI 0.20, 0.82)], and TST (10mm) had the highest specificity [0.87 (95%CrI 0.76, 0.97)]. In general, among recent arrivals from high burden countries, the TST (5mm) had the highest pooled sensitivity [0.90 (95%CrI 0.78, 0.98)] compared with QFT-GIT [0.70 (95%CrI 0.46, 0.88)] and T-SPOT.TB [0.76 (95%CrI 0.47, 0.93) in this subgroup. Specificity was highest using the TST (15 mm) [0.76, (95%CrI 0.59, 0.92)] and lowest when using TST (5mm) [0.34, 95%CrI 0.04, 0.58)] (Table 4). In the subgroup HIV population, pooled information from the head-to-head studies showed that testing with QFT-GIT had the highest pooled sensitivity [0.59, (95%CrI 0.15, 0.92)] and specificity [0.85 (95%CrI 0.51, 0.96)].[35] level 1

Table 3: Percentage of positive and negative results for TST 5mm, TST 10mm, QFT-GIT and T.SPOT tests that progress to active TB and the respective overall CIR

Population	Progression to active TB											
	TST 5mm (+)(%)	TST 5mm (-)(%)	Overall CIR (95%CI)	TST 10mm (+)(%)	TST 10mm (-)(%)	Overall CIR (95%CI)	QFT-GIT (+)	QFT-GIT (-)	Overall CIR (95%CI)	T.SPOT (+)	T.SPOT (-)	Overall CIR (95%CI)
Children	1.57	0.50	**3.14** (1.68-5.94)	2.81	0.78	**3.60** (1.93-6.71)	1.86	0.46	4.01 (2.51-6.40)	-	-	-
Immuno-compromised patients	-	-	-	2.06	0.74	**1.86** (0.58-5.92)	3.02	0.65	4.65 (1.87-11.51)	10.37	2.04	5.08 (3.09-8.33)
Recent arrivals from high burden countries	-	-	-	3.12	0	**3.42** (0.20-57.83)	3.13	0.55	5.69 (1.86-17.28)	3.31	1.69	1.96 (0.40-9.53)

Table 4: Pooled estimates of sensitivity and specificity for TST and IGRA to predict LTBI progressing to active TB

Population	Progression to active TB							
	Sensitivity (95%CrI)				Specificity (95%CrI)			
	TST			IGRA	TST			IGRA
	TST 5mm	TST 10mm	TST 15mm	QFT-GIT	TST 5mm	TST 10mm	TST 15mm	QFT-GIT
Children	**0.79** (0.55–0.95)	**0.54** (0.25–0.79)	**0.29** (0.00–0.65)	**0.67** (0.35–0.90)	**0.51** (0.20–0.76)	**0.77** (0.57–0.92)	**0.94** (0.79–1.00)	**0.73** (0.36–0.93)
Immuno-compromised patients	**0.38** (0.14–0.69)	**0.11** (0.15–0.35)	-	**0.51** (0.20–0.82)	**0.81** (0.66-0.89)	**0.87** (0.76–0.97)	-	**0.86** (0.64–0.96)
Recent arrivals from high burden countries	**0.90** (0.78–0.98)	**0.77** (0.58–0.90)	**0.59** (0.30-0.80)	**0.70** (0.46–0.88)	**0.34** (0.04–0.58)	**0.59** (0.37–0.79)	**0.76** (0.59-0.92)	**0.65** (0.43–0.82)

Greenaway C et al. (2018) conducted a systematic review to determine effectiveness of diagnostic tests for LTBI.[36 level 1] The authors identified three systematic reviews that assessed the properties of the diagnostic tests used in LTBI screening. Two systematic reviews evaluated the performance of TST and IGRA in populations not vaccinated with bacillus Calmette–Guérin (BCG) and found that the TST, at a 10 mm cut-off, and IGRA had similar and good sensitivity (79%) and high specificity (>97%) to detect LTBI. The evidence showed that the TST was limited by lower specificity (59%) in BCG-vaccinated populations. The third systematic review estimated the ability of TST or IGRA to predict the risk of developing active TB among those with LTBI. The positive predictive value (PPV) and the pooled incidence rate ratios (IRR) estimated by comparing test-positive and -negative cohorts were similar for TST and IGRA. Both predicted the development of active TB poorly. The PPV (range) and the IRR (95% CI) were, respectively, 1–7% and 2.07 (1.38, 3.11) for the TST and 0–13% and 2.40 (1.26, 4.60) for the IGRA.[36 level I]

Nasiri MJ et al. (2019) conducted a systematic review and meta-analysis to evaluate the diagnostic accuracy of TST and IGRA for LTBI among patients preparing for organ transplantation.[37 level I] Sixteen cohort studies conducted in ten different countries, were included in the review. The average length of follow-up was 15 months. The accuracy measures of TST and IGRA from nine studies were pooled and meta-analysed. In comparison, IGRAs were shown to be more sensitive and specific than TST in diagnosing LTBI among transplant candidates as shown in Table 5. The influence of BCG vaccination and/or *M.tuberculosis* exposure were evaluated in 13 studies. The positive result of IGRAs/TST was associated with M.tuberculosis exposure only in 15% of the studies. A poor agreement between two tests within

individual study was observed [statistical agreement between IGRA and TST: 0.06-0.49 (95%CI 0.02-0.83)].[37] level 1

Table 5: Pooled accuracy measures for LTBI diagnosis in transplant candidates by IGRA and TST assays

Type of test	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	DOR (95%CI)	AUROC (95%CI)
T-SPOT.TB	55% (40-70%)	92% (87-95%)	60.4% (47-72%)	90.2% (86-92%)	16 (7-37)	-
QFT-G	58% (41-73%)	89% (77-95%)	72.7 (68–76%)	80.6% (78–82%)	11 (3-46)	0.80 (0.76-0.83)
TST	46% (38-54%)	86% (75–93%)	46.3% (40–52%)	88.7% (87–89)	5 (2-12)	0.52 (0.48-0.57)

Concordance/discordance and agreement between IGRAs and TST

Auguste P et al. (2016) in the systematic review reported the degree of concordance (inter-rater or intra-rater agreement, kappa statistic) and discordance between the results of the two tests (IGRAs and TST) in population of children, immunocompromised people and those recently arrived from countries with high TB burden as shown in Table 6. [34] level 1

Table 6: Agreement between IGRA and TST in different high risk populations

Population	Comparison	Agreement between tests
Children and adolescents	QFT-GIT vs TST 5mm	K = 0.27-0.91
	QFT-GIT vs TST 10mm	K = 0.13-0.64
	T-SPOT.TB vs TST 10mm	K = 0.53-0.71
	BCG vaccinated Concordance =46.7% K = 0.16 Non-BCG vaccinated Concordance =96.2% K = 0.91	
Immunocompromised patients		
i. HIV infection	QFT-GIT vs TST	Concordance = 75-96% K = 0.29-0.48 Indeterminate result of IGRA: QFT-GIT 0.30–17.87% T-SPOT.TB 32.80%
ii. Haematological disorders		Concordance = 70.6-80% K = 0.09-0.16 Indeterminate result of IGRA: QFT-GIT 6.00–13.93%
iii. Solid organ transplantation candidates		Concordance = 65-80% K = 0.09-0.57 Indeterminate result of IGRA: QFT-GIT 2.11–4.76% T- SPOT.TB 11.96%

Population	Comparison	Agreement between tests
iv. Post-kidney transplantation		Concordance = 80% K = 0.09-0.27 Indeterminate result of IGRA: QFT-GIT 1.64–4.30%, T-SPOT.TB 11%
v. ESRD/haemodialysis		Concordance = 60-86.4% K = 0.21-0.49 Indeterminate result of IGRA: QFT-GIT 0–10.55% T-SPOT.TB 0%
vi. Immune-mediated inflammatory diseases before antiTNF-α therapy		Concordance = 60-93% K = 0.09-0.56 Indeterminate result of IGRA: QFT-GIT 0–7.69% T-SPOT.TB 0– 15.63%
	Between-test agreement parameters by BCG vaccination status showed a lower percent concordance and kappa values for BCG-vaccinated participants than for non-vaccinated participants (no value mentioned)	
Recent arrivals from countries with a high incidence of TB	IGRA vs TST 5mm	Concordance = 60.7-90%
	IGRA vs TST 10mm	Concordance = 63.6-84.2%
	The kappa values between the IGRA and the TST (regardless of TST threshold and BCG vaccination status) ranged from 0.08 to 0.68, with most values being < 0.45.	
	Both concordance and kappa were greater among BCG-unvaccinated (or total sample) than among vaccinated-only group.	

5.2.2 Efficacy of preventive therapy

A systematic review by Zenner D et al. (2017) examined the comparative efficacy of LTBI treatment regimens for preventing active TB among adults and children.[38] level I Zenner D et al. conducted a network meta-analysis of 61 randomised controlled trial of different latent TB regimens in which 43 were directly compared. In the network meta-analysis, isoniazid (INH) regimens of six months or 12 to 72 months, rifampicin-only (RMP) regimens, rifampicin-isoniazid (RMP-INH) regimens of three to four months, rifampicin-isoniazid-pyrazinamide (RMP-INH-PZA) regimens and rifampicin-pyrazinamide (RMP-PZA) regimens were shown to be efficacious in comparison to placebo, with the odds of developing active TB among those who took the respective regimens as shown in Table 4. Evidence existed for efficacy of weekly rifapentine-isoniazid (RPT-INH) regimens compared with no treatment [OR 0.36; 95% Credible Interval (CrI) 0.18, 0.73]. No conclusive evidence showed that HIV status altered treatment efficacy. (Table 7) [38] level I

Table 7: The odd ratios for the prevention of active TB

Regimen	OR vs Placebo (95% CrI)
Placebo	1.00 (reference)
INH 3–4 months	0.93 (0.55–1.50)
INH 6 months	0.65 (0.50–0.83)
INH 9 months	0.75 (0.35–1.62)
INH 12–72 months	0.50 (0.41–0.62)
RFB-INH	0.30 (0.05–1.50)
RPT-INH	0.58 (0.30–1.12)
RMP	0.41 (0.19–0.85)
RMP-INH 1 month	1.05 (0.37–2.77)
RMP-INH 3–4 month	0.53 (0.36–0.78)
RMP-INH-PZA	0.35 (0.19–0.61)
RMP-PZA	0.53 (0.33–0.84)
INH-EMB	0.87 (0.32–2.36)

* CrI = credible interval; EMB = ethambutol; INH = isoniazid; OR = odds ratio; PZA = pyrazinamide; RFB = rifabutin; RMP = rifampicin; RPT = rifapentine

The Cochrane systematic review by Sharma et al. (2013) found similar efficacy for the following three comparisons: (i) RMP monotherapy for three to four months versus INH for six to nine months, (ii) RMP-INH for three months versus INH for six to nine months and (iii) weekly RPT-INH for three months versus daily, INH for nine months.[39] level 1 The authors identified ten randomised controlled trials that included 10,717 adults and children, who were mostly HIV-negative (2% HIV positive), with a follow-up period ranging from two to five years. The comparative relative risks (RR) of developing active TB for these rifamycin combinations versus INH were 0.81 (95%CI 0.47, 1.4), 1.08 (95%CI 0.65, 1.79) and 0.44 (95%CI 0.18, 1.07), respectively. [39] level I

5.3 Safety

Harmful effects of preventive therapy

Hepatotoxicity

The direct comparison results from network meta-analysis conducted by Zenner D et al. (2017) suggested that the RMP-only and RPT-INH regimens had lower rates of hepatotoxicity than an INH-only regimen of six, nine or 12 to 72 months.[38] level I The RMP-INH regimens also had lower hepatotoxicity than the INH-only regimen, although evidence for this was good only when compared with INH regimens of 12 to 72 months. A good evidence was found that regimens containing PZA had higher hepatotoxicity compared with six months of INH or 12 weeks of RPT-INH. No data were available on the hepatotoxicity of the RFB-INH and INH-EMB regimens. Stratifying the results on the basis of immunosuppression, HIV status, and TB incidence did not affect the conclusions (Table 8). A total of five toxicity-attributable deaths were reported, mostly from a single trial. All were due to severe hepatitis in

INH treatment groups, and at least four occurred in patients who were receiving INH for 12 to 72 months.[38] level I

Table 8: The odd ratios for hepatotoxicity, derived from the network meta-analysis

Regimen	OR vs Placebo (95% CrI)
Placebo	1.00 (reference)
INH 6 months	0.27 (0.10–0.60)
INH 9 months	0.41 (0.08–1.62)
INH 12–72 months	0.66 (0.26–1.32)
RPT-INH	0.13 (0.03–0.42)
RMP	0.03 (<0.02–0.16)
RMP-INH 3–4 month	0.17 (0.05–0.46)
RMP-INH-PZA	0.58 (0.07–3.72)
RMP-PZA	0.80 (0.25–2.17)

* CrI = credible interval; INH = isoniazid; OR = odds ratio; PZA = pyrazinamide; RMP = rifampicin; RPT = rifapentine.

Other adverse events

Pease C et al. (2018) conducted a systematic review to determine the rate of adverse events of five LTBI treatment regimens (RPT-INH for three months, INH for nine months, INH for six months, RMP-INH for three to four months and RMP for three to four months).[40] level 1 A total of 78 studies (23 randomised and 55 non-randomised studies) were included the review. Among data from RCTs, RPT-INH three months had the lowest rate among regimens of having any adverse event (median rate of 11.5%). The highest rate of adverse events was associated with INH six months (median rate of 36.1%). Based on limited data, rates of adverse events were lower in children than in adult or mixed populations. The INH nine months had the highest adverse events rate in children (median rate 10.1%). In comparison, median rates of withdrawals associated with INH 9 months (6.4%) and INH six months (3.8%) were the largest among the five regimens. The median rate of grade 3 to 4 adverse events was higher for INH 6 months (8.2%) and RPT-INH 3 months (6.0%) and lower for INH-9 (3.3%). The review defined Grade 3 adverse events as those that were medically significant but not imminently life-threatening. Grade 4 adverse events was defined as life-threatening events. Data from non-randomised studies found that the highest median rate of withdrawals from adverse events was associated with INH six months (median 5.8%, range 2.3%-24.5%; nine studies), followed by RPT-INH three months (median 4.3%, range 1.3%-8.4%; seven studies), INH nine months (median 2.6%, range 0.4%-26.8%; 13 studies), RMP-INH three to four months (median 1.8%, range 0.5%-5.1%; four studies), and RMP three to four months (median 0%, range 0%-5.2%; six studies). One study reported the incidence of angioedema in 2% of patients who withdrew from RPT-INH three months. [40] level I

Fifty-three included randomised control trials in a systematic review by Stagg et al. (2014) reported that RMP-PZA regimens had the highest risk for gastrointestinal

adverse events, and RMP regimens had the highest risk for central nervous system adverse events. Serious adverse events were rare across all studies.(Table 9) [41] level I

Table 9: The percentage of adverse events occurrence by regimen

Regimen	GI symptoms (%)	Rash & skin symptoms (%)	Peripheral Neuropathy (%)	Dizziness, fatigue, other CNS (%)	Headaches (%)	Seizure (%)	Haematological symptoms (%)	Possible drug allergy (%)
Placebo	0.8	0.1	8.6	1.2	-	-	1.0	-
INH 6 m	2.8	1.1	<0.1	1.1	0.5	0.1	0.2	-
INH 9 m	0.7	0.8	-	0.4	-	-	<0.1	0.4
INH 12-72 m	1.7	0.2	7.4	-	1.0	0.1	1.0	-
RPT-INH	-	0.8	-	-	-	-	-	3.8
RMP	4.3	4.1	-	3.8	-	-	0.3	0.1
RMP-INH 3-4 m	7.5	1.4	-	2.1	0.5	-	0.1	-
RMP-PZA	10.8	7.2	-	1.0	-	-	-	-

* The percentage are dependent upon the length of the trial(s) in question. CNS- central nervous system, m- month, GI- gastrointestinal, EMB-ethambutol, INH- isoniazid, PZA- pyrazinamide, RFB- rifabutin, RFP-INH (high)- a higher dose of RFB, RMP- rifampicin, RPT- rifapentine

In a Cochrane systematic review, studies that compared the efficacy of RMP-PZA for three months and INH for six months had shown that people receiving RMP-PZA had more treatment-limiting adverse events [pooled RR 3.61 (95%CI 1.82, 7.19); two trials, 368 participants], and hepatotoxicity [pooled RR 4.59 (95%CI 2.14, 9.85); three trials, 540 participants]. [39] level I

5.4 Cost/Cost-effectiveness

5.4.1 Costs

Diagnostic Tests

Based on costing data from a local pilot LTBI screening project for smear positive PTB contacts, the cost per test for TST and IGRA(QFT-Plus) (including additional costs incurred) are RM8 and RM78, respectively.

