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CURRENT STRATEGY AND INTERVENTIONAL APPROACH FOR THE MANAGEMENT OF LATENT TB IN INDIA

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1. INTRODUCTION

Tuberculosis (TB) has evolved to be one of the major global public health challenges, infecting nearly one-fourth of the global population and killing approximately 1.5 million individuals, every year **(WHO, 