SYSTEMATIC REVIEW

Screening and Treatment of Latent Tuberculosis: A Systematic Review of Current Evidence

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Abstract

Introduction: Latent tuberculosis is an infection by the bacteria *Mycobacterium tuberculosis* where the individual affected does not have active infection or symptoms of tuberculosis infection. Individuals with latent tuberculosis infection (LTBI) remain asymptomatic and non-infectious until the bacteria become reactivated. The purpose of screening and treating LTBI is to prevent reactivation and active disease. The aim of this review is to examine the current screening criteria for LTBI, their validity, and specificity for diagnosis by looking at the currently accepted treatment options and the evidence that supports their efficacy.

Methods: Articles for review were sourced from the academic databases EMBASE and PubMed. Results were screened using PICOS criteria looking at a population of latent TB infected patients screened using a variety of screening tools.

Results: Initial database searches identified 476 articles. 19 articles fit the eligibility criteria and were included for analysis. Current screening procedures include the tuberculin skin test (TST), T-SPOT.TB, and QuantiFERON-TB (QFT-GIT) tests. Evidence showed that the T-SPOT.TB was the most cost-effective test to perform although its accuracy is not as reliable as the IGRA. Treatment plans for those with LTBI are diverse and can be beneficial in a variety of settings. The most effective treatments include isoniazid for 6 or 9 months, rifampicin for 3 to 4 months and isoniazid and rifampicin for 3 to 4 months.

Conclusion: Overall, IGRAs are the most reliable screening tests but are advised to be used in conjunction with TSTs as the TST alone has been determined to be less accurate. There are different treatment regimens, all of similar efficacy. Longer regimes were as effective than those of a shorter duration, but shorter regimes showed higher completion rates.

Keywords: Latent tuberculosis, Screening, Treatment, TST, IGRA

Introduction

An estimated one-third of the world's population are infected with *Mycobacterium tuberculosis* (MTB). Infection may be cleared by the host immune system or suppressed into an inactive form called latent tuberculosis infection (LTBI), caused by a dormant form of the bacteria that can reactivate later under favourable conditions. An estimated 2 billion people worldwide have LTBI [1].

People with LTBI are not infectious but they usually have a positive tuberculin skin test (TST) or interferon gamma release assays (IGRA) as a marker of exposure. However, neither TST nor IGRA can distinguish active TB disease from LTBI. Chest X-ray findings are usually normal or may reveal evidence of healed infection, such as granulomas or calcification in the lung and hilar lymph nodes. Such patients are at a 5–10% lifetime risk for progressing to active tuberculosis disease if LTBI is untreated[1].

The rationale for the screening and treatment of LTBI is to kill any residual dormant bacilli, thus reducing the reactivation and development of TB disease. Current therapeutic options can reduce the risk of active TB by as much as 90% if adhered to[2]. However, completion of therapy is less than 50% in many regimens due to the long duration of therapy and the risk of adverse events such as hepatotoxicity discourages patients[2]. In this paper we discuss the evidence comparing the preferred regimens for the treatment of LTBI: four months of daily rifampicin, isoniazid and rifapentine once a week for 12 weeks, three to four months of rifampicin and isoniazid, or six to nine months of daily isoniazid monotherapy.

Methods

Eligibility Criteria

We included studies meeting the following PICOS criteria:

Population: Studies that reported on patients of any age with LTBI. This included adults, children, human immunodeficiency virus (HIV) infected persons and non-HIV infected persons.

Interventions: Studies that reported on the

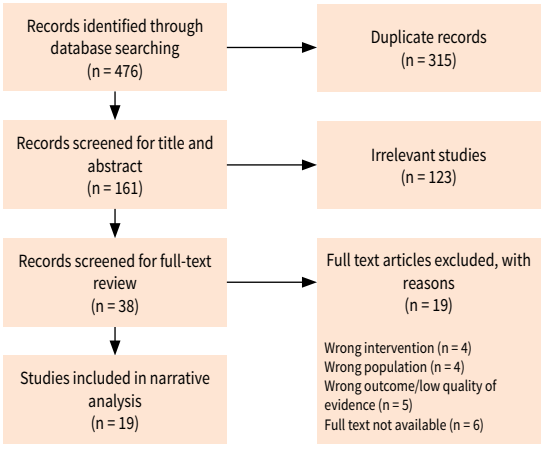
Table 1. **Search Methodology**

Search	Search Query	Filters	No. of Results
#1	(latent tuberculosis[Title/Abstract]) AND (treatment[Title/Abstract])	Meta-analysis, Randomised Control Trial, Systematic Review, English, from 2005–3000/12/12	369
#2	(latent tuberculosis[Title/Abstract]) AND (screening[Title/Abstract])	Meta-analysis, Randomised Control Trial, Systematic Review, English, from 2005–3000/12/12	107