<u>Costing data from international literatures</u>

In an HTA (2016), Auguste P et al. presented the cost of diagnostic tests in children, immunocompromised patients and recently arrived populations (e.g. migrants) as being GBP 17.48 for TST, GBP 48.73 for QFT-GIT, GBP 59.57 for TB-specific Elispot assay (T-SPOT.TB), GBP 35 for CXR and GBP 7 for sputum examination.[42] level I For children, the costs of gastric lavage procedures were also presented: GBP 916. All costs were adjusted to 2012/2013 prices using the Hospital and Community Health Services pay and price index and discounted at a rate of 3.5 % per annum. It was

assumed that TST was costed similarly for those that were read and those that were not read, that people being assessed for initial active TB undergo CXR and, if positive, receive a sputum examination and that children being assessed for initial active TB undergo CXR and, if positive, undergo a gastric lavage procedure.[42]

In Campbell et al. (2015), the cost of the TST ranged from USD 15.55 to USD 42.33 (in 2013), the cost of the IGRA ranged from USD 53.58 to USD 90.31 (excluding two studies that were performed from a healthcare programme perspective).[43] level I

Nienhaus et al. (2011) provided an overview of TST and IGRA costs per country in different currencies extracted from multiple studies.[44] In one study performed in Germany, the reported cost of TST was USD 145.99 and of IGRA USD 171.78 (in 2007, including CXR and consultation if test is positive), while in another study performed in Germany the TST and IGRA (including salary of staff) cost EUR 117.5 and EUR 145.98, respectively. In the United Kingdom, the prices of a test were GBP 15.43 for TST and GBP 45 (QFT-GIT) or GBP 55 (T-SPOT) for IGRA. In France, prices were EUR 10.86 and EUR 44.83, respectively.[44]

Preventive Therapy

Based on data from Tuberculosis & Leprosy Sector, Disease Control Division, MOH, the costs of treatment per case at MOH facilities with 6 months INH, 9 months INH and 4 months RMP are RM129.60, RM194.40 and RM79.30, respectively.

Costing data from international literatures

The estimated costs per person of treatment of LTBI with 6 months of INH was Great Britain Pound (GBP) 677.07, including full blood count, liver function test, outpatient visits, nurse contact and drugs. The cost of adherence and non-adherence to LTBI treatment in children, immunocompromised patients and recently arrived (e.g. migrants) populations were also presented. For all groups, the costs were set at GBP 677.07 for adherence (based on NHS drug tariff) and GBP 112.85 for non-adherence (based on assumptions, not further specified). All costs were adjusted to 2012/2013 prices using the Hospital and Community Health Services pay and price index and discounted at a rate of 3.5 % per annum, and it was assumed that people who do not adhere to LTBI treatment take medication for one month. [42]

5.4.2 Cost-effectiveness

Diagnostic Tests

A systematic review on cost-effectiveness studies was conducted by Auguste P et al. (2016) as part of HTA of LTBI screening tools. [42] Ten studies reported evidence on decision-analytic models to determine the cost-effectiveness of IGRAs compared with the TST for LTBI diagnosis. In children, TST (≥ 5 mm) negative followed by QFT-GIT was the most cost-effective strategy, with an incremental cost-effectiveness ratio

(ICER) of £18,900 per quality-adjusted life-year (QALY) gained. In immunocompromised people, QFT-GIT negative followed by the TST (≥ 5 mm) was the most cost-effective strategy, with an ICER of approximately £18,700 per QALY gained. In those recently arrived from high TB incidence countries, the TST (≥ 5 mm) alone was less costly and more effective than TST (≥ 5 mm) positive followed by QFT-GIT or T-SPOT.TB or QFT-GIT alone. [42]

Campbell et al. (2015) did a systematic review of cost-utility analyses evaluating LTBI screening in high-risk populations.[43] Eight studies were included in the review. Three studies evaluated the cost effectiveness of screening tests on the basis of the options of no screening and screening with a TST. Cost-effectiveness in the review was defined as follows: ICER < USD 20 000 = strongly cost-effective; ICER between USD 20 000 and USD 100 000 = moderately cost-effective; ICER > 100 000 US = not cost-effective. Screening new adult immigrants and PLHIV was strongly cost-effective with a TST. The IGRA was found moderately cost-effective in new adult immigrants and 6- to 44-year-old immigrants that landed more than 5 years prior, while the TST was dominated by no screening in both cases. One study reported HIV screening was strongly cost-effective with a TST and moderately cost- effective with an IGRA, while the other reported either dual TST/QFT or T-SPOT.TB alone would be the most cost-effective, depending on the situation. No test was cost-effective for renal diseases; however, the IGRA was found to be the most cost-effective test more often than the TST, if screening had to be performed. While screening for diabetics was not cost-effective, the TST was found to be most cost-effective if screening was done. All ICERs for other immunocompromising conditions were cost prohibitive, although the TST was found to be the most cost-effective test if screening had to occur. [43]

A cost-effectiveness study by Tasillo A et al. (2017) sought to estimate cost-effectiveness of LTBI testing and treatment among non-US born residents with and without medical comorbidities.[45] The analysis assumed a health care sector perspective and lifetime horizon with a 3% annual discount to costs and benefits, willingness-to-pay threshold of $100 000 per QALY gained. Strategies compared included no testing, TST, IGRA, confirm positive (initial TST, IGRA only for TST-positive results; both tests positive indicates LTBI), and confirm negative (initial IGRA, then TST for IGRA-negative; any test positive indicates LTBI). All strategies were coupled to treatment with three months of self-administered rifapentine and isoniazid. The best-performing strategies (cost-effective) with ICER below $100 000/QALY were patients with no comorbidities and IGRA testing (ICER $83 000/QALY), patients with diabetes and confirm positive (ICER $53 000/QALY), HIV patients with confirm negative (ICER $63 000/QALY) and ESRD patients with no testing. Testing ESRD patients for LTBI improved QALYs, but ICERs for all strategies were over $2 million/QALY gained. Strategies above $100 000/QALY likely to improve outcomes were patients with no comorbidities and confirm negative (ICER $147 000/QALY), and diabetic patients with both IGRA testing (ICER $120 000/QALY) and confirm negative (ICER $230 000/QALY). In populations with high LTBI prevalence, the confirm

negative approach was the most cost-effective. When TST specificity among the non-US born patients with no comorbidity's cohort was greater than 92.5% (base case, 88.6%) and more than 91.5% of individuals returned (base case, 82%) for follow-up, TST became the cost-effective strategy.[45]

Preventive therapy

One systematic review concluded that chemoprophylaxis for TB (INH versus no intervention; ICER of USD12,625 per year of life gained and USD35,011 per death averted, rifampin versus no intervention; ICER of USD2,494 per case prevented, RPT-INH versus rifampin; $48,999 per QALY gained) appears to be cost-effective.[46]

One systematic review concluded that screening and treatment for LTBI appears to be a cost-effective intervention for some population groups characterised by high prevalence of LTBI and/or high risk of progression to active TB, such as persons migrating from high-TB-incidence countries, contacts of active TB cases and PLHIV.[47]

Doan TN et al. (2019) conducted cost effectiveness analysis for four preventive therapy regimens with six different treatment strategies for treating LTBI.[48] The treatment strategies were self-administered daily isoniazid for six (6-INH) or nine (9-INH) months, self-administered daily rifampicin plus isoniazid for 3 months (3RMP-INH), self-administered daily rifampicin for four months (4RMP) and weekly rifapentine plus isoniazid for three months self-administered (3RPT-INH-SAT) or administered by a healthcare worker as directly observed therapy (3RPT-INH-DOT). These were compared to serial radiographic surveillance without preventive treatments. Cost-effectiveness was evaluated from a health system perspective over a 20 year time horizon. Relative to serial radiographic surveillance, administration of 3RPT-INH-DOT, 3RPT-INH-SAT, 4RMP, 3RPT-INH, 9INH or 6INH would reduce 82%, 78%, 73%, 69%, 61% and 46% incident cases of active TB per 10,000 patients over 20 years, respectively. The 3RPT-INH-SAT and 3RPT-INH-DOT were more cost-effective compared with other regimens from a health system perspective at a WTP threshold of US$50,000 per QALY gained. The 3RPT-INH was more cost-effective under DOT than under SAT at a cost of US$27,948 [95% Uncertainty Range (UR) 18089–46330] per QALY gained. The cost effectiveness acceptability curve (CEAC) showed that the likelihood that 3HP-DOT was cost-effective at a WTP threshold of US$50,000 per QALY gained was 66%. At this threshold, the probabilities that 3RPT-INH-SAT and 4RMP were cost- effective were 22% and 12%, respectively. Threshold analysis showed that the treatment completion rate of 3HP-DOT needed to be at least 83% (base-case value 85%) for this regimen to be more cost-effective than 3HP-SAT at a WTP threshold of $50,000 per QALY gained. [48]

5.5 Organisational Issues

5.5.1 Identification of target risk groups

Reviews that were identified recognising two types of risks in LTBI infection;

- risk of becoming (latently) infected with TB
- risk of developing active TB

The reported findings were presented according to risk groups namely;

a) Clinical risk groups	- Patient living with HIV (PLHIV) - Immunocompromised patients which include patients with autoimmune diseases receiving TNF alpha inhibitors, patients with renal failure/dialysis
b) Population risk groups	- TB contacts - Migrants
c) Vulnerable hard-to-reach populations	- Prisoners - Homeless people - People with drug/substance use disorders
d) Occupational groups	- Healthcare workers

Clinical risk groups

a. PLHIV

Based on the reported pooled risk ratios, no significant evidence for increased risk of LTBI was found in PLHIV (identified by TST and IGRA) in low- (TB incidence rate: < 40 cases per 100 000) and high-TB-burden countries (TB incidence rate:> 100 cases per 100 000). For intermediate-TB-burden countries (TB incidence rate: 40-100 cases per 100 000), the pooled estimate risk ratio (RR) for PLHIV was identified by TST. For this group, no significant evidence for increased risk of LTBI was found either. (Table 8) The pooled prevalence of LTBI (established by TST and IGRA) in PLHIV in low, intermediate and high-TB-burden countries, ranged from 12% to 55%.[33 level I]

The commissioned systematic reviews by WHO reported data on active TB development in PLHIV infected with TB. The incidence rate ratio (IRR) of active TB in PLHIV with TST positive results (untreated; with concomitant risk factor) compared to HIV-negatives (LTBI status unknown) in two prospective cohort studies was 10.46 (95%CI 1.34, 471.2) and 9.42 (95%CI 2.90, 27.11), respectively. In comparison to the general population (LTBI status unknown), PLHIV with a positive LTBI test (test not defined) had a relative risk of developing active TB of 345 (95%CI 158, 753) (Table 10).[33 level I]

b. Immunocompromised

The WHO commissioned systematic review calculated pooled risk ratios for LTBI infection in various immunocompromised populations compared to the general population. Based on this, no significant evidence for increased risk of LTBI was found in patients with renal or liver conditions (identified by TST and IGRA) in low and high-TB-burden countries (Table 8). For intermediate-TB-burden countries, the pooled estimate risk ratio only available for patients with renal or liver conditions identified by TST. For this group, there was also no significant evidence for increased risk of LTBI found. In low-TB-burden countries, candidates for anti-tumour necrosis factor (TNF) therapy (identified by IGRA) seemed to have a higher risk of LTBI compared to the general population, while no significant evidence for increased risk of LTBI was found in candidates for anti-TNF-alpha therapy identified by TST. No measure of risk for intermediate and high-TB-burden countries available. No significant evidence for increased risk of LTBI was found in patients with autoimmune disorders or immune-mediated inflammatory disorders (identified by TST and IGRA) in low-TB-burden countries and in this population identified by TST in high-TB-burden countries. The WHO reported data on active TB development in immunocompromised individuals infected with TB. For LTBI-positive patients with autoimmune diseases receiving anti-TNF-alpha inhibitors, LTBI-positive patients with silicosis and LTBI-positive patients with diabetes mellitus, the RR of TB compared to the general population (LTBI status unknown) was 16.2 (95%CI 14.6, 18.0), 170.3 (95%CI 137.9, 210.2) and 10.3 (95%CI 5.9, 17.6), respectively. The adjusted RR per 100 person-years (pyr) of active TB for ESRD patients undergoing dialysis versus the general population ranged over TST reaction categories (0-4 mm; 5-9 mm; > 9 mm) from 24.5/100 pyr, 8.4/100 pyr, and 41.1/100 pyr, respectively, and for LTBI-positive patients with terminal renal failure/dialysis the relative risk of TB compared to the general population (LTBI status unknown) was 703.2 (95%CI 38.1, 12 984.5).(Table 10)[33] level I

Campbell JR et al. performed a systematic review and meta-analysis to determine the longitudinal risk of TB in dialysis patients (n=5 studies). The crude estimate of likely TB reactivation (positive test with subsequent TB) was 35.15 cases/1 000 pyr, the IRR of TB development was found to be 2.59 (95%CI 1.20, 5.57) and the PPV of TST was 11.93 % (range 4.60-29.39).[49] level I

Population risk groups

c. Migrants

Based on WHO commissioned systematic review, in low-TB-burden countries, immigrants and refugees (as measured by TST) seemed to have higher risk of LTBI compared to the general population. No significant evidence for increased risk of LTBI was found in immigrants and refugees identified by IGRA, in low-TB-burden countries.(Table 10) LTBI prevalence in migrants was included in eight studies, varying from 0.3% to as high as 50.0%. The reported relative risk of active TB in LTBI-positive migrants/refugees from high- to low-burden countries compared to the general

population (LTBI status unknown) was 90.7 (95%CI 22.8, 361.5). The annual LTBI reactivation rate in migrants ranged from 0.08 to 13.35%.(Table 10)[33 level I]

Campbell et al. calculated ORs to assess predictors for a positive TST (n=23 studies) or IGRA (n=8). In this study, BCG-vaccinated immigrants had a higher likelihood of a positive TST. Immigrants from countries with ≥ 30 cases per 100 000 (compared to immigrants from countries with < 30 cases per 100 000) tested with TST or IGRA had a higher likelihood of a positive test: 2.38 (95 % CI 1.14, 4.98) (TST) or 17.25 (95%CI 1.03, 289.34) (IGRA).[50 level I] Another systematic review by Campbell et al. showed that positive TST or IGRA results were found significantly more often in immigrants ≥ 18 years of age compared to those aged < 18 years. For immigrants tested with TST the positivity rate was 41.6 %, while for those tested with IGRA the positivity rate was 23.8%. Campbell et al. reported the number of active TB cases in TST-positive migrants for three studies. For the two studies on TSTs, 13 of the 591 TST- positive immigrants developed active TB. The IGRA study followed up 238 QuantiFERON-TB Gold in-Tube (QFT- GIT)-positive immigrants not treated for LTBI for development of active TB and found eight cases.[51 level I]

d. TB contacts

In intermediate-TB-burden countries, TB contacts (identified by TST) were at higher risk of LTBI compared to the general population. No significant evidence for increased risk of LTBI was found in TB contacts (identified by IGRA) in intermediate-TB-burden countries. Also, no significant evidence for increased risk of LTBI was found in TB contacts (identified by TST and IGRA) in low and high-TB-burden countries.(Table 10) [33 level I]

Fox et al. in a systematic review and meta-analysis provided the proportion of LTBI in screened contacts in low/middle-income settings (51.5%; 95%CI 47.1, 55.8), high-income settings (28.1%; 95%CI 24.2, 32.4), for contacts born locally (17.0%; 95%CI 11.8, 24) and born overseas (39.2%; 95%CI 30, 49.3). The prevalence of LTBI among contacts was significantly less in high-income countries than in low–middle-income countries, although this difference was not evident among household contacts. Foreign-born contacts are significantly more likely to have LTBI than locally born contacts in high-income countries (OR 3.39; 95%CI 3.10, 3.71, p<0.0001).[52 level I]

Studies presenting data on active TB in TB contacts did not always provide information on LTBI or TST status before being exposed to a TB index case. Still, these data were included in the review to provide insight into the risk of active TB in TB contacts. The RR of active TB of close contacts versus casual contacts varied over TST reaction categories from 5.2 to 10.6, while the risk of progression in TST positive contacts with CXR lesions was found to be five times greater compared to TST positive contacts without CXR lesions abnormalities. The annual LTBI reactivation rate in contacts ranged from 0.10 to 12.60%.[33 level I] A review on contact investigation after TB exposure in an airplane found a rough estimate of TST positivity of 0.1-1.3% of aircraft contacts

in long-haul flights (> 8 hours), which might have contracted the infection from a sputum-smear-positive index case. The risk of infection seems to be the highest among passengers seated within two rows of the index case.[53] level I

e. Healthcare workers

The WHO commissioned systematic review reported the risk ratio for LTBI infection in healthcare workers and students (identified by TST and IGRA) compared to the general population. No significant evidence for increased risk of LTBI was found for this population in low-, intermediate- and high-TB-burden countries. LTBI prevalence was present in healthcare workers (HCW) in five included studies, varying from 10.0% to 17.0%. The annual risk of TB disease in HWCs was 69-5,780/100 000 population. The annual LTBI reactivation rate in HWC ranged from 0.40% to 1.20%.(Table 9)[33] level I

One systematic review on outbreak studies reported the proportion of cases who acquired TB infection after exposure to index healthcare workers. Among the included studies, the proportion was 2.62% (95%CI 1.05, 4.88) in healthcare workers, which was lower than in adult contacts, but higher than in children and infant contacts. [54] level I

f. Prisoners

In low and intermediate-TB- burden countries, prisoners (as identified by TST) seemed to have a higher risk of LTBI and developing active TB compared to the general population. (Table 10)[33] level I

g. Homeless people

In low-TB-burden countries, homeless people (identified by TST and IGRA) seemed to have a higher risk of LTBI and developing active TB compared to the general population. (Table 10)[33] level I

h. People with drug use disorders

No significant evidence for an increased risk of LTBI was found in people with drug use disorders (identified by TST and IGRA) in low-TB-burden countries.(Table 10) [33] level I

i. Other factors

Age

A meta-analysis conducted by Campbell et al. aimed to assess predictors for a positive TST (n = 23 studies). In the analysis, age was identified as a predictor of TST positivity in five studies resulting in a higher likelihood of a positive TST in those ≥ 35 years of age (OR 1.59; 95%CI 1.32, 1.92).(Figure 5) [50] level I Campbell et al. performed a statistical analysis in another systematic review which showed that risk of infection may be associated with age: a significantly higher proportion of positive TST or IGRA

results were found in immigrants ≥ 18 years of age [26.1 % (IGRA) – 44.7 % (TST)] – compared to those aged < 18 years [13.9% (IGRA) – 24.0% (TST)].[51 level I] One systematic review on outbreak studies reported the pooled proportion of cases who acquired TB infection after exposure to index healthcare workers (HCWs). The proportion was the highest in adults, followed (besides healthcare worker contacts) by children and infants. [Combined proportions of individuals who acquired TB infection were: 0.57 (95%CI 0.00, 2.02) for infants, 0.90% (95%CI 0.40, 1.60) for children, 4.32% (95%CI 1.43, 8.67) for adults and 2.62% (95%CI 1.05, 4.88) for HCWs]. Children exposed to an infectious case were reported to show the highest pooled proportions of developing active TB, followed by infants, adults and healthcare workers. [Combined proportions of active TB cases among exposed individuals were: 0.11% (95%CI 0.04, 0.21) for infants, 0.38% (95%CI 0.01, 1.60) for children, 0.09% (95%CI 0.02, 0.22) for adults and 0.00% (95%CI 0.00, 0.38) for HCWs].[54 level I]

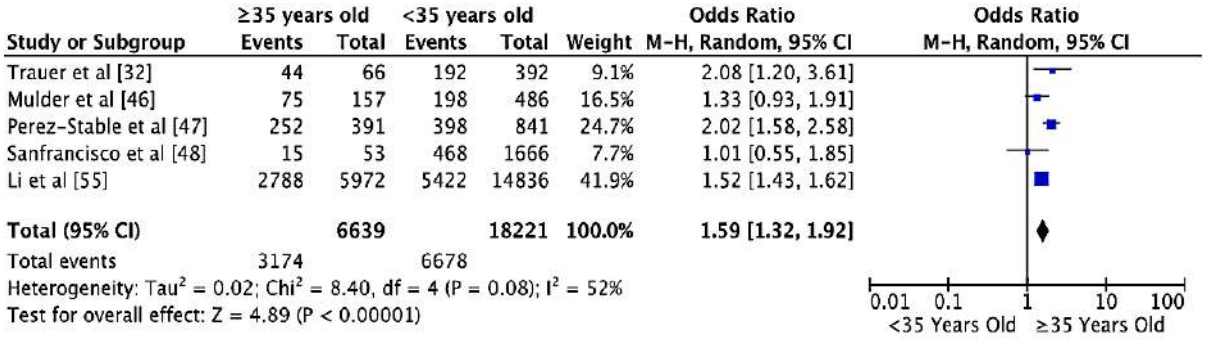


Figure 5: Forest plot of association between tuberculin skin test positivity and age ≥35 years

Smoking

A systematic review and meta-analysis involving 18 studies with 30,757 children and 44,432 adult non-smokers, was conducted to investigate the role of second-hand smoke (SHS) exposure as a risk factor for TB among children and adults. Pooled effect estimates showed that second-hand smoking exposure has been associated with an increased risk of LTBI after controlling for age (RR 1.78, 95%CI 1.19, 2.68), biomass fuel use (RR 2.66, 95%CI 1.31, 5.39) and contact with a TB patient in the household (RR 2.03, 95%CI 1.25, 3.28). Relative risk was higher in the South-East Asia Region (RR 2.93, 95%CI 1.97, 4.36) and African Region (RR 2.11, 95%CI 1.00, 4.49) than in the other regions. However, there was no significant association of second-hand smoking exposure with LTBI after adjustment for socioeconomic status and study quality.[55 level I]

Male gender

A meta-analysis by Campbell et al. included 11 studies assessing gender as predictors for a positive TST. Male gender was found to be a predictor of TST positivity (OR 1.38; 95%CI 1.20, 1.58). Males were also found to have a higher likelihood of positive IGRAs (n= 8 studies)(OR 1.34; 95%CI 1.08, 1.66). [50 level I]

History of travelling

Freeman et al. in a systematic review and meta-analysis, reported the cumulative incidence of LTBI among long-term travellers (military and civilian) from low-prevalence countries, as measured by TST conversion of 2.0% (99%CI 1.6, 2.4), with a range in individual study estimates from 0.96% to 3.59% (n=9 studies). The overall incidence density was 2.9 conversions per 1000 person-months (99% CI: 2.5–3.4). The cumulative incidence risk estimates for studies on military travellers was 2.0% (99%CI 1.6, 2.4) and for studies on civilian travellers was 2.3% (99%CI 2.1, 2.5). Stratification by travel to recent conflicts in Southwest Asia (SWA) only versus travel elsewhere resulted in an estimated cumulative incidence of 1.7% (99%CI 0.6, 2.9) for data from SWA and 2.3% (99%CI 1.6, 3.0) from all other locations.[56] level I

Table 10: Risk of becoming (latently) infected with TB and risk of progression to active TB in different type of risk groups stratified according to low, intermediate and high TB burden countries

Risk group	Risk of becoming (latently) infected with TB Pooled RR (95%CI)						Risk of progression to active TB
	Low TB burden countries		Intermediate TB burden countries		High TB burden countries		
	TST	IGRA	TST	IGRA	TST	IGRA	
CLINICAL RISK GROUPS							
PLHIV	0.99 (0.43-3.09)	0.89 (0.31-3.09)	0.86 (0.77-1.17)	1.54 * *Based on two studies, no range provided*	0.76 (0.24-2.08)	0.94 (0.48-1.68)	**Increased risk of active TB in PLHIV compared to the general population.** IRR (95% CI) of active TB in TST+ PLHIV (with concomitant risk factor) compared to HIV- negatives: PLHIV and people who inject drugs: 10.46 (1.34-471.2) PLHIV and homeless people: 9.42 (2.90-27.11) Pooled RR (95% CI) of active TB in PLHIV with LTBI (determination of LTBI status not specified) compared to the general population (LTBI status general population unknown): 345 (158-753).
Immuno-compromised a) Patients with renal or liver conditions (31 cross-sectional and cohort studies)	1.43 (1.40-3.68)	2.21 (0.40-5.14)	1.02 (0.63-2.71)	1.19 * *Based on two studies, no range provided*	0.74 (0.24-3.32)	1.23 (0.49-3.16)	**1 cohort study reporting on ESRD patients receiving dialysis** Adjusted RR/100 person years (95% CI) of progression from LTBI to TB disease in ESRD patients receiving dialysis compared to the general population: TST (5-9mm): 8.4 (3.1-13.6); TST (>9mm): 41.4 (37.9-44.8). **3 cohort studies reporting on patients with terminal renal failure/dialysis** Pooled RR (95% CI) of active TB of LTBI positive patients with terminal renal failure/dialysis compared to the general population (LTBI status general population unknown): 703.2 (38.1-12984.5)

Risk group	Risk of becoming (latently) infected with TB Pooled RR (95%CI)						Risk of progression to active TB
	Low TB burden countries		Intermediate TB burden countries		High TB burden countries		
	TST	IGRA	TST	IGRA	TST	IGRA	
b) Candidates for anti-TNF alpha therapy (20 cross-sectional and cohort studies)	1.84 (0.38-5.94)	2.40 (1.56-3.30)	0.54 * *Based on two studies, no range provided*	-	-	2.11 * *Based one studies, no range provided*	**One cohort study reporting on patients with autoimmune diseases receiving TNF alpha inhibitors** Pooled RR (95% CI) of active TB for LTBI positive patients with autoimmune diseases receiving TNFα inhibitors compared to the general population (LTBI status general population unknown): 16.2 (14.6-18.0).
c) Patients with autoimmune disorders or immune-mediated inflammatory disorders (20 cross-sectional and cohort studies)	1.62 (0.07-4.42)	0.95 (0.04-3.33)	0.84	0.52 * *Based on one study, no range provided*	1.24 (0.90,2.15)	0.78 * *Based on two studies, no range provided*	**One cohort study reporting on patients with silicosis** Pooled RR (95% CI) of active TB of LTBI positive patients with silicosis compared to the general population (LTBI status general population unknown): 170.3 (137.9- 210.2). **One cohort study reporting on patients with diabetes** Pooled RR (95% CI) of active TB for LTBI positive patients with diabetes mellitus compared to the general population (LTBI status general population unknown): 10.3 (5.9-17.6).
POPULATION RISK GROUP							
TB Contacts (71 cross-sectional and cohort studies)	2.25 (0.15-11.7)	1.58 (0.06-8.33)	2.09 (1.29-2.44)	0.97 (0.54-1.80)	1.07 (0.43-2.2)	1.06 (0.40-2.59)	**3 cohort studies reporting on TB contacts** Pooled relative risk (95% CI) of active TB for LTBI positive contacts compared to the general population (LTBI status general population unknown) in children: 425.4 (208.14-869.4) and adults: 8.0 (4.8- 13.4).
Migrants (23 cross-sectional and cohort studies on immigrants/refugees)	3.27 (1.00-8.31)	2.26 (0.79-8.08)	-	-	-	-	**4 cohort studies reporting on migrants/refugees** Pooled RR (95% CI) of active TB of LTBI positive migrants compared to the general population (LTBI status general population unknown): 90.7 (22.8-361.5)(from high to low TB burden countries).

Risk group	Risk of becoming (latently) infected with TB Pooled RR (95%CI)						Risk of progression to active TB
	Low TB burden countries		Intermediate TB burden countries		High TB burden countries		
	TST	IGRA	TST	IGRA	TST	IGRA	
VULNERABLE AND HARD TO REACH POPULATIONS							
Prisoners (9 cross-sectional and cohort studies)	2.33 (2.40-3.57)	-	2.77 (2.58-2.92)	-	-	-	RR (95% CI) of active TB for LTBI-positive prisoners compared to the general population (LTBI status general population unknown): 15.3 (7.6-30.5)
Homeless people (6 cross-sectional and cohort studies)	2.43 (1.15-3.81)	2.40 (1.56-3.30)	-	-	-	-	Pooled RR (95% CI) of active TB for LTBI positive persons residing in homeless shelters compared to the general population (LTBI status general population unknown): 7.3 (0.5-103.7)
People with drug use disorder (9 cross-sectional and cohort studies)	0.91 (0.04-3.44)	3.24 (0.02-5.00)	-	-	-	-	-
OCCUPATIONAL RISK GROUPS							
Healthcare workers and undergraduate health sciences students (63 cross-sectional and cohort studies)	1.88 (0.12-8.25)	0.59 (0.03-8.83)	1.13 (0.28-2.06)	0.79 (0.32-2.15)	1.14 (0.42-1.68)	0.75 (0.15-1.32)	Pooled RR (95% CI) of active TB of LTBI positive healthcare workers compared to the general population (LTBI status general population unknown): 2.97 (2.43-3.51).

Published Malaysian studies on prevalence of LTBI in risk groups

There are four published studies on local prevalence of LTBI. Two cross-sectional studies were conducted among healthcare workers. The other two studies focussed on LTBI prevalence in prison setting [prison employees (one study) and prisoners (one study)]. (Table 11)

Table 11: Local published studies on prevalence of LTBI in risk groups

Authors (year)	Study design	Population (N)	Setting	Main outcome
Munisamy M et al. (2017) [57]	Cross-sectional study	Healthcare workers (N=399)	Tertiary public hospital (Kuala Lumpur Hospital)	- Point prevalence 46% (identified by TST 15mm) - Health professional (OR 2.07, 95%CI 1.34–3.55), allied health staff (OR: 2.03, 95%CI 1.02– 2.78) and support staff (OR 2.21, 95%CI 1.19–3.89) were more likely to have evidence of LTBI compared with management staff - Staff in intensive care/operating theatres (OR 1.36, 95%CI 1.09–3.94), outpatient areas (OR 1.51, 95% CI 1.07–4.46) and inpatient wards (OR 1.67, 95% CI 1.10–4.32) demonstrated a higher risk of LTBI compared with those working in non-clinical areas -Staff working >5 years (OR: 1.77, 95% CI 1.04–4.67) and >10 years (OR: 1.59, 95% CI 1.12–3.93) showing higher odds of positive LTBI status than staff who had worked for shorter periods -Those who had diabetes mellitus (OR 1.38, 95%CI 1.11–2.85) or any chronic disease (OR 1.19, 95% CI 1.03–2.14) also had higher odds of having evidence of LTBI compared with those who did not
Rafiza S et al. (2011) [58]	Cross-sectional study	Healthcare workers (N=953)	4 hospitals in Klang Valley (no further specified)	-Prevalence 10.6% (identified by QFT-GIT) -Higher prevalence of LTBI was associated with duration of employment ≥ 11 years(3.48; 95%CI 1.57-7.72), aged ≥ 35 (9.49; 95%CI 2.22-40.50), history of living in the same house with close family members or friends who had active tuberculosis (8.69; 95%CI 3.00-25.18), worked as a nurse (4.65; 95%CI 1.10-19.65)] and being male (3.70; 95%CI 1.36-10.02) - The agreement between QFT GIT and TST in this study was 50.5% for TST with a cut-off point of 10 mm and

Authors (year)	Study design	Population (N)	Setting	Main outcome
				82.1% for the cut-off point of 15 mm. The K agreement was however poor for both cut off points, at 0.12 and 0.31 respectively
Al-Darraji HA et al. (2015) [59]	Cross-sectional study	Prison employees (N=420)	Kajang Prison	- Prevalence 81% (identified by TST 10mm) -TST positivity was independently associated with having worked in the correctional system for 12 months or more (Adjusted OR 4.9, 95%CI 1.5-15.9) and smoking tobacco (Adjusted OR 1.9, 95%CI 1.2-3.2)
Al-Darraji HA et al. (2014) [60]	Cross-sectional study	Prisoners (N=286) -HIV infected (n=138) -HIV-uninfected (n=148)	Kajang Prison	-Prevalence 88.8% (84.7% among HIV-infected and 92.5% among HIV-uninfected participants) (identified by TST 5mm and TST 10 mm for HIV-infected and HIV-uninfected participants, respectively) -TST positivity was independently associated with being HIV-seronegative (Adjusted OR 2.97; 95%CI 1.12-7.04, p=0.01) and having been frequently incarcerated previously (Adjusted OR 1.22; 95%CI 1.04-1.42 for every one previous incarceration, p=0.01)

5.5.2 Determinants of LTBI treatment initiation, adherence and completion

Four systematic reviews reported on the LTBI care cascade including the uptake of screening and treatment as well as initiation, adherence and completion of therapy.