Table 2. **Oxford Levels of Evidence (Adapted from Oxford Centre for Evidence-based Medicine Levels of Evidence, March 2009[4])**

Level	Therapy/Prevention, Aetiology/Harm
1a	Systematic Review (with homogeneity) of RCTs
1b	Individual RCT (with narrow Confidence Interval)
1c	All or none
2a	Systematic Review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g. <80% follow-up)
2c	"Outcomes" Research; Ecological studies
3a	Systematic Review (with homogeneity) of case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor-quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Figure 1. **PRISMA Flow Diagram for Record Selection Process**



pharmacological treatment of LTBI or screening of LTBI.

Outcomes: The primary outcomes of interest were progression to active TB infection or completion of treatment. Secondary outcomes of interest included hepatotoxicity and adverse events requiring discontinuation of treatment.

Studies: The search was limited to systematic reviews, randomised controlled trials (RCTs) and meta-analyses.

Information Sources

Searches were conducted from EMBASE and PubMed. The search methodology is shown in the table in **Table 1**. The search was limited to research articles published in English and available in full text. Other exclusion criteria included obstetric populations because of differences in disease management, doses, and follow-up.

Study Selection

Duplicates were removed by comparing database search results and eliminating redundant records. The remaining records' relevance were evaluated through examination of titles and abstracts followed by the application of our eligibility criteria to full text records. Quality assessment of selected articles was done using the National Institutes of Health (NIH) screening tools for controlled interventional studies, observational cohort studies, and case-control studies[3]. Levels of evidence were assessed using the Oxford Centre for Evidence-based Medicine Levels of Evidence (**Table 2**).

Results

Database Search

The database search identified 476 citations for consideration against the eligibility criteria.

A full text review of 38 articles was performed, after which a further 19 citations were excluded. Nineteen studies were included for final analysis in which 10 detailed about screening tests for LTBI and 9 described the treatment options. The database search and exclusions are shown schematically in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram in **Figure 1**. Summaries of the studies can be referred to in **Table 3** and **Table 4**.

Discussion

Screening of Latent TB

TB is the number one cause of death worldwide by a single infectious agent[1], so there is a global health need for screening to be sensitive, specific, and reliable. Available screening tests include the TST and IGRA (i.e. QuantiFERON/ QFT-GIT, T-SPOT.TB).

Guidelines written by the World Health Organisation (WHO) in 2015 outline the groups of people that should be tested for latent TB. These include contacts of active TB cases, people from high-risk regions, HIV patients, patients before starting anti-tumour necrosis factor (TNF) treatment, dialysis patients, and patients prior to organ transplant[14]. There is conflicting evidence surrounding which test more effectively predicts progression to active TB. There is inadequate evidence that either test should be used over the other to predict progression from latent to active TB. Ultimately, use of either test must be influenced by availability and cost effectiveness of diagnostic tools[19].