Alsdurf et al. (2016) performed a systematic review and meta-analysis of aspects influencing the cascade of care in diagnosis and treatment of LTBI.[61 level I] The authors found that only 18.8% of all those eligible for screening completed LTBI therapy and that the rate was low for all sub-groups, including migrants (14.3%). This was due to progressive losses at all stages of the care cascade: 71.9% (95%CI 71.8, 72.0) completed testing, 43.7% (95%CI 42.5, 44.9) completed medical evaluation, 35.0% (95% CI 33.8, 36.4) were recommended for treatment and 18.8% (95%CI 16.3, 19.7) completed treatment if started (Figure 6). Steps with fewer losses included receiving test results, referral for evaluation if test positive and agreeing to start therapy if recommended. Factors associated with fewer losses were immune-compromising medical indications, being part of contact investigations and use of rifamycin-based regimens. [61 level I]

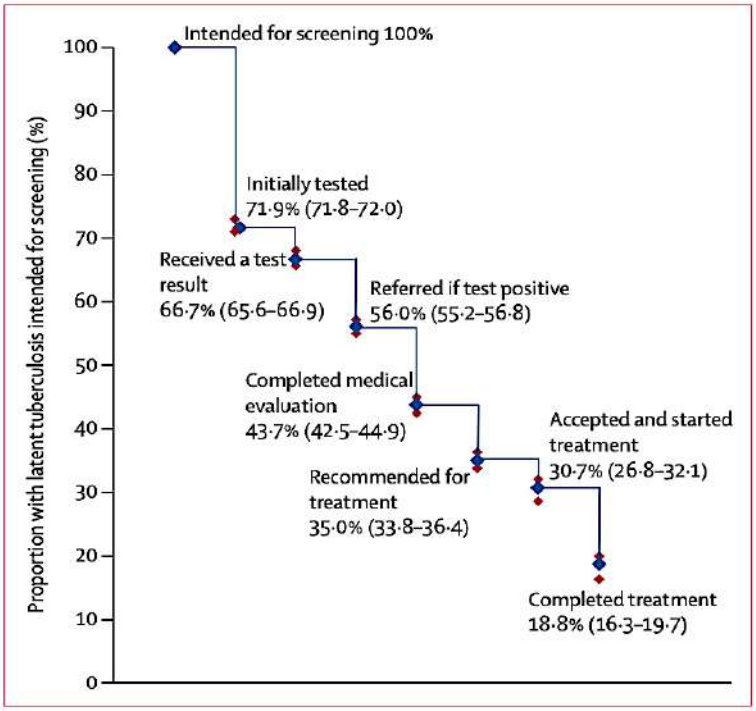


Figure 6: Losses and drop-outs at each stage of the cascade of care in latent tuberculosis

Sandgren et al. (2016) systematically review data on initiation rates and completion rates for LTBI treatment regimens in the general population and specific populations with LTBI. Forty-five studies on initiation rates and 83 studies on completion rates of LTBI treatment were found.[62] level I These studies provided initiation rates (IR) and completion rates (CR) in people with LTBI among the general population (IR 26-99 %, CR 39-96 %), case contacts (IR 40-95 %, CR 48-82 %), healthcare workers (IR 47-98 %, CR 17-79 %), the homeless (IR 34-90 %, CR 23-71 %), people who inject drugs (IR 52-91 %, CR 38-89 %), HIV-infected individuals (IR 67-92 %, CR 55-95 %), inmates (IR 7-90 %, CR 4-100 %), immigrants (IR 23-97 %, CR 7-86 %), and patients with comorbidities (IR 82-93 %, CR 75-92 %). Generally, completion rates were higher for short than for long LTBI treatment regimens. [62] level I

One full commissioned systematic review, using the GRADE methodology, was performed by Stuurman et al. (2016), that comprehensively summarised data on any determinant of LTBI treatment initiation, adherence and completion in all types of populations.[63] level I The most frequently reported determinant associated with LTBI treatment uptake in the general population was age, though the direction of the effect was inconsistent. With regards to LTBI treatment initiation, two studies found healthcare workers (versus non healthcare workers) to be less likely to initiate treatment (no study found a positive association); three studies found case contacts (versus no case contacts), and two studies found immigrants or refugees (versus born in country of study) to be more likely to initiate LTBI treatment (no study found an inverse association). With regards to LTBI treatment completion, five studies found a positive association between completion and immigrant or refugee status (versus born

in country of study), whereas two studies found an inverse association. Two studies each found that currently homeless individuals (versus not currently homeless) and people who injected drugs (versus people who do not inject drugs) were less likely to complete treatment (no study found a positive association). Throughout the populations, unfavourable social risk factors were associated with worse completion (no study found a positive association). Short (vs. long) treatment regimens and treatments with DOT [versus self-administered therapy (SAT)] were found to be completed more often in the general population with LTBI in six and three studies, respectively, (no study found an inverse association). Adverse events were inversely associated with completion in seven studies (no study found a positive association). Similar results were found for determinants of completion in individuals from the different populations. Female (versus males) were more likely to complete treatment (no study found men were more likely to complete treatment). Additionally, alcohol use (versus no alcohol use) was inversely associated with completion in four studies (no study found a positive association). [63] level I

In a systematic review by Liu Y et al. (2018), retrievable evidence on the factors affecting adherence were categorized into patient-, provider- or system-level barriers as summarized in Table 6. The main barriers to adherence included the fear or experience of adverse effects, long duration of treatment, financial barriers, lack of transport to clinics (for patients) and insufficient resources for LTBI control.(Table 12) [64] level I

Table 12: Factors affecting adherence according to different level of barriers

Type of barrier		**Findings**
Patient-level barrier	Fear or experience of treatment adverse effects	-LTBI patients in Sweden were less likely to accept treatment (RR = 0.781; 95%CI 0.643, 0.950) and less likely to complete treatment (RR = 0.640; 95%CI 0.462, 0.885) when concerned about the adverse effects of medication *(Kan et al.).* - Younger patients were reported to be less likely to adhere if adverse effects occurred (OR = 0.5; 95%CI 0.33, 0.83) *(Chang et al.).*
	Duration of the treatment	-Completion of treatment was significantly higher in the 4-month rifampicin treatment group compared with the 6-month isoniazid treatment group in Switzerland (83% vs 74%, p = 0.02) and Spain (72% vs 52.4%, p = 0.001).
	Social barriers	-Low adherence rates were associated with the relative poverty of LTBI patients (2 studies) and work conflicts, which posed challenges for attending clinic appointments. -Travel time to and from the clinic represented time absent from work, resulting in patients missing appointments and abandoning treatment. (2 studies) -Lack of transportation to clinics was another important patient-level barrier.(2 studies)

Type of barrier		Findings
	Lack of knowledge	-Many LTBI patients believed there was no need to treat LTBI (5 studies). -Confusion of the potential link between BCG vaccination and LTBI status and indicated that they did not comply with treatment because they thought their LTBI status was caused by the BCG vaccine and therefore believed treatment was not necessary. (2 studies)
	Language and cultural barriers, stigmatisation	-Commonly perceived to affect adherence among migrant populations. (5 studies)
	Quality of health service	-Unsatisfactory experience with health service providers. (2 studies)
Provider-level barrier	Insufficient prioritisation of and resources for LTBI control in individual setting	-Lack access to education and training for health professionals to ensure they were able to remain up-to-date with current LTBI guidelines and treatment strategies ie the challenge of not being able to receive credit or approved study leave to attend LTBI in-service training. -LTBI patients often presented with complex issues and providers discussed the need for longer appointments to address complex cases and have sufficient time to conduct appropriate adherence and adverse effect counseling. -Greater support from specialists to better manage complex cases.
	Inconsistent or contradictory messages from different providers (nurses, healthcare workers, private providers) leads to lack of coordination of LTBI care.	-*White et al.* found that information given by providers was not always appropriately targeted, particularly to patients with lower levels of education and who did not speak English as their first language.
System-level barrier	Treatment of LTBI was felt to be a low priority	- Control efforts tended to focus on active TB treatment, contact tracing, and care and did not tend to include comprehensive strategies for LTBI management as part of the broader TB control strategies. (2 studies)
	Lack access to comprehensive national health insurance structures	-In US, insurance coverage was variable and did not cover all the treatment costs associated with LTBI care (eg, medication costs for adverse effects and liver function tests.
	Lack of well targeted programmes and services	Programmes and services inaccessible by high-risk populations such as drug users and the homeless.

5.5.2 Interventions to improve LTBI treatment initiation, adherence and completion

Based on findings from two systematic reviews [Stuurman et al. (2016) and Liu Y et al. (2018)] provided evidence for five interventions; short treatment regimens, directly observed therapy (DOT), incentives, social interventions and other or combination of interventions.(Table 13) [63, 64 level I]

Table 13: Different type of interventions to improve LTBI treatment initiation, adherence and completion

Intervention	Evidence
a) Short treatment regimens	- Case contacts showed better adherence when receiving short treatment (2 studies; pooled OR = 1.5; 95%CI 1.0-2.3). - All other studies found higher completion rates in the short treatment group: in immigrants with LTBI (1 study; OR = 2.5; 95%CI 1.7–3.6), in the general population with LTBI (2 studies; pooled OR = 1.9; 95%CI 1.1–3.5) and in case contacts (1 study; OR = 2.1; 95%CI 1.9–2.3)
b) DOT	-Undocumented migrants had significantly lower completion rates among those receiving twice weekly clinic-based DOT compared to daily SAT (OR = 0.1; 95%CI 0.0–0.3) or twice weekly SAT (OR = 0.2; 95%CI 0.1–0.6) -In drug abusers, no effect of DOT administered by an outreach nurse on completion rates of LTBI treatment was found (OR = 1.1; 95%CI 0.5–2.1). However, when looking at the proportion of people who took all doses, the DOT group performed significantly better (OR = 31.5; 95%CI 14.1–70.6) - Higher completion rates were found in the DOT group among both case contacts (OR = 2.1; 95%CI 1.9– 2.3) and IV drug abusers (OR = 14.5; 95%CI 5.1–42) compared to SAT. (2 studies)
c) Incentives [(a) cash or monetary incentive;(b) noncash incentives -clothing, toys for children, free lunch, grocery store coupons, phona cards, transportation or food vouchers]	- IV drug abuser with LTBI who received either a monetary incentive (adjusted OR = 32.0; 95%CI 7.1–145 or methadone treatment (OR = 14.5; 95%CI 5.0–42 was found to have a higher completion rates for LTBI treatment compared to those who received no incentive. (2 studies) -The provision of food or transportation vouchers to released inmates with LTBI if they attended a TB clinic upon release (OR = 1.1; 95%CI 0.5–2.4) did not lead to better completion rates. -No difference was found between the provision of cash-incentives versus non-cash-incentives to homeless individuals with LTBI (OR = 1.7; 95%CI 0.7–4.3) (1 study)
d) Social interventions **- peer counseling** **- cultural case management (use of interpreter, translated material)** **-nurse-led case management** **-education outreach**	-Adherence coaching among the general population with LTBI at clinics and a cultural intervention among immigrants resulted in better adherence. -Social interventions were found to improve completion rates of LTBI treatment compared to the standard care group in all but one study, which provided peer-support among IV drug abuser with LTBI (OR = 1.0; 95 % CI 0.7–1.5) and found no effect on completion.

Intervention	Evidence
	-Counselling and contingency contracting, adherence coaching and self-esteem counselling, and peer-based interventions in the general population showed better completion rates (pooled OR = 1.4; 95 % CI 1.1–19). -Education among inmates (OR = 2.2; 95%CI 1.0–4.7), nurse case management among homeless individuals (adjusted OR = 3.0; 95%CI 2.2–4.2). - Case management with attention for the cultural background of each individual among immigrants also led to higher initiation rates (OR = 2.7; 95%CI 1.9–3.8).
e) Other or combination of interventions	-The use of IGRAs rather than TSTs for diagnosis of LTBI improved the initiation rate of LTBI treatment in healthcare workers with LTBI (OR = 8.8; 95 % CI 3.1–23)(1 study). -In the general population with LTBI, there were significantly higher completion rates in the groups that received DOT, behaviour modification techniques in combination with incentives, or home to clinic follow-up, respectively (3 studies). --Nurse-led case management (direct health education, psychosocial support, and linkage to medical and social services) combined with education and incentives was also found to significantly improve adherence (62% vs 39%)(1 study).

*__contingency contracting__ – negotiation of incentive to be received if adhere to the prescribed TB treatment; **adherence coaching** – discussion of adherence strategies between patients and their coaches as well as provision of moral support (encouragement, praise) by coaches to patients.

5.5.4 Training

The administration and interpretation of the LTBI diagnostic tests requires adequate training for healthcare workers to guarantee the reliability of the results. For TST, crucial technical aspects relate to the use of the correct injection technique and reading and interpretation of induration.[65] Although IGRA testing is not affected by healthcare worker perception or bias in relation to BCG and most environmental mycobacteria, it is pertinent to establish clear standard operating procedures and quality assurance programmes for the laboratory work in order to capture any significant variation in performance.[66]

Education and training of healthcare workers designed to increase the knowledge of TB/LTBI and raise awareness of the disease are important. It will help in informing and effectively treating TB patients, thereby contributing to the control of LTBI.[67]

5.6 Ethical Considerations

Testing and treatment of LTBI introduce risk of harm to targeted groups and individuals, which may include inconvenience, social harms such as stigma and the risk of physical harm from the adverse effects of preventive treatment. The policy development should address three distinctive characteristics of LTBI management; potentiality (the risk of future development of active disease and not the current risk), uncertainty (current limitations imposed by scientific and technological methodology, both diagnosis and treatment of LTBI) and vulnerability (poverty and social marginalisation).[63]

Testing for LTBI should be done with the intention of offering treatment when the screening is positive, although the feasibility, the individual's characteristics and the balance between benefits and harm should be taken into consideration. While majority of TST or IGRA positive will never develop to active TB, the positive test result may potentially cause anxiety and prejudice. Screening strategies must be accompanied by appropriate individual and community education to avoid unintended harm for tested individuals.[8]

Since LTBI management is a preventive, rather than a curative measure, benefits for otherwise healthy people need to outweigh risks, such as the daily burden of taking medications and potential adverse events due to treatment. In programmatic management of LTBI, both individual aspects and TB control through prevention of transmission should be considered. While individuals themselves benefit from a reduction in the future risk of TB, benefits also flow to communities at decreased risk of transmission after treatment completion. Individuals at higher risk of adverse effects from treatment may, however, suffer greater potential harm in order to achieve an equivalent personal and communal benefit.[68, 69]

5.7 Social Implication

5.7.1 Health related quality of life

A systematic review and meta-analysis by Bauer M et al. (2013) was conducted to compare the impact of TB on quantitative measures of self-reported health-related quality of life (HRQOL) between subjects treated for active TB with subjects treated for LTBI, at similar time points with respect to diagnosis and/or treatment. [70] level I Subjects with active TB consistently reported poorer HRQOL than subjects treated for LTBI, across a variety of questionnaires and settings. Estimates of pooled standardized mean differences (SMDs) demonstrated that subjects treated for active TB had mean scores 0.66 (95%CI -0.82, -0.50; I^2 17%) and 0.51 (95%CI -0.77, -0.26; I^2 54%) standard deviations below those treated for LTBI within 2 weeks of diagnosis and after 6–8 months of treatment, respectively. Pooled estimates of SMDs in health utilities among subjects treated for active TB compared to those treated for LTBI within the first 2 weeks of treatment showed similar results [-0.62 (95%CI -0.82, -0.42; I^2

89%). ·Among subjects treated for LTBI, longitudinal measurements of HRQOL did not suggest meaningful changes between time of diagnosis and six months of treatment.[70] level I

A cohort study by Bauer M et al. (2015) reported similar results when they compared HRQOL between persons diagnosed and treated for TB disease, persons treated for LTBI, and persons screened but not treated for TB disease or LTBI (control group), over one year following diagnosis/initial assessment. The mean SF-36 scores reported by participants treated for LTBI and control participants were comparable throughout the study (at baseline, and at 1, 2, 4, 6, 9, and 12 months).[71] level II-2 Participants treated for TB disease reported significantly worse mean scores. Thirty-eight percent of participants treated for LTBI reported at least one episode of treatment intolerance between the baseline and 1-month evaluations. No participant experienced an adverse event that led to hospitalization. Eighty-five percent of the participants prescribed the 9-month regimen of INH for the treatment of LTBI completed their treatment, and 80% prescribed the 4-month regimen of Rifampin for the treatment of LTBI completed their treatment. [71] level II-2

A mixed method study by Shedrawy J et al. (2019) aimed to measure HRQOL and qualitatively explore patients' experiences during diagnosis and treatment of LTBI in Stockholm. The HRQOL was assessed using the instrument EQ- 5D-3L and Refugee Health Screening-15 (RHS-15), was used to screen for mental health issues among study subjects with a migration background.[72] level III The study excluded patients with disabling medical conditions that were the main indication for LTBI screening, such as systemic rheumatic diseases, dialysis, transplantation, and other conditions requiring immunosuppressive therapy. The quantified HRQOL of LTBI patients was similar to the general population and there was thus no HRQOL decrements detectable with EQ-5D. A small percentage of patients reported problems with physical functioning in term of mobility (7.4%) and usual activity or self-care (1.8%). Problems with the pain/discomfort domain in the EQ-5D questionnaire were reported by 24.1% of survey participants. Anxiety/depression was the domain with the highest percentage of problems reported (27.8% of participants). Thirty-eight percent of participants screened positive on RHS-15 indicating some form of mental distress. Based on the qualitative findings, three themes emerged for the mental health concerns; ambiguous threat, fear of being contagious and future uncertainties. The diagnosis created some fears due to lack of knowledge and information about this type of disease and its severity, especially that TB is often associated with death and severe consequences in their home country. Patients expressed fear of being contagious and affecting their surrounding which was especially emphasized by pregnant women who were concerned about breastfeeding and being in close contact with their children. Patients also expressed their worries about activation of the latent disease in the future or "getting sick again" despite adherence to treatment.[72] level III

5.8 LIMITATION

This technology review has several limitations. The selection of studies was done by one reviewer. Only English full text articles were included in this review. Most of retrievable systematic reviews consist of studies conducted outside Malaysia which are different with regard to the healthcare system and population. Hence, the results cannot always simply be extrapolated to the Malaysian setting. The review of local literatures was limited by a small number of retrievable local published studies. Most of the studies included in the systematic reviews were of short follow-up duration. This could cause possible misestimation of certain effect or outcome measures.

6. CONCLUSION

6.1 Efficacy/Effectiveness

Diagnostic tests for programmatic management of LTBI

There was good level of retrievable evidence to suggest that both TST and IGRA poorly predict the development of active TB (low PPV). Limited evidence had shown that neither test was preferred above the other when assessing progression to TB disease. Among non-BCG vaccinated population, both had similar sensitivity and high specificity to detect LTBI. However, TST displayed lower specificity compared to IGRA in BCG-vaccinated population.

Children

The predictive performance of TST 5mm and IGRA for progression to active TB were similar. Interferon gamma release assays performed better than TST 10mm in predicting the development of active TB. In detection of LTBI, IGRA appeared to outperform TST in low TB burden settings but not high TB burden settings, Interferon gamma release assays had reduced sensitivity and specificity in high TB burden settings. This type of effect modification could be explained by higher frequency of exposure to *M. tuberculosis*, different transmission dynamics, malnutrition, comorbidity, coinfection with HIV or helminthic infection.

Immunocompromised people

There was large variation in the performance of IGRAs compared with TST across different clinical subgroups. QFT-GIT and T-SPOT.TB performed better than TST 5 mm/10 mm in those undergoing haemodialysis and those with hepatitis C. In contrast, QFT-GIT performed significantly worse than TST 10mm in people with HIV/AIDS. Among transplant candidates, IGRAs were shown to be more sensitive and specific. For other clinical subgroups of immunocompromised people the evidence was inconclusive because of the high level of uncertainty around the statistically non-significant effect estimates.

Migrants

Among recently arrived people from countries with a high TB burden, there was no significant difference between the performance of IGRAs and the performance of TST in identifying LTBI.

Preventive Therapy

There was good level of retrievable evidence to suggest that in comparison to placebo, INH regimen of six months or 12 to 72 months, RMP regimen, RMP-INH regimen of 3 to 4 months, RMP-INH-PZA regimen and RMP-PZA regimen were shown to be efficacious in preventing the development active TB. A well tolerated, lesser side effects and shorter duration regimen was associated with better adherence and higher completion rate.

6.2 Safety

There was good level of retrievable evidence to suggest that regimens containing PZA had higher hepatotoxicity compared with six months of INH or 12 weeks of RPT-INH [pooled RR 4.59 (95%CI 2.14, 9.85)]. Serious adverse events were documented to be rare. However, RMP-PZA regimens were reported to have the highest risk for gastrointestinal adverse events, and RMP regimens were reported to have the highest risk for central nervous system adverse events.

6.3 Cost effectiveness

Diagnostic test

- Evidence on screening of high risk populations identified the influence of TST and IGRA sensitivity and specificity, TB and LTBI prevalence, treatment effectiveness, duration and treatment costs on cost-effectiveness.
- Based on WTP threshold of USD100,000, from US and Canadian healthcare perspective;

  <u>Migrants</u>
  - The IGRA was found moderately cost-effective in adult migrants, while the TST was dominated by no screening

  <u>Immunocompromised people</u>
  - Screening of people with HIV was strongly cost effective with a TST and moderately cost effective with an IGRA
  - Neither TST nor IGRA was cost effective for screening of LTBI in renal diseases and diabetic patients, however, the IGRA was found to be the most cost-effective test more often than the TST, if screening had to be performed for renal diseases patients and TST was found to be most cost effective for diabetic patients if screening was done

    - All ICERs for other immunocompromising conditions were cost prohibitive, although the TST was found to be the most cost-effective test if screening had to occur

- The economic model for diagnostic tests showed that the best-available options (the most cost-effective strategies) from NHS UK perspective were:
    - In children: TST (≥5 mm) followed by IGRAs if negative
    - In immunocompromised people: IGRAs followed by TST (≥5 mm) if negative
    - In the recently arrived population from high TB burden countries: TST alone (≥5 mm)

Preventive therapy

- Three months of weekly RPT-INH was more cost-effective than other WHO-recommended regimens or serial radiographic surveillance, from US and other comparable health system perspective at a WTP threshold of USD50,000 per QALY gained.
- Since RPT-INH-DOT prevented more incident cases of active TB, it was found to be more cost-effective than the same regimen when self-administered (RPT-INH -SAT). The cost-effectiveness of RPT-INH-DOT was strongly driven by treatment completion rates.

6.4 Organisational

Identification of target risk groups

- There was fair level of retrievable evidence to suggest that clinical risk groups had no increased risk of LTBI in comparison to general population except for candidates of anti-TNF alpha therapy. However, there was evidence of increased risk of progression to active TB in people with LTBI belonging to clinical risk groups.
- Based on limited evidence, it was found that migrants and close contacts of TB cases had an increased risk of being infected and progressing to active TB disease, depending on socioeconomic and epidemiological determinants.
- For healthcare workers, there was no increased risk of LTBI, but an increased risk of active TB of LTBI positive healthcare workers compared to the general population.
- Based on local published studies, the prevalence of LTBI among healthcare workers and prison employees were 10.6-46% and 81%, respectively. The risk factors for LTBI among healthcare workers were working in clinical areas, duration of employment more than five years, aged ≥ 35, close contacts, having chronic disease, working as a nurse and being male. While the increased risk among prison employees was associated with having worked in the correctional system for 12 months or more and smoking tobacco.

Determinants of LTBI treatment initiation, adherence and completion

- The progressive losses at all stages of the care cascade resulted in low completion rate of LTBI treatment.
- Factors associated with higher compliance rate were people with immune-compromising medical indications, female gender, being part of contact investigations, immigrant or refugee status and shorter LTBI treatment regimens with DOTS.
- Barriers from patients, providers and within the health system exacerbated nonadherence. The main patient-level barriers included fear or experience of adverse effects, the treatment regimen, lack of transportation to clinics, and lack of knowledge of LTBI. Provider-level barriers included insufficient prioritization of and resources for LTBI control in their setting and lack of coordination of LTBI care, while system-level barriers included a lack of prioritization of LTBI control by governments.

Interventions to improve LTBI treatment initiation, adherence and completion

- Incentives may have positive effects on adherence in the short term, particularly for marginalized populations such as drug users, recently released prisoners, and the homeless
- Cultural case management which included targeted and culturally appropriate programming that was focused on specific population was also found to be effective.
- Education approaches with innovative strategies for both LTBI patients and health care workers may improve adherence.

Training

- The administration and interpretation of the LTBI diagnostic tests requires adequate training for healthcare workers to guarantee the reliability of the results.
- Education and training of healthcare workers designed to increase the knowledge of TB/LTBI and raise awareness of the disease are important. It will help in informing and effectively treating TB patients, thereby contributing to the control of LTBI.

6.5 Ethical considerations

LTBI management is a preventive, rather than a curative measure, hence benefits for otherwise healthy people need to outweigh risks. In programmatic management of LTBI, both individual aspects and TB control through prevention of transmission should be considered. The policy development should address three distinctive characteristics of LTBI management; potentiality (the risk of future development of active disease and not the current risk), uncertainty (current limitations imposed by scientific and technological methodology, both diagnosis and treatment of LTBI) and vulnerability (poverty and social marginalisation). Testing for LTBI should be

done with the intention of offering treatment when the screening is positive. Screening strategies must be accompanied by appropriate individual and community education to avoid unintended harm for tested individuals.

6.6 Social implication

Health-related quality of life

There was no meaningful change in HRQOL among subjects treated for LTBI between time of diagnosis and treatment completion in comparison to subjects treated for TB disease or general population (no decrement detactable by either SF-36 or EQ-5D scores).However, three themes emerged for the mental health concerns; ambiguous threat, fear of being contagious and future uncertainties.

7.0 RECOMMENDATION

The tuberculin skin test (TST) and interferon gamma release assays (IGRA) or a combination of both tests may be used to diagnose LTBI. The choice of test should be based on target risk group and available resource. Screening of LTBI should consider availability of and accessibility to diagnostic tests, the intention to provide LTBI treatment (if appropriate), the implementation of interventions promoting the uptake and completion of LTBI screening procedures.

Provision of LTBI treatment should be using treatment regimens that are of shorter duration and lesser toxicity in order to promote adherence and enhance completion by different target groups. The selection of LTBI treatment regimen may be based on an individual risk assessment. The following regimens can be considered: isoniazid alone (for 6–9 months), rifampicin alone (for 3–4 months), isoniazid and rifapentine (for 3 months), isoniazid and rifampicin (for 3–4 months).

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9.0 APPENDIX

Appendix 1: LITERATURE SEARCH STRATEGY

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to December 17, 2019>
Search Strategy:
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1 LATENT TUBERCULOSIS/ (2511)
2 (latent tuberculosis adj1 infection$1).tw. (2289)
3 ((tuberculos#s or tuberculosis infection$1) adj1 latent).tw. (3423)
4 latent TB.tw. (1716)
5 latent tuber*.tw. (3648)
6 inactive tuber*.tw. (141)
7 programmatic management.tw. (118)
8 (disease adj1 management$1).tw. (14404)
9 (patient adj2 management).tw. (23863)
10 ((screening or contact or investigation or finding) adj1 tuberc*).tw. (1089)
11 quantiferon*.tw. (1782)
12 QFT*.tw. (1170)
13 enzyme linked immunospot assay/ (1179)
14 exp interferon gamma release assay/ (1372)
15 ((interferon* or IFN*) adj3 gamma* adj3 (release* or test* or assay*)).tw. (6544)
16 ((y-interferon or interferon-y) adj3 (release* or test* or assay*)).tw. (12)
17 IGRA*.tw. (1234)
18 ltbi treatment.tw. (313)
19 (treatment* or therap* or prevent* or management or control or prophyla* or chemoprophyla* or DOT or DOTS or isoniazid or INH or IPT or rifapentine or RPT or rifampin or RIF or ethambutol or EMB or ethionamide or ETH or pyrazinamide or PZA or fluroquinolones or FLQ or moxifloxacin or levofloxacin or gatifloxacin).tw. (8868768)
20 medication compliance.tw. (1456)
21 "patient attitude".tw. (141)
22 treatment withdrawal.tw. (1381)
23 medication therapy management.tw. (670)
24 (adher* or complian* or comply* or accordance or according or agreement or Initiat* or start* or commenc* or begin or introduc* or enroll* or complet* or finaliz* or finalis* or fulfill* or ending or finish* or terminat* or accomplish* or realiz* or realis* or attain* or implement* or apply* or application* or refus* or attitud*).tw. (6227260)
25 1 or 2 or 3 or 4 or 5 or 6 (5681)
26 7 or 8 or 9 (38027)
27 11 or 12 or 13 or 14 or 15 or 16 or 17 (8947)
28 18 or 19 (8868768)
29 20 or 21 or 22 or 23 or 24 (6228216)
30 25 and 26 (28)

31 25 and 27 (1800)
32 25 and 28 (3797)
33 25 and 29 (2475)
34 30 or 31 or 32 or 33 (4746)
35 limit 34 to (english language and humans) (3531)

****

OTHER DATABASES

EBM Reviews - Cochrane Central Register of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
EBM Reviews – NHS Economic Evaluation Database	

PubMed

(((((“latent tuberculosis” [Mesh] OR “latent tuberculosis” [tiab] OR LTB [tiab] OR LTBI [tiab] OR ((laten* [tiab] OR dorman* [tiab]) AND (TB [tiab] OR tuberc* [tiab])) AND (screen*[tiab] OR find*[tiab]) AND ((risk*[tiab] OR target[tiab] OR vulnerab*[tiab]) AND (group*[tiab] OR people*[tiab] OR population*[tiab])) OR (QFT [Mesh] OR enzyme linked immunospot assay [tiab] OR interferon gamma release assay [tiab] OR IGRA [tiab]) AND ("therapeutics" [Mesh] OR "therapy" [Subheading] OR "treatment outcome" [Mesh] OR "primary prevention" [Mesh] OR "secondary prevention" [Mesh] OR “prevention and control” [Subheading] OR treatment* [tiab] OR therapy [tiab] OR therapies [tiab] OR therapeutics [tiab] OR prevent* [tiab] OR management [tiab] OR “antibiotic prophylaxis” [Mesh] OR “chemoprevention“ [Mesh] OR prophyla* [tiab] OR chemoprophylaxis [tiab] OR DOT [tiab] OR DOTS [tiab] OR "isoniazid" [Mesh] OR isoniazid [tiab] OR INH [tiab] OR IPT [tiab] OR "rifapentine" [Supplementary Concept] OR rifapentine [tiab] OR RPT [tiab] OR "rifampin" [Mesh] OR rifampin [tiab] OR RIF [tiab] OR rifampicin [tiab] OR ethambutol [tiab] OR EMB [tiab] OR ethionamide [tiab] OR ETH [tiab] OR pyrazinamide [tiab] OR PZA [tiab] OR fluroquinolones [tiab] OR FLQ [tiab] OR moxifloxacin [tiab] OR levofloxacin [tiab] OR gatifloxacin [tiab])) AND ("attitude" [Mesh] OR adher* [tiab] OR “medication adherence” [Mesh] OR “guideline adherence” [mesh] OR “patient compliance” [mesh] OR complian* [tiab] OR comply* [tiab] OR accordance [tiab] OR according [tiab] OR agreement [tiab] OR “withholding treatment” [mesh] OR initiat* [tiab] OR start [tiab] OR commenc* [tiab] OR begin* [tiab] OR introduc* [tiab] OR enroll* [tiab] OR complet* [tiab] OR finaliz* [tiab] OR finalis* [tiab] OR fulfill* [tiab] OR ending [tiab] OR finish* [tiab] OR terminat* [tiab] OR accomplish* [tiab] OR realiz* [tiab] OR realis* [tiab] OR attain* [tiab] OR implement* [tiab] OR apply* [tiab] OR application* [tiab] OR “medication therapy management” [mesh])) NOT Animals [Mesh] NOT (Humans [Mesh] AND Animals [Mesh])

Appendix 2

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Appendix 3

Evidence Table: Efficacy / Effectiveness
Question: Which tests are effective for diagnosis of LTBI?

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF PARTICIPANTS/ PATIENT'S CHARACTERISTICS	INTERVENTION	COMPARATOR	LENGTH OF FOLLOW UP	OUTCOME MEASURE(S)	GENERAL COMMENT
Kik SV, Rangaka MX. Predictive utility of the tuberculin skin test and interferon-gamma release assay among individuals who are not prescribed tuberculosis preventive therapy. WHO, 2014.	**Systematic Review** **Objective:** To comprehensively summarise data on the effectiveness of diagnostic tests for LTBI among persons at high risk of LTBI who are not on TB-preventive therapy. The results included in our analysis are extracted from the initial review performed for the WHO guidelines and correspond to the period 1999 up to 25 February 2014.	**I**	29 studies included. Study populations were diverse: 13 studies assessed TB contacts (2 studies in children and 11 studies in adolescents and adults), 11 studies assessed cohorts of individuals with medical conditions leading to impaired immune response (seven studies included PLHIV, 4 studies included other medical conditions), 1 study was performed among prisoners, 1 study was performed among asylum seekers, 1 study was performed among adolescents living in high-TB-prevalence countries and 1 study was performed among silicosis patients.	IGRAs	TST	20-35 months	Overall pooled estimate RR for progression to active TB TST: 2.58 (95%CI 1.72, 3.88) IGRA: 4.94 (95%CI 1.79,13.65) Immunocompromised patients TST: 2.96 (95%CI 0.38, 23.18) IGRA: 5.95 (95%CI 0.57, 62.05) TB case-contacts TST: 2.3 (95%CI 1.76, 3.70) IGRA: 5.96 (95%CI 0.57-62.05) In all analyses the CIs around effect estimates for the TST and IGRA overlapped and were imprecise.	

Evidence Table: Efficacy / Effectiveness
Question: Which tests are effective for diagnosis of LTBI?

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF PARTICIPANTS/ PATIENT'S CHARACTERISTICS	INTERVENTION	COMPARATOR	LENGTH OF FOLLOW UP	OUTCOME MEASURE(S)	GENERAL COMMENT
Auguste P, Tsertsvadze A, Pink J, et al. Accurate diagnosis of latent tuberculosis in children, people who are immunocompromised or at risk from immunosuppression and recent arrivals from countries with a high incidence of tuberculosis: systematic review and economic evaluation. Health Technol Assess 2016;20(38)	**Systematic Review** **Objective:** To investigate the clinical effectiveness of screening tests [interferon- gamma release assays (IGRAs) and tuberculin skin tests (TSTs)] in latent tuberculosis infection (LTBI) diagnosis for 3 population groups: children, immunocompromised people and those who have recently arrived from high-incidence countries (annual incidence ≥ 40 per 100,000). **Inclusion criteria:** - Head to head comparative studies IGRAs (QFT-GIT, T-SPOT.TB) vs TST, which followed-up	**I**	17 included studies (5 were conducted in children, 10 in immunocompromised people and 2 studies were undertaken in people recently arrived from countries with a high incidence of TB) <u>Children & adolescents</u> **Mean age and /or median age**: *Children*: 29 months-8 years old *Adolescents*:12-20years old **Prevalence of BCG vaccination**: 36-94% The five studies were undertaken in Germany, Turkey, Iran, South Africa and South Korea.	IGRAs	TST	Mean length of follow up to diagnosis of active TB;1-4 years	**QFT-GIT** Fifty-six of the 3007 (1.86%) QFT-GIT-positive children (4 studies) progressed to active TB compared with 25 of the 5376 (0.46%) QFT-GIT-negative children (overall crude CIR for QFT-GIT: 1.86/0.46= 4.01, 95% CI: 2.51, 6.40). **TST (5 mm)** Forty-six of the 2934 (1.56%) TST (≥5 mm)-positive children (2 studies) progressed to TB compared with 12 of 2414 (0.49%) TST (<5 mm)-negative children of whom only 12 (0.49%) progressed to active TB (over- all crude CIR for TST-5 mm: 1.57/0.50 = 3.14, 95% CI: 1.68, 5.94). **TST (10 mm)** Twenty of the 711 (2.81%) TST (≥10 mm)-positive children (3 studies) progressed to TB compared with 19 of the 2433 (0.78%) TST (<10 mm)-negative children (crude CIR	