Table 3. **Details of Records on Screening of Latent Tuberculosis**

Paper Title	Author(s), Year	Level of Evidence	Details of Study	Patient Population	Outcomes (Prognosis)	Adverse Effects
Tuberculin Skin Test - Outdated or Still Useful for Latent TB Infection Screening?[5]	Gualano et al., 2019	1A	Systematic Review (n=13)	All ages	Neither IGRAs nor TSTs can differentiate active from latent TB. TSTs will continue to be of clinical use until more accurate tests become available	N/A
The Impact of BCG Vaccination on Tuberculin Skin Test Responses in Children is Age Dependent: Evidence to be Considered when Screening Children for Tuberculosis Infection[6]	Seddon et al., 2016	2B	Individual cohort study (n=422)	Children <15	BCG vaccination had insignificant effect on TST size in children older than 5	N/A
Primary Care Screening and Treatment for Latent Tuberculosis Infection in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force[7]	Kahwati et al., 2016	1A	Report and systematic review (n=72)	18 and over	TSTs and IGRAs are moderately sensitive and very specific in countries with low TB prevalence	N/A
Management of Latent *Mycobacterium tuberculosis* Infection: WHO Guidelines for Low Tuberculosis Burden Countries[8]	Getahun et al., 2015	1A	WHO report and systematic review (n=71)	N/A	N/A	N/A
New Tests for the Diagnosis of Latent Tuberculosis Infection: Areas of Uncertainty and Recommendations for Research[9]	Menzies et al., 2007	1A	Systematic Review	All ages	Further longitudinal studies are required to define the predictive values of IGRAs	N/A
Gamma Interferon Release Assays for Detection of *Mycobacterium tuberculosis* Infection[10]	Pai et al., 2014	1A	Systematic review (n=137)	All ages	IGRAs improvement over TST is incremental rather than transformative	N/A
Screening for Latent Tuberculosis Infection: Performance of Tuberculin Skin Test and Interferon-γ Release Assays Under Real-Life Conditions[11]	Kleinert et al., 2012	1B	RCT with 1529 patients tested across 62 centres. Every patient was tested with a TST and one form of IGRA (either T. SPOT.TB or QFT)	All ages	In populations with high TB rates, the use of IGRA and TST can improve sensitivity in detecting LTBI but can also reduce specificity	N/A
Prospective Comparison of QFT-GIT and T-SPOT.TB Assays for Diagnosis of Active Tuberculosis[12]	Du et al., 2008	2B	746 suspected pulmonary TB patients across 4 hospitals in China were enrolled and diagnostic performance of QFT vs T. SPOT.TB tests were compared	All ages	The two IGRAs have similar sensitivities to aid in the diagnosis of active tuberculosis. The two assays may also be of value in diagnosis of probable TB when used in tandem High false positive rates of these diagnostic tests may limit their value in routine clinical practice in countries where prevalence of LTBI is high	N/A
QuantiFERON-TB Gold Test and T. SPOT.TB Test for Detecting Latent Tuberculosis Infection in Patients with Rheumatic Disease Prior to Anti-TNF therapy[13]	Sargin et al., 2018	2B	Individual Cohort study (n=109)	18-70 years	IGRAs are useful for detecting LTBI in patients treated with corticosteroids due to lack of correlation between corticosteroid therapy and test negativity	N/A

Table 4. **Details of Records on Treatment of Latent Tuberculosis**

Paper Title	Author(s), Year	Level of Evidence	Details of Study	Patient Population	Outcomes (Prognosis)	Adverse Effects
Diagnosing Latent Tuberculosis Infection: The 100-year Upgrade[1]	Barnes et al., 2001	2C	Report	N/A	N/A	N/A
Managing Latent Tuberculosis Infection and Tuberculosis in Children[2]	Carvalho et al., 2018	1A	Review of studies pertaining to the management of paediatric LTBI	Age 2-14	Isoniazid 9 month is preferred although rifampicin regimens are also effective. Higher doses of rifampicin may be required due to pharmacokinetics	N/A
A Systematic Review of Adverse Events of Rifapentine and Isoniazid Compared to Other Treatments for Latent Tuberculosis Infection[14]	Pease et al., 2018	1A	Systematic review (n=78)	All ages	Isoniazid and rifapentine once weekly for 12 weeks had low frequency of adverse effects. However, reporting of events was limited	Adverse effects were inconsistently reported
Isoniazid-Rifapentine for Latent Tuberculosis Infection: A Systematic Review and Meta-analysis[15]	Njie et al., 2018	1A	Meta-analysis (n=15)	All ages	3 months isoniazid and rifapentine (once weekly) had high treatment completion rates and efficacy	Similar safety profile to other LTBI treatments
Treatment of Latent Tuberculosis Infection: A Network Meta-Analysis[16]	Stagg et al., 2014	1A	Network meta-analysis	All ages	Studies were from Europe, Canada and the USA comparing 15 regimens. Effective regimens: isoniazid monotherapy 6-12+ months and rifampicin 3-4 months monotherapy or combination therapy	Regimens containing rifampicin had a lower hepatotoxicity than isoniazid only regimens. Serious adverse effects were rare in all studies. Adverse effects were infrequently recorded
Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020[17]	Sterling and Njie et al., 2020	1A	Systematic literature review with additional network meta-analysis (n=63)	All ages	Short course 3-4-month rifampicin-based treatments regimens are preferred over 6-9-month isoniazid monotherapy	Isoniazid 6-9-month monotherapies have higher toxicity risk and lower completion rates
Treatment of Latent Tuberculosis Infection: An Update[18]	Lobue and Menzies et al., 2010	1A	Systematic Review	All ages	9 months isoniazid LTBI treatment is expensive and an undesirable risk profile along with poor adherence. Rifampicin based regimens are acceptable alternatives	4 months rifampicin monotherapy has significantly lower toxicity when compared to isoniazid monotherapy
WHO Global Progress Report on Tuberculosis Elimination[19]	Harding et al., 2019	2C	WHO report	All ages	N/A	N/A
Mycobacterium tuberculosis Pathogenesis and the Dynamics of the Granuloma Battleground[20]	Rao et al., 2019	1A	Review of LTBI pathogenesis	N/A	N/A	N/A
Efficacy and Completion Rates of Rifapentine and Isoniazid (3HP) Compared to Other Treatment Regimens for Latent Tuberculosis Infection: A Systematic Review with Network Meta-analyses[21]	Pease et al., 2017	1A	Systematic review and network meta-analysis of 30 RCTs (n=88,277)	Any age confirmed with LTBI with TST and or IGRA	Shorter treatment regimens were associated with higher completion rates	N/A