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF PARTICIPANTS/ PATIENT'S CHARACTERISTICS	INTERVENTION	COMPARATOR	LENGTH OF FOLLOW UP	OUTCOME MEASURE(S)	GENERAL COMMENT
	people to incidence of active TB after testing. **Exclusion criteria:** -Studies of people treated with anti-tuberculosis prophylaxis after testing for LTBI -Studies which used 'in-house' assays, -Single-arm studies testing people for LTBI with only IGRAs or TST						for TST-10 mm: 2.81/0.78=3.60, 95% CI: 1.93, 6.71).	
			<u>Immunocompromised people</u> Six of the 10 studies were conducted in South Korea and Taiwan, 1 each in Iran, Switzerland, and Denmark and the remaining study across various European countries **Type of patients** Haemodialysis for end-stage renal disease (ESRD), haematopoietic stem cell transplantation candidates and haematopoietic stem cell transplantation recipients,people with 'rheumatic disease, people who had undergone kidney transplantation, people living with human immunodeficiency				**IGRAs (QFT-GIT and T-SPOT.TB)** In the immunocompromised population (4 studies), seven of the 232 (3.02%) QFT-GIT positive people progressed to active TB compared with 13 of the 1999 (0.65%) QFT-GIT that tested negative (crude CIR for QFT-GIT: 3.02/0.65=4.65, 95% CI: 1.87, 11.51). 34 of the 328 (10.37%) T-SPOT.TB posi- tive people (5 studies) progressed to TB compared with 26 of the 1273 (2.04%) T-SPOT.TB that tested negative (crude CIR for T-SPOT.TB: 10.37/ 2.04 = 5.08, 95% CI: 3.09, 8.33). **TST (10 mm)** Four of the 107 (3.74%) people with TST (≥10 mm) (5 studies) progressed to TB com- pared with eight of 389 (2.06%) with TST (<10 mm) (crude CIR for TST-10 mm: 3.74/2.06 = 1.82, 95%CI 0.58, 5.92)	

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF PARTICIPANTS/ PATIENT'S CHARACTERISTICS	INTERVENTION	COMPARATOR	LENGTH OF FOLLOW UP	OUTCOME MEASURE(S)	GENERAL COMMENT
			virus (PLWHIV), people being treated for inflammatory arthritis, people being treated for sarcoidosis					
			<u>People who recently arrived from countries with high TB incidence</u> These studies were undertaken in Norway and the Netherlands. T Most of the participants in both studies had arrived from Europe, Africa, and Asia. Mean length of follow-up ranged from 2 years to 3 years.				**IGRAs (QFT-GIT and T-SPOT.TB)** Across two studies, 13 of 416 (3.13%) recent ar- rivals who tested positive with QFT-GIT progressed to TB compared to four of 726 (0.55%) that tested negative (crude CIR for QFT-GIT: 3.13/0.55 = 5.69, 95% CI: 1.86, 17.28). Six of 181 (3.31%) people who tested positive with T-SPOT.TB progressed to TB compared to two of 118 (1.69%) that tested negative (crude CIR for T-SPOT.TB: 3.31/1.69 = 1.96, 95% CI: 0.40, 9.53). **TST (≥10 mm)** 9 of the 288 (3.12%) people with a TST (≥10 mm) progressed to TB as compared to none of the 51(0%) people that tested negative (crude CIR for TST-10 mm: 3.42, 95%CI 0.20, 57.83).	

Evidence Table: Efficacy / Effectiveness
Question: Which tests are effective for diagnosis of LTBI?

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF PARTICIPANTS/ PATIENT'S CHARACTERISTICS	INTERVENTION	COMPARATOR	LENGTH OF FOLLOW UP	OUTCOME MEASURE(S)	GENERAL COMMENT
Greenaway C, Pareek M, Abou Chakra CN et al. The effectiveness and cost-effectiveness of screening for latent tuberculosis among migrants in the EU/EEA: a systematic review. Euro Surveill. 2018;23(14).	**Systematic Review** Objective: To determine effectiveness of diagnostic tests for LTBI	**I**	3 SRs included i. Asymptomatic adults at increased risk for active TB (n=10,693) ii.BCG vaccinated versus non-vaccinated (n = 1,879) iii. Persons at high risk of LTBI, not on TB preventive treatment (n = 54,833)	IGRA	TST	Not specified	SR 1 Sensitivity, specificity (95% CI) of LTBI screening tests: TST (5 mm): sensitivity: 79% (69–89), specificity 30–97%; TST (10 mm): sensitivity: 79% (71–87), specificity: 97% (96–99); TST (15 mm): sensitivity: 52% (35–68), specificity: 99% (98–99); IGRA (T-SPOT.TB): sensitivity: 90% (87–93), specificity: 95% (92–98); IGRA (QFT-G): sensitivity: 77% (74–81), specificity: 98% (90-1.0); SR2 Sensitivity, specificity (95% CI) of LTBI screening tests: TST overall: sensitivity:77% (71–82). TST in BCG-vaccinated: specificity: 59% (46–73). TST in non-BCG-vaccinated: specificity: 97% (95–99). IGRA (QFT): sensitivity: 76% (72–80), specificity: 98% (96–99). IGRA in BCG-vaccinated: specificity: 96%(94–98). IGRA in non-BCG-vaccinated: specificity: 99% (98–100).	

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							IGRA (T-SPOT.TB/ ELISpot): sensitivity: 90% (86–93), specificity: 93% (86–100). IGRA (T-SPOT.TB): specificity: 87% (80–92). <u>SR3</u> <u>Screening tests characteristics:</u> The PPV: TST: 1–7%, IGRA: 0–13%. The NPV: TST: 92–100%, IGRA: 88–100%. The pooled IRR: TST: 2.07 (95% CI:1.38–3.11), IGRA: 2.40 (95% CI: 1.26–4.60).	

Evidence Table: Efficacy / Effectiveness
Question: Which tests are effective for diagnosis of LTBI?

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Nasiri MJ, Pormohammad A, Goudarzi H et al. Latent tuberculosis infection in transplant candidates: a systematic review and meta-analysis on TST and IGRA. Infection. 2019;47(3):353-361.	**Systematic Review** Objective**:** To evaluate the diagnostic accuracy of TST and IGRA for LTBI among patients preparing for organ transplantation	**I**	16 cohort studies - 9 studies evaluated the IGRAs and/or TST sensitivity and specificity (n= 2023 subjects) -13 studies assessed the influence of BCG vaccination and/or M. tuberculosis exposure on tests positivity Sample size: 48-735 <u>Countries:</u> Canada, Korea, Iran, Egypt, USA, Germany, Spain, Saudi Arabia, China, Italy	IGRA	TST	Mean follow-up 15 months	<u>TST</u> (pooled results): Sensitivity 46% (95%CI 38–54%) Specificity 86% (95%CI 75–93%) PPV 46.3% (95% CI 40–52) NPV 88.7% (95% CI 87–89) PLR 3.3 (95%CI 1.6–6.4) NLR 0.63 (95%CI 0.52–0.77) DOR 5 (95%CI 2–12) <u>QFT-G (pooled results)</u> Sensitivity 58% (95%CI 41–73%) Specificity 89% (95%CI 77–95%) PPV 72.7% (95%CI 68–76) NPV 80.6% (95%CI 78–82) PLR 5.3 (95%CI 2.0–14.0) NLR 0.47 (95 CI 0.30–0.75) DOR 11 (95%CI 3–46) <u>T-SPOT.TB (pooled results)</u> Sensitivity 55% (95%CI 40–70%) Specificity 92% (95%CI 87–95%) PPV 60.4% (95%CI 47–72) NPV 90.2% (95%CI 86–92) PLR 6.7 (95%CI 4.0–11.1) NLR 0.52 (95% CI 0.31–0.85) DOR 16 (95% CI 7–37) **Authors' conclusion** IGRAs were more sensitive and specific than the TST with regard to	

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							the diagnosis of LTBI in the transplant candidates. They have added value and can be complementary to TST.	

Evidence Table: Efficacy / Effectiveness
Question: What is the effectiveness of different preventive treatment regimens?

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF PARTICIPANTS/ PATIENT'S CHARACTERISTICS	INTERVENTION	COMPARATOR	LENGTH OF FOLLOW UP	OUTCOME MEASURE(S)	GENERAL COMMENT
Zenner D, Beer N, Harris R et al. Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. Ann Intern Med. 2017;167(4):248-255.	**Systematic Review** Objective: To evaluate the comparative efficacy and harms of LTBI treatment regimens aimed at preventing active TB among adults and children	**I**	61 included RCTs	**12 different regimens** INH 3–4 mo INH 6 mo INH 9 mo INH 12–72 mo RFB-INH RFB-INH (high) RPT-INH RMP RMP-INH 1 mo RMP-INH 3–4 mo RMP-INH-PZA RMP-PZA INH-EMB INH-EMB 12 mo	Placebo	**-**	Isoniazid regimens of 6 months (odds ratio [OR], 0.65 [95% credible interval, 0.50 to 0.83]) or 12 to 72 months (OR, 0.50 [CrI, 0.41 to 0.62]), rifampicin-only regimens (OR, 0.41 [CrI, 0.19 to 0.85]), rifampicin-isoniazid regimens of 3 to 4 months (OR, 0.53 [CrI, 0.36 to 0.78]), rifampicin-isoniazid-pyrazinamide regimens (OR, 0.35 [CrI, 0.19 to 0.61]), and rifampicin-pyrazinamide regimens (OR, 0.53 [CrI, 0.33 to 0.84]) were efficacious compared with placebo. Evidence existed for efficacy of weekly rifapentine-isoniazid regimens compared with no treatment (OR, 0.36 [CrI, 0.18 to 0.73]). No conclusive evidence showed that HIV status altered treatment efficacy.	

Evidence Table: Efficacy / Effectiveness
Question: What is the effectiveness of different preventive treatment regimens?

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Sharma S, Sharma A, Kadhiravan T et al. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database Syst Rev. 2013(7):Cd007545.	**Systematic Review** Objective: To compare the effects of rifampicin monotherapy or rifamycin-combination therapy versus INH monotherapy for preventing active TB in HIV-negative people at risk of developing active TB. **Selection criteria** RCTs of HIV-negative adults and children at risk of active TB treated with rifampicin, or rifamycin-combination therapy with or without INH (any dose or duration), compared with INH	**I**	10 trials are included, enrolling 10,717 adults and children, mostly HIV-negative (2% HIV-positive), with a follow-up period ranging from two to five years.	Rifampicin (three/four months) Rifampicin plus INH (three months) Rifampicin plus pyrazinamide (two months) Weekly, directly-observed rifapentine plus INH (three months)	INH (6-9 months)	2-5 years	**Rifampicin (three/four months) vs. INH (six months)** Five trials published between 1992 to 2012 compared these regimens, and one small 1992 trial in adults with silicosis did not detect a difference in the occurrence of TB over five years of follow up (one trial, 312 participants; *very low quality evidence*). However, more people in these trials completed the shorter course (RR 1.19, 95% CI 1.01 to 1.30; five trials, 1768 participants; *moderate quality evidence*). Treatment-limiting adverse events were not significantly different (four trials, 1674 participants; *very low quality evidence*), but rifampicin caused less hepatotoxicity (RR 0.12, 95% CI 0.05 to 0.30; four trials, 1674 participants; *moderate quality evidence*). **Rifampicin plus INH (three months) vs. INH (six months)** The 1992 silicosis trial did not detect a difference between people receiving rifampicin plus INH compared to INH alone for occurrence of active TB (one trial, 328 participants; very low quality evidence). Adherence was similar in this and a 1998 trial in people without silicosis (two trials, 524	

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	for six to nine months.						participants; high quality evidence). No difference was detected for treatment-limiting adverse events (two trials, 536 participants; low quality evidence), or hepatotoxicity (two trials, 536 participants; low quality evidence). **Rifampicin plus pyrazinamide (two months) vs. INH (six months)** Three small trials published in 1994, 2003, and 2005 compared these two regimens, and two reported a low occurrence of active TB, with no statistically significant differences between treatment regimens (two trials, 176 participants; very low quality evidence) though, apart from one child from the 1994 trial, these data on active TB were from the 2003 trial in adults with silicosis. Adherence with both regimens was low with no statistically significant differences (four trials, 700 participants; very low quality evidence). However, people receiving rifampicin plus pyrazinamide had more treatment-limiting adverse events (RR 3.61, 95% CI 1.82 to 7.19; two trials, 368 participants; high quality evidence), and hepatotoxicity (RR 4.59, 95% 2.14 to 9.85; three trials, 540	

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							participants; moderate quality evidence). **Weekly, directly-observed rifapentine plus INH (3 months) vs. daily, self-administered INH (nine months)** A large trial conducted from 2001 to 2008 among close contacts of TB in the USA, Canada, Brazil and Spain found directly observed weekly treatment to be non-inferior to nine months self-administered INH for the incidence of active TB (0.2% vs 0.4%, RR 0.44, 95% CI 0.18 to 1.07, one trial, 7731 participants; moderate quality evidence). The directly-observed, shorter regimen had higher treatment completion (82% vs 69%, RR 1.19, 95% CI 1.16 to 1.22, moderate quality evidence), and less hepatotoxicity (0.4% versus 2.4%; RR 0.16, 95%CI 0.10 to 0.27; high quality evidence), though treatment-limiting adverse events were more frequent (4.9% versus 3.7%; RR 1.32, 95% CI 1.07 to 1.64 moderate quality evidence)	

Evidence Table: Safety
Question: How safe are the preventive treatment regimens?

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Zenner D, Beer N, Harris R et al. Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. Ann Intern Med. 2017;167(4):248-255.	**Systematic Review** Objective: To evaluate the comparative efficacy and harms of LTBI treatment regimens aimed at preventing active TB among adults and children	**I**	61 included RCTs	**12 different regimens** INH 3–4 mo INH 6 mo INH 9 mo INH 12–72 mo RFB-INH RFB-INH (high) RPT-INH RMP RMP-INH 1 mo RMP-INH 3–4 mo RMP-INH-PZA RMP-PZA INH-EMB INH-EMB 12 mo	Placebo	**-**	**Safety** <u>Pooled odd ratios for hepatotoxicity (95%CI)</u> INH 6 months 0.27 (0.10–0.60) INH 9 months 0.41 (0.08–1.62) INH 12–72 months 0.66 (0.26–1.32) RPT-INH 0.13 (0.03–0.42) RMP 0.03 (<0.02–0.16) RMP-INH 3–4 month 0.17 (0.05–0.46) RMP-INH-PZA 0.58 (0.07–3.72) RMP-PZA 0.80 (0.25–2.17) -RMP-only and RPT-INH regimens had lower rates of hepatotoxicity than an INH-only regimen of 6, 9, or 12 to 72 months -RMP- INH regimens also had lower hepatotoxicity than the INH-only regimen (only when compared with INH regimens of 12 to 72 months) -Regimens containing PZA had higher hepatotoxicity compared with 6 months of INH or 12 weeks of RPT-INH. -No data were available on the hepatotoxicity of the RFB-INH and INH- EMB regimens.	

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							-Stratifying the results on the basis of immunosuppression, HIV status, and TB incidence did not affect our conclusions.	

Evidence Table: Safety
Question: How safe are the preventive treatment regimens?

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Pease C, Hutton B, Yazdi F et al. A systematic review of adverse events of rifapentine and isoniazid compared to other treatments for latent tuberculosis infection. Pharmacoepidemiol Drug Saf. 2018;27(6):557-566.	**Systematic Review** Objective: To determine whether the INH/RPT-3 regimen had similar or lesser rates of adverse events compared to INH for 9 months, INH for 6 months, rifampin for 3 to 4 months, and rifampin plus INH for 3 to 4 months.	**I**	23 randomised (n= 373) and 55 non-randomised studies (n= 404) were included.	i. 3-month INH/RPT ii.9-month INH iii.6-month INH iv.3-4-month rifampin v.3-4-month rifampin plus INH	Between. one another	**-**	**Total and grade 3 to 4 adverse events and adverse event-related withdrawals** - INH/RPT-3 had the lowest rate among regimens of having any adverse event (median rate of 11.5%), lowest rate of withdrawals because of adverse events (median 1.7%). - Median rates of withdrawals associated with INH-9 (6.4%) and INH-6 (3.8%) - The median rate of grade 3 to 4 adverse events was higher for INH-6 (8.2%) and INH/RPT-3 (6.0%) and lower for INH-9 (3.3%). -Data from non-randomised studies found that the highest median rate of withdrawals from adverse events was associated with INH-6 (median 5.8%, range 2.3%-24.5%; 9 studies), followed by INH/RPT-3 (median 4.3%, range 1.3%-8.4%; 7 studies), INH-9 (median 2.6%, range 0.4%-26.8%; 13 studies), INH/RMP 3-4 (median 1.8%, range 0.5%-5.1%; 4 studies), and RMP 3-4 (median 0%, range 0%- 5.2%; 6 studies).	

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							Angioedema Ho et al83 reported this outcome in 7/350 (2%) who withdrew from INH/RPT-3. **Adverse events in children** -Rates of adverse events were lower in children than in adult or mixed populations (limited data). --INH 9 months had the highest adverse events rate in children (median rate 10.1%).	

Evidence Table: Safety
Question: How safe are the preventive treatment regimens?