Table 5. **Comparison Between TST and IGRA (QuantiFERON and T-SPOT.TB) as Screening Tools for Latent TB.**

Investigation	Specificity	Sensitivity	Cost	Follow up Required?
TST	60.3% [12]	47.8-79% [12, 13, 14]	Low [6]	Yes [9]
QFT-GIT	85.7-97.7% [12, 13]	73.6-96% [12, 13, 14]	High [6]	No [6]
T-SPOT.TB	73.5-92.5% [12, 13]	66.7-96% [12, 13, 14]	High [6]	No [6]

TSTs are useful for initial investigations because they can require less equipment and are cheaper but they can also be unreliable[21,22]. TSTs are considered to be inaccurate in individuals with other conditions, especially autoimmune diseases, as the skin test is an interpretation of the body's reaction to the injection of the tuberculin in the skin. This can result in false positives in the skin test, due to an error in interpretation or a reaction to the injection rather than the tuberculin itself[5]. Another downfall of TST is that they require multiple clinic visits for interpretation. The inaccuracy of TST and the difficulties associated with multiple visits to the clinic for monitoring were identified by several studies[15] **(Table 5)**.

IGRAs are widely known to be more accurate markers than TST and present advantages such as high specificity, high sensitivity, and easier administration and monitoring, as an *ex vivo* blood test. T-SPOT.TB and QFT-GIT are both techniques for detecting interferon-gamma (IFN-γ). T-SPOT.TB is a measure of the amount of IFN-γ released from peripheral blood mononuclear cells and QFT-GIT measures the concentration of IFN-γ in whole blood. As IFN-γ can be released by T cells in response to many infections and not just against MTB exposure, the possibility of false positives cannot be ruled out[15,16]. Disadvantages include the high cost compared to TST, the need for specific laboratory equipment, and the lack of specific criteria for analysing results **(Table 5)**. When comparing the performance of TST and IGRAs, it is important to know the Bacillus Calmette–Guérin (BCG) status of the patient as this can influence the outcome of the TST result[17]. While IGRA tests are more reliable, the most effective method to get the most accurate result is to perform both TSTs and IGRAs[21]. However, IGRAs have decreased specificity in countries with a high incidence of latent tuberculosis, so it cannot be used as a confirmatory diagnostic tool but rather as a negative prognostic marker[11]. IGRAs can rule out TB but may not be able to confirm it as different types of testing and investigations are needed to do so.

Treatment of Latent TB

Treatment of LTBI is indicated for those at increased risk for progression measured by risk factors as seen in the patient's history and previous IGRAs or TSTs[11]. Patients with LTBI are considered effectively treated if they were administered ≥1 medication to which their TB strain was likely susceptible[2]. Currently, no gold standard of treatment is recognised, however, there are five treatment regimens that have been proven to be effective when compared to no treatment/placebo[8]. These regiments are:

- Isoniazid (INH) daily for 9 months
- INH daily for 6 months
- INH + rifampicin (RIF) for 3-4 months
- RIF daily for 4 months
- INH with rifapentine once weekly for 12 weeks

Shorter regimens are also known to have similar efficacy, favourable tolerability, and higher treatment completion rates[19]. Some patients with HIV cannot undergo the shorter regimens due to interactions with antiviral drugs, and therefore two alternative monotherapy options are included in the discussion.