<table>
<tr><th>BIBLIOGRAPHIC CITATION</th><th>STUDY TYPE/ METHODOLOGY</th><th>LE</th><th>NO. OF PARTICIPANTS/ PATIENT'S CHARACTERISTICS</th><th>INTERVENTION</th><th>COMPARATOR</th><th>LENGTH OF FOLLOW UP</th><th>OUTCOME MEASURE(S)</th><th>GENERAL COMMENT</th></tr>
<tr><td>Stagg HR, Zenner D, Harris RJ et al. Treatment of latent tuberculosis infection: a network meta-analysis. Ann Intern Med. 2014;161(6):419-428.</td><td>Systematic Review

Objective:
To determine the most efficacious regimen for preventing active TB with the lowest likelihood of adverse events to inform LTBI treatment policies.</td><td>I</td><td>53 RCTs included</td><td>INH 6 m
INH 9 m
INH 12-72 m
RPT-INH
RMP
RMP-INH 3-4 m
RMP-PZA</td><td>Placebo</td><td>-</td><td>-RMP-PZA regimens had the highest risk for gastrointestinal adverse events
-RMP regimens had the highest risk for central nervous system adverse events. Serious adverse events were rare across all studies</td><td></td></tr>
</table>

Regimen	GI symptoms (%)	Rash & skin symptoms (%)	Peripheral Neuropathy (%)	Dizziness, fatigue, other CNS (%)	Headaches (%)	Seizure (%)	Haematological symptoms (%)	Possible drug allergy (%)
Placebo	0.8	0.1	8.6	1.2	-	-	1.0	-
INH 6 m	2.8	1.1	<0.1	1.1	0.5	0.1	0.2	-
INH 9 m	0.7	0.8	-	0.4	-	-	<0.1	0.4
INH 12-72 m	1.7	0.2	7.4	-	1.0	0.1	1.0	-
RPT-INH	-	0.8	-	-	-	-	-	3.8
RMP	4.3	4.1	-	3.8	-	-	0.3	0.1
RMP-INH 3-4 m	7.5	1.4	-	2.1	0.5	-	0.1	-
RMP-PZA	10.8	7.2	-	1.0	-	-	-	-

* The percentage are dependent upon the length of the trial(s) in question. CNS- central nervous system, m- month, GI- gastrointestinal, EMB-ethambutol, INH- isoniazid, PZA- pyrazinamide, RFB- rifabutin, RFP-INH (high)- a higher dose of RFB, RMP- rifampicin, RPT- rifapentine

Evidence Table: Cost / Cost Effectiveness
Question: Which diagnostic tests are cost-effective for LTBI?

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF PARTICIPANTS/ PATIENT'S CHARACTERISTICS	INTERVENTION	COMPARATOR	LENGTH OF FOLLOW UP	OUTCOME MEASURE(S)	GENERAL COMMENT
Auguste P, Tsertsvadze A, Pink J et al. Accurate diagnosis of latent tuberculosis in children, people who are immunocompromised or at risk from immunosuppression and recent arrivals from countries with a high incidence of tuberculosis: systematic review and economic evaluation. Health Technol Assess. 2016;20(38):1-678.	**Systematic review** Objective: To investigate the clinical effectiveness and cost-effectiveness of screening tests (IGRAs and TST) in LTBI diagnosis in three population groups: children, immunocompromised people and those who have recently arrived in the UK from high-incidence countries.		10 CEA studies (children n = 2; immunocompromised n = 6; recently arrived from high-incidence countries n = 2) Review authors developed a de novo CEA model **Perspective:** National health payer perspective n = 5; Societal perspective n=5 **Time horizon** Range 1 year-lifetime	IGRA	TST		**Children:** — TST (≥ 5 mm)-negative followed by QFT-GIT was the most cost-effective strategy (b), with an incremental cost-effectiveness ratio (ICER) of £18 900 per QALY gained. — T-SPOT.TB was the most cost-effective strategy (b) with an ICER of approximately £2 700 per diagnostic error avoided compared with TST (≥ 10 mm). **Immunocompromised people:** — QFT-GIT-negative followed by TST (≥ 5 mm) was the most cost-effective strategy (b) with an ICER of approximately £18 700 per QALY gained. — QFT-GIT-positive followed by TST (≥ 5 mm) was the most cost-effective strategy (b) with an ICER of approximately £300 per diagnostic error avoided compared with TST (≥ 10 mm).	

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							In the recently arrived population from high-TB-incidence countries: — TST (≥ 5 mm) alone was the most cost-effective strategy (b) with an ICER of approximately £1 500 per QALY gained compared with QFT-GIT. — TST (≥ 5 mm)-positive followed by QFT-GIT was the most cost-effective strategy (b) with an ICER of approximately £700 per diagnostic error avoided compared with QFT-GIT alone. — TST (≥ 5 mm) alone was less costly and more effective than TST (≥ 5 mm)-positive followed by QFT-GIT or T-SPOT.TB or QFT-GIT alone.	

Evidence Table: Cost / Cost-Effectiveness
Question: Which diagnostic tests are cost-effective for LTBI?

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Campbell JR, Sasitharan T, Marra F. A Systematic Review of Studies Evaluating the Cost Utility of Screening High-Risk Populations for Latent Tuberculosis Infection. Appl Health Econ Health Policy. 2015;13(4):325-340.	**Systematic review** Objective: To compile cost-utility analyses evaluating latent tuberculosis infection (LTBI) screening in high-risk populations that used quality-adjusted life-years (QALYs) as their measure of effectiveness.	**I**	n = 8 CEA studies (children n = 2; immunocompromised n = 6; recently arrived n = 2) **Perspective:** Societal perspective n = 4; Healthcare system perspective n = 2; Healthcare programme perspective n=2 **Time horizon:** Range 20 years-lifetime	Screening with IGRA +/ TST	No screening		— Three studies evaluated the cost-effectiveness of screening tests on the basis of the options of no screening and screening with a TST. Screening new adult immigrants and PLHIV was strongly cost-effective with a TST. — The remaining five studies evaluated screening more comprehensively through evaluating TST, IGRA, no screening, and other options. The IGRA was found moderately cost-effective ([d]) in new adult immigrants and 6- to 44-year-old immigrants that landed more than 5 years prior, while the TST was dominated by no screening in both cases. One study reported HIV screening was strongly cost-effective ([d]) with a TST and moderately cost- effective with an IGRA, while the other reported either dual TST/QFT or T-SPOT.*TB* alone would be the most cost-effective, depending on the situation. No test was cost-effective	

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							([d]) for renal diseases; however, the IGRA was found to be the most cost-effective ([d]) test more often than the TST, if screening had to be performed. While screening for diabetics was not cost-effective ([d]), the TST was found to be most cost-effective if screening was done. All ICERs for other immunocompromising conditions were cost prohibitive, although the TST was found to be the most cost-effective test if screening had to occur.	

Evidence Table: Cost / Cost-Effectiveness
Question: Which diagnostic tests are cost-effective for LTBI?

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Nienhaus A, Schablon A, Costa JT et al. Systematic review of cost and cost-effectiveness of different TB-screening strategies. BMC Health Serv Res. 2011;11:247.	**Systematic review** Objective: To undertake a structured review and critical appraisal of the methods used for the model-based cost-effectiveness analysis of TB screening programmes.	**I**	n = 5 cost analyses and n = 8 cost-effectiveness analyses **Time horizon** Range 1 year-lifetime	IGRA	TST		— One study analysed the alternative use of TST or IGRA and seven studies compared the (1) TST- only, (2) positive TST followed by IGRA and (3) IGRA-only strategies. — Two studies favoured the IGRA-only strategy, and four studies found the IGRA in TST-positives to be the most cost-effective. The available studies on cost-effectiveness provide strong evidence in support of the use of IGRAs in screening high-risk groups, such as healthcare workers, immigrants from high- incidence countries and close contacts. In general, the higher unit cost of the IGRAs compared to that of the TST is compensated for by cost savings through the more targeted performance of CXRs and offering of chemoprevention. If the increasing evidence that IGRA-positive subjects have a higher probability of progression to active TB holds true, the IGRA-only screening strategy should prove to be the more cost- effective test.	

Evidence Table: Cost / Cost-Effectiveness
Question: What is the cost-effectiveness of different preventive treatment regimens ?

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Girardi E, Angeletti C, Goletti D et al. Systematic literature review on cost effectiveness of management of LTBI. WHO. 2014.	**Systematic review**	**I**	39 cost-effectiveness analyses. n = 32 articles reported on analyses conducted in upper-middle-income countries with TB incidence less than 100/100 000 **Perspective** Healthcare system n = 24; societal n = 7; local TB- control programme n = 1; not reported n = 7 **Time horizon**: range < 10 years- lifetime	Preventive therapy	No treatment		**Migrants:** — Eight studies analysing screening and treatment of LTBI in persons migrating to high or upper-middle-income countries with TB incidence less than 100/100 000 show that this intervention may determine savings for the healthcare system or have a favourable incremental cost-effectiveness ratio, when screened persons originate from countries with high TB incidence (above 120-150/100 000). **TB contacts:** — Six studies (all conducted in upper-middle-income countries with TB incidence less than 100/100 000) on contacts of patients with active TB also show that this intervention may determine savings for the healthcare system or have a favourable incremental cost-effectiveness ratio. **PLHIV:** — Six studies on PLHIV both in upper-middle-income countries with TB incidence less than 100/100 000	

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							and in low-income or high-TB-incidence countries also show that this intervention may determine savings for the healthcare system or have a favourable incremental cost-effectiveness ratio. The effect of antiretrovirals in lowering TB risk in PLHIV was not taken into account in all but one of these studies. **Healthcare workers:** — For healthcare workers there is an indication of possibly favourable incremental cost- effectiveness ratio (b) in some of the analyses on these persons.	

Evidence Table: Cost / Cost-Effectiveness
Question: What is the cost-effectiveness of different preventive treatment regimens ?

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Diel R, Lampenius N, Nienhaus A. Cost Effectiveness of Preventive Treatment for Tuberculosis in Special High-Risk Populations. Pharmacoeconomics. 2015;33(8):783-809.	**Systematic review**	**I**	24 cost-effectiveness analyses **Perspective** Societal costs n = 9; public healthcare provider n = 7; direct costs n = 7; national health service n=1 **Time horizon** Range 1 year-lifetime	Preventive therapy	No treatment		— With the exception of one study focusing on active TB case-finding rather than LTBI screening, a general statement in favour of preventive treatment was given for PLHIV and healthcare workers. One single study on the cost-effectiveness of preventive treatment in Japanese prisoners was available; however, further study of that risk group (incarcerated individuals) is needed before a generalising statement can be made. — No clear recommendation can be given on the basis of currently available cost- effectiveness analyses on preventive treatment as intervention prior to starting immunosuppressive medication, in patients with end-stage renal disease or in immigrants. — Only one cost-effectiveness analysis in patients with diabetes mellitus suggested that, from an economic point of view, the old principle 'intention to test is intention to treat' is clearly not applicable to random diabetic patients due to a	

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							general low LTBI prevalence and a very low annual probability of progression to TB in the United States. — When the concept of a fixed willingness-to-pay threshold as a prerequisite for final categorisation was used, the sums ranged between 'no specification' and USD 100 000 per quality-adjusted life-year	

Evidence Table: Cost / Cost-Effectiveness
Question: What is the cost-effectiveness of different preventive treatment regimens ?

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF PARTICIPANTS/ PATIENT'S CHARACTERISTICS	INTERVENTION	COMPARATOR	LENGTH OF FOLLOW UP	OUTCOME MEASURE(S)	GENERAL COMMENT
Chavan S, Newlands D, Smith C. A systematic review of economic evaluations of chemoprophylaxis for tuberculosis. J Trop Med. 2011;2011:130976.	**Systematic review** **Objective:** To critically reviewing the evidence of cost effectiveness of chemoprophylaxis against tuberculosis, identifying the important knowledge gaps and the current issues which confront policy makers.	**I**	8 economic evaluations (study design not reported)	Preventive therapy	No treatment		— INH dominates (i.e. it costs less and provides greater health benefits) vs no intervention for all groups or high risk groups. — Two studies found that RIF dominates INH. — Only three studies presented incremental cost-effectiveness ratio (ICER) results but none were comparable, one being the ICER of INH over no intervention, for low risk groups, the second RIF over no intervention and the third INH + RPT over RIF. The ICER values reported were all reasonable, implying that each first named (more expensive) treatment is cost-effective.	

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Doan TN, Fox G, Meehan M et al. Cost-effectiveness of 3 months of weekly rifapentine and isoniazid compared with other standard treatment regimens for latent tuberculosis infection: a decision analysis study. J Antimicrob Chemother. 2019;74(1):218-227.	Cost effectiveness analysis **Objective**: To evaluate the cost-effectiveness preventive treatment regimens for treating LTBI		10 000 adults with LTBI **Perspective** Health system **Time horizon** 20 years	**Self-administered (SAT)** -Daily isoniazid 300mg 6m (6-INH) -Daily isoniazid 300mg 9m (9-INH) -Daily rifampicin 4m (4-RMP) -Weekly rifapentine plus isoniazid 3m (3-RPT-INH) Administered by a healthcare worker as **directly observed therapy** (DOT) -weekly 3-RPT-INH	Serial radiographic surveillance without treatment		-Compared with the scenario of serial radiographic surveillance without preventive treatment, administration of 3RPT-INH-DOT, 3RPT-INH-SAT, 4RMP, 3RMP-INH, 9INH or 6INH would avert 496 (82% reduction relative to serial radiographic surveillance only), 470 (78%), 442 (73%), 418 (69%), 370 (61%) or 276 (46%) incident cases of active TB per 10,000 patients over 20 years, respectively -All regimens reduced costs and increased QALYs compared with no preventive treatment. -3RPT-INH-SAT and 3RPT-INH-DOT for LTBI treatment were more cost-effective compared with other regimens from a health system perspective at a WTP threshold of $50,000 per QALY gained -3RPT-INH was more cost-effective under DOT than under SAT at a cost of US$27,948 [95% Uncertainty Range (UR) 18089–46330] per QALY gained	

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							-CEAC showed that the likelihood that 3RPT-INH-DOT was cost-effective at a WTP threshold of $50000 per QALY gained was 66%. At this threshold, the probabilities that 3RPT-INH-SAT and 4RMP were cost- effective were 22% and 12%, respectively, -The cost-effectiveness of 3RPT-INH-DOT relative to 3RPT-INH-SAT was most sensitive to the treatment completion rate and the risk of progression from LTBI to active TB. -Threshold analysis showed that the treatment completion rate of 3RPT-INH-DOT needed to be at least 83% (base-case value 85%) for this regimen to be more cost-effective than 3RPT-INH-SAT at a WTP threshold of $50,000 per QALY gained.	

Evidence Table: Organisational Issues
Question: Which population are at increased risk of becoming (latently) infected with *M. tuberculosis*?
Which population are at increased risk of developing active TB?

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF STUDIES/ STUDY DESIGN		POPULATION	OUTCOME MEASURE(S)
			Risk of LTBI	Progression to active TB		
WHO. Evidence to decision framework. Appendix to the Guidelines on the management of latent tuberculosis infection. Geneva.; 2015.	**Systematic review and meta-analysis** **Objective:** To systematically review the literature on the prevalence of LTBI and risk of progression of LTBI to active TB in high-risk groups	**I**	34 cross-sectional and cohort studies	10 cohort studies	PLHIV	1. Pooled estimate risk ratio in low-, intermediate-, high-TB-burden countries per type of test. 2. Pooled prevalence of LTBI in low-, intermediate-, high-TB-burden countries per type of test. See Table 9 (pg32-34)
			31 cross-sectional and cohort studies	3 cohort studies (ESRD on dialysis)	Immuno-compromised_patients with renal or liver conditions	
			20 cross-sectional and cohort studies	1 cohort study	Immuno-compromised_candidates for anti-TNF alpha therapy	
			20 cross-sectional and cohort studies	2 cohort studies	Immuno-compromised_patients with autoimmune disorders or immune-mediated inflammatory disorders	
			71 cross-sectional and cohort studies	3 cohort studies	TB contacts	
			23 cross-sectional and cohort studies	4 cohort studies	Migrants	
			9 cross-sectional and cohort studies	1 cohort	Prisoner	
			6 cross-sectional and cohort studies	2 cohort	Homeless people	
			9 cross-sectional and cohort studies	No retrievable study	People with drug use disorders	
			63 cross-sectional and cohort studies	Not specified	Healthcare workers	

Evidence Table: Organisational Issues
Question: Which population are at increased risk of becoming (latently) infected with *M. tuberculosis*?
Which population are at increased risk of developing active TB?

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF PARTICIPANTS/ PATIENT'S CHARACTERISTICS	LENGTH OF FOLLOW UP	OUTCOME MEASURE(S)	GENERAL COMMENT
Campbell JR, Krot J, Marra F. Latent tuberculosis diagnostic tests to predict longitudinal tuberculosis during dialysis: a meta-analysis. Int J Tuberc Lung Dis. 2016;20(6):764-770.	**Systematic review and meta-analysis** **Objective:** To determine the longitudinal risk of TB in dialysis patients Random-effects meta-analysis was used to determine the incidence rate ratio (IRR) of longitudinal TB development. <u>Inclusion criteria</u> Prospective studies using a TST or IGRA in dialysis patients who were subsequently followed up for longitudinal TB development <u>Exclusion criteria</u> -Studies that evaluated TB in dialysis patients but were not LTBI diagnostic studies -Studies that took place in transplant recipients	**I**	8 cohort studies were included <u>Sample size:</u> 32-1619 <u>TB incidence/100,000</u> 5-103 <u>Mean age(years)</u> 52.7-62.5 <u>Male sex</u> 39.8-71% <u>Mean length of dialysis months</u> 30-71 <u>Diabetes prevalence</u> 10.9-27.4%	Mean: 12-36 months	-Active TB developed in 19 TST-positive dialysis patients over 540.6 py of follow-up -26 cases of active TB developed over 1044.6 py of follow-up in TST-negative dialysis patients. -This yielded a crude estimate of likely TB reactivation (positive with subsequent TB) of 35.15 cases/1000 py. -A rate of 24.89 cases/1000 py was observed in dialysis patients testing negative. <u>IRR of TB development (TST 10mm)</u> 2.59 (95%CI 1.20–5.57)(I^2= 26.4%, p>0.1) This cut-off point was associated with a PPV of 7.98–22.52% and an NPV of 88.02–96.10% for future TB over a reactivation rate of between 5% and 15%.	