Based on analysis of the current academic evidence, the dose of the drug is not as significant to the results as the timeframe of the drug regimen. INH daily for 6 months and daily for 9 months were often not completed. INH daily for nine months is the regimen recommended for all groups. In many studies INH daily for 9 months was used as the standard comparator[19]. INH reduces the risk of active TB by as much as 90% if taken daily for nine months[2]. Hepatotoxicity of INH is up to 2.9%[3], therefore, long duration of treatment is not always advantageous. Close monitoring and surveillance are strongly suggested[2]. INH daily for 9 months showed a statistically significant benefit in preventing active TB compared to a placebo[12]. This treatment is recommended in patients aged 2-11[8]. INH daily for 6 months had similar efficacy to INH daily for 9 months but greater adherence due to a shorter course of treatment[12].

Three to four months of INH with RIF had decreased frequency of hepatotoxicity, though discontinuation due to adverse effects was more common[19]. The adverse event profile of INH with RIF for three months had an increased frequency of flu-like reaction, but lower frequency of hepatotoxicity[7].

RIF monotherapy for four months duration had an equal effect and lower rates of hepatotoxicity when compared to other treatments of six or more months[5]. The regimen is strongly recommended for HIV negative adults, and children of all ages. The four-month monotherapy of RIF had better compliance when compared with INH daily for 9 months[19].

Combination INH with rifapentine once weekly for 12 weeks allowed a shorter time frame of treatment and can be used in individuals with HIV who are not prescribed antiretrovirals[8]. Rifapentine with INH had equivalent effectiveness and lower hepatotoxicity than INH daily for 6 months[5].

Regimens containing RIF are considered more effective than INH monotherapy when considering adverse effects and cost[5]. Treatment completion rates

were higher with the three-month regimen at 87.5%, compared with other regimens at 65.9%.

RIF-Pyrazinamide combination is not recommended due to adverse effects, including hepatotoxicity in HIV-negative individuals. However, this combination appears to be safe in HIV positive individuals.

Poor adherence was found to be the most common reason for the failure of LTBI treatment. The choice of treatment regimen for LTBI will depend on the clinician's assessment of the likely adherence level of the patient, antibiotic susceptibility of the presumed source case, drug tolerance, and overall feasibility.

There were several limitations to this research. One limitation found during the research phase was that most papers came out of the United States of America rather than Ireland or other European countries, so the data found may be less relevant to Ireland as well as the rest of the world. Also, it is important to note is that comparison of regimen adverse events was limited to hepatotoxicity as this was the only toxicity consistently compared across studies, and this review does not account for variation in duration of follow up across studies. Studies with longer follow up are expected to have a higher incidence of adverse events.

Conclusion

Tuberculosis remains as one of the most important infectious diseases with a high mortality rate. We reviewed up to date studies on the effectiveness of various screening and treatment methods and identified some successful tests and agents that can yield better detection of LTBI and better clinical outcomes. Overall, IGRAs are the most reliable screening tests but are advised to be used in conjunction with TSTs as the TST alone has been determined to be less accurate. High risk groups that should be screened for LTBI are those infected with HIV, infants, children, those prescribed with immunosuppressants, and the elderly. Treatment plans for those with LTBI are diverse and can be beneficial in a variety of settings. The most effective treatments include isoniazid for 6 or 9 months, rifampicin for 3 to 4 months, isoniazid and rifampicin for 3 to 4 months. Shorter treatment regimens are more effective than longer regimens due to higher treatment completion rates. These findings are important as they represent valuable diagnostic and therapeutic strategies that could be used to guide policies and improve the prognosis of those with LTBI.

Contributorship Statement

Morgan Lowe, Ailbhe Kenny, Sean Clarke, Charlie Eddershaw, and Michael O'Driscoll all contributed equally to this work.

Declarations

The authors declare no conflicts of interest. Stefan Elekes holds the position of feature writer on the editorial committee of the TSMJ Volume 21. This article was anonymised following submission and subsequently reviewed and accepted by an independent team of editors and peer reviewers as per the TSMJ's peer review and article acceptance protocol.

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