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Campbell JR, Chen W, Johnston J et al. Latent tuberculosis infection screening in immigrants to low-incidence countries: a meta-analysis. Mol Diagn Ther. 2015;19(2):107-117.	**Systematic review and meta-analysis** **Objective:** To compare LTBI diagnostic tests by positive test prevalence and proportion of positive tests by TB incidence. <u>Inclusion criteria</u> - study that took place in a low TB incidence country (defined as \30 culture positive cases per 100,000 persons) - TST, ELISA and/or ELISPOT based IGRA were used -the study population included immigrants or listed results for immigrant populations - data were stratified by at least one of gender, age, country of origin, BCG status or test result - a 10 mm induration diameter was used as a cut-off for a positive TST; and the TST was read between 48 and 72 h after administration <u>Exclusion criteria</u> self-reported results; immunocompro-mised populations—including HIV; and the use of outdated TST techniques.	**I**	-23 studies were included for a positive TST -8 studies were included for a positive IGRA	Not specified	-BCG-vaccinated immigrants had a higher likelihood of a positive TST (OR 2.10; 95 % CI 1.54–2.88) -Immigrants from countries with ≥ 30 cases per 100 000 (compared to immigrants from countries with < 30 cases per 100 000) tested with TST or IGRA had a higher likelihood of a positive test: 2.38 (95%CI 1.14, 4.98) (TST) or 17.25 (95%CI 1.03, 289.34)	

Evidence Table: Organisational Issues
Question: What are determinants of LTBI treatment initiation, adherence and completion?

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF PARTICIPANTS/ PATIENT'S CHARACTERISTICS	INTERVENTION	COMPARATOR	LENGTH OF FOLLOW UP	OUTCOME MEASURE(S)	GENERAL COMMENT
Alsdurf H, Hill PC, Matteelli A et al. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(11):1269-1278.	**Systematic review & meta-analysis** **Objective:** To systematically review the published research about the cascade of care in latent tuberculosis diagnosis and treatment.	**I**	58 cohort studies were included with N=748,572	LTBI management	-	Not stated	**Losses and drop-outs at each stage of the cascade of care in latent tuberculosis** Initially tested 71·9%(71·8–72·0) Received a test result 66·7%(65·6–66·9) Referred if test positive 56·0%(55·2–56·8) Completed medical evaluation 43·7%(42·5–44·9) Recommended for treatment 35·0%(33·8–36·4) Accepted and started treatment 30·7%(26·8–32·1) Completed treatment 18·8%(16·3–19·7) <u>The most important losses in the cascade occurred at four steps:</u> -initial testing of those intended for screening -completing medical evaluation if test was positive - provider recommendation of treatment - completing therapy if started **Characteristics associated with completed screening [pooled event rate (95%CI)]** <u>Country income level</u> High 75·6% (67–84) Low or middle 51·3% (19–83)	

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF PARTICIPANTS/ PATIENT'S CHARACTERISTICS	INTERVENTION	COMPARATOR	LENGTH OF FOLLOW UP	OUTCOME MEASURE(S)	GENERAL COMMENT
							<u>Services</u> Routine 66·9% (53–81) Outbreak investigation 88·0% (75–100) Pilot intervention 74·1% (60–89) <u>Study populations</u> Medical 86·1% (68–100) Contacts 79·3% (69–90) Marginalised. 83·3% (69–98) Migrants 43·4% (20–67) General population 62·1% (37–87) <u>Age</u> Adults only 66·9% (54–80) Children only 60·4% (33–88) All ages 86·4% (77–96) <u>Testing for latent TB</u> TST alone 75·1% (66–84) IGRA with/without TST 62·3% (28–97) <u>Treatment for LTBI</u> Isoniazid 71·5% (60–83) Rifamycin containing (with or without isoniazid) 80·3% (64–97) Moxifloxacin and ethambutol 59·9% (0–100) **Characteristics associated with starting treatment [pooled event rate (95%CI)]** <u>Country income level</u> High 64.6% (56–74) Low or middle 72.2% (48–96)	

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							<u>Services</u> Routine 62.7% (51–75) Outbreak investigation 80.9% (63–99) Pilot intervention. 63.9% (49–78) <u>Study populations</u> Medical 84.8% (67–100) Contacts 74.8% (64–85) Marginalised. 56.4% (35–77) Migrants 54.6% (36–73) General population 50.8% (29–73) <u>Age</u> Adults only 62.6% (51–74) Children only 69.1% (47–91) All ages 68.9% (54–84) <u>Testing for latent TB</u> TST alone 64·2% (55–73) IGRA with/without TST 75·3% (53–98) <u>Treatment for LTBI</u> Isoniazid 62·3% (52–72) Rifamycin containing (with or without isoniazid) 83·3% (72–94) Moxifloxacin and Ethambutol 87·7%(58–100) **Characteristics associated with completing treatment** -Of people who started therapy, only 62% completed overall	

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							-In LMICs only 52% of those who started completed treatment compared with 70% in high-income countries. -Only 50% of people with medical indications completed latent tuberculosis infection treatment, compared with 14% of migrants, and 10% of the general population cohorts -Reasons for not completing screening were put into two main categories: social situations impeding the completion of screening and health-system issues - Barriers to the referral and recommendation of treatment included: being considered too old (older than 35 years), low health-provider knowledge about the benefits and risks of therapy for latent tuberculosis infection, and social situations. - Barriers to treatment completion included side-effects to drugs, health-systems issues and social situations (panel).	

Evidence Table: Organisational Issues
Question: What are determinants of LTBI treatment initiation, adherence and completion?
What interventions are effective at improving initiation, adherence and completion of LTBI treatment??

BIBLIOGRAPHIC CITATION	STUDY TYPE/ METHODOLOGY	LE	NO. OF PARTICIPANTS/PATIENT'S CHARACTERISTICS	OUTCOME MEASURE(S)	GENERAL COMMENT
Stuurman AL, Vonk Noordegraaf-Schouten M, van Kessel F et al. Interventions for improving adherence to treatment for latent tuberculosis infection: a systematic review. BMC Infect Dis. 2016;16:257.	**Systematic review** **Objectives:** 1.To systematically review data on determinants of initiation, adherence and completion of LTBI treatment 2.To identify interventions with demonstrated efficacy to improve LTBI treatment initiation, adherence and completion in different populations	**I**	<u>Objective 1: Determinants of initiation, adherence and completion of LTBI treatment</u> 62 studies were included - determinants of initiation (12 studies) - determinants of adherence (8 studies) - determinants of completion (51 studies) <u>Study design</u> -RCT (11 studies) -Cohort studies (50 studies) -Cross-sectional study (1 study) <u>Sample size</u> 92-15035	<u>Treatment initiation</u> - Healthcare workers (vs. non healthcare workers) to be less likely to initiate treatment (2 studies) - Case contacts (vs. no case contacts) (3 studies), and immigrants or refugees (vs. born in country of study) (2 studies) to be more likely to initiate LTBI treatment <u>Treatment completion</u> -5 studies found a positive association between completion and immigrant or refugee status (vs. born in country of study), whereas 2 studies found an inverse association. -Currently homeless individuals (vs. not currently homeless) (2 studies) and people who injected drugs (vs. people who do not inject drugs)(2 studies) were less likely to complete treatment (no study found a positive association). -Short (vs. long) treatment regimens and treatments with DOT (vs. self-administered therapy (SAT)) were found to be completed more often in the general population with LTBI in 6 and 3 studies, respectively, (no study found an inverse association). -Adverse events were inversely associated with completion in 7 studies (no study found a positive association). -Females (vs. males) were more likely to complete treatment. (2 studies) (no study found men were more likely to complete treatment). -Alcohol use (vs. no alcohol use) was inversely associated with completion in 4 studies (no study found a positive association).	

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			Objective 2: Interventions to improve LTBI treatment initiation, adherence and completion 23 studies were included (17 RCTs, 4 cohort studies, 1 before and after study, 1 pre-experimental design) **Type of Intervention:**			
			1. Short treatment regimen	7 RCTs, 1 cohort Sample size: 116-7731 Population: -General population (4 studies) -Immigrants (1 study) -Case contacts (2 studies)	-Case contacts showed better adherence when receiving short treatment (sOR = 1.5; 95%CI 1.0-2.3) -Higher completion rates were found in the short treatment group: in immigrants with LTBI (OR = 2.5; 95 % CI 1.7–3.6; moderate quality of evidence) , in the general population with LTBI (sOR = 1.9; 95%CI 1.1–3.5), and in case contacts (OR = 2.1; 95%CI 1.9–2.3). The latter result is confounded, however, by the use of DOT in the short treatment group and self-administered therapy (SAT) in the long treatment group.	
			2. DOT	4 RCTs Sample size: 111-7731 Population: -Patient who inject drug (2 studies) -Immigrants (1 study) -Case contacts (1 study)	-In undocumented migrants, significantly lower completion rates were found among those receiving twice weekly clinic-based DOT compared to daily SAT (OR = 0.1; 95%CI 0.0–0.3) or twice weekly SAT (OR = 0.2; 95%CI 0.1–0.6). -In PWID, no effect of DOT administered by an outreach nurse on completion rates of LTBI treatment was found (OR = 1.1; 95 % CI 0.5–2.1). However, when looking at the proportion of people who took all doses, the DOT group performed significantly better (OR = 31.5; 95%CI 14.1–70.6). -Higher completion rates were found in the DOT group among case contacts (OR = 2.1; 95%CI 1.9– 2.3).	

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			3. Incentive	4 RCTs, 1 cohort study Sample size: 111-216 Population: - Patient who inject drug (2 studies) -Homeless individuals (1 study) -Ex-prisoner (1 study) -General population (1 study)	-Two studies in PWID with LTBI found higher completion rates for LTBI treatment among those who received either a monetary incentive (adjusted OR [aOR] = 32.0; 95%CI 7.1–145) or methadone treatment (OR = 14.5; 95%CI 5.0–42) compared to those who received no incentive. The results from the methadone treatment study were confounded, however, by the use of DOT in the methadone treatment group and SAT in the control group. -The provision of food or transportation vouchers to released inmates with LTBI if they attended a TB clinic upon release (OR = 1.1; 95%CI 0.5–2.4) did not lead to better completion rates. -In another study, no difference was found between the provision of cash-incentives versus non-cash incentives to homeless individuals with LTBI (OR = 1.7; 95%CI 0.7–4.3)	
			4. Social intervention	6 RCTs, 1 pre-experimental study, 1 cohort study, 1 before and after study Sample size: 107-946 Population: - Patient who inject drug (1 study) - General population (3 studies) - Immigrants (2 studies) - Healthcare workers (1 study) - Homeless individuals (1 study) - Inmates (1 study)	-Social interventions were found to improve completion rates of LTBI treatment compared to the standard care group in all but one study, which provided peer-support among PWID with LTBI (OR = 1.0; 95 % CI 0.7–1.5) and found no effect on completion. -Counselling and contingency contracting, adherence coaching and self-esteem counselling, and peer-based interventions in the general population showed better completion rates (sOR = 1.4; 95%CI 1.1–19). -Education among inmates (OR = 2.2; 95 % CI 1.0–4.7), nurse case management among homeless individuals (aOR = 3.0; 95 % CI 2.2–4.2; high quality of evidence) [35], and case management with attention for the cultural background of each individual among immigrants (aOR = 7.8; 95 % CI 5.7–10.7; improved completion. The latter study also found that this intervention led to higher initiation rates (OR = 2.7; 95% CI 1.9–3.8).	

Evidence Table: Social Implication
Question: What is the health-related quality of life (HRQoL) of persons diagnosed and treated for LTBI?

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Bauer M, Leavens A, Schwartzman K. A systematic review and meta-analysis of the impact of tuberculosis on health-related quality of life. Qual Life Res. 2013;22(8):2213-2235.	Systematic review and meta-analysis **Objective:** To determine the impact of tuberculosis (TB) on quantitative measures on self-reported health-related quality of life (HRQOL), between subjects treated for active TB with subjects treated for LTBI, or with healthy controls, at similar time points with respect to diagnosis and/or treatment.	**I**	28 studies included with 6028 subjects from 16 countries, across 5 continents -21 cross-sectional studies -7 cohort studies 639 subjects treated for LTBI (11 % of the total sample)- 6 studies 88% of subjects with LTBI were diagnosed by a positive TST	LTBI treatment	Active TB treatment	6-8 months	-Subjects with active TB consistently reported poorer HRQOL than subjects treated for LTBI, across a variety of questionnaires and settings. -Estimates of pooled standardized mean differences (SMDs) demonstrated that subjects treated for active TB had mean scores 0.66 (95%CI -0.82, -0.50; I2 17%) and 0.51 (95%CI -0.77, -0.26; I2 54%) standard deviations below those treated for LTBI within 2 weeks of diagnosis and after 6–8 months of treatment, respectively. -Pooled estimates of SMDs in health utilities among subjects treated for active TB compared to those treated for LTBI within the first 2 weeks of treatment showed similar results [-0.62 (95%CI -0.82, -0.42; I^2 89%). . - Among subjects treated for LTBI, longitudinal measurements of HRQOL did not suggest meaningful changes between time of diagnosis and six months of treatment	

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Bauer M, Ahmed S, Benedetti A et al. Health-related quality of life and tuberculosis: a longitudinal cohort study. Health Qual Life Outcomes. 2015;13:65	Cohort study **Objective:** To measure HRQOL of patients treated for TB disease and LTBI at each milestone of treatment, along with untreated individuals with a similar socio-demographic profile to treated participants. <u>Group of participants with active TB disease</u> Patients initially hospitalized and those treated solely as outpatients; all participants treated for TB dis-ease had culture-	**II-2**	N=263 **Treated for active TB** 48 Mean age: 37 years **Treated for LTBI** 105 Mean age: 33 years **Screened for TB but healthy and untreated** 110 Mean age: 35 years 90% were foreign-born 54% women	LTBI treatment	Active TB treatment	**12 months**	- Participants treated for TB disease reported significantly worse mean scores at baseline compared to control participants [mean physical component summary (PCS) scores: 50.0 vs. 50.7; mean mental component summary (MCS) scores: 46.4 vs. 51.1], with improvement in mean MCS scores throughout the study period. - Scores reported by participants treated for LTBI and control participants were comparable throughout the study.	

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	confirmed disease. <u>Participants treated for LTBI</u> Diagnosed with asymptomatic infection, typically based on positive results from a TST and/or an IGRA, and/or presence of scarring on a chest radiograph <u>Control group</u> Patient evaluated for possible TB disease and/or LTBI, and judged not to require treatment of any kind. **Exclusion criteria** -Individuals with multi-drug resistant TB disease -Concomitant physical or mental illness likely to							

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	affect their HRQOL Participants were evaluated during clinic or home visits at 1, 2, 4, 6, 9, and 12 months post-baseline, corresponding to important milestones in TB treatment regimens **Tool:** SF-36 questionnaire							

Evidence Table: Social Implication
Question: What is the health-related quality of life (HRQoL) of persons diagnosed and treated for LTBI?

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Shedrawy J, Jansson L, Rohl I et al. Quality of life of patients on treatment for latent tuberculosis infection: a mixed-method study in Stockholm, Sweden. Health Qual Life Outcomes. 2019;17(1):158.	Mixed method study **Objective:** To measure HRQoL of LTBI patients and to qualitatively explore patients' experiences during diagnosis and treatment of LTBI **Inclusion criteria** Patients aged 16 or older diagnosed and under treatment for LTBI -HRQoL was assessed using the validated instrument EQ-5D-3 L developed by the EuroQol Group	-	Cross sectional study: 108 participants Mean age: 30 years old Qualitative interview: 20 participants Mean age: 31 years old	LTBI treatment	No treatment	-	1.**Quality of life** There was no statistically significant difference in EQ- 5D utility score between LTBI patient and the general population (p = 0.079). Median score (IQR) 1 (0.796- 1) LTBI patients had a significantly higher median EQ-VAS score than the general popula- tion (p = 0.032, Phi value = − 0.015). Median VAS score (IQR) 90 (75-100) 2. **Physical functioning and pain** Reported problems with physical functioning - mobility (7.4%) - usual activity or self-care (1.8%) - pain/discomfort (24.1%) 3. **Psychosocial health** - Anxiety/depression (27.8%) Related stressing factors	

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	-Refugee health screening-15 (RHS- 15), was used to screen for mental health issues among study subjects with a migration background						- fear and distress related to lack of clarity about LTBI diagnosis - perceived risk of infecting others - uncertainties about the future. **Conclusion**: The quantified HRQoL of LTBI patients was similar to the general population and there was thus no HRQoL decrements detectable with EQ-5D.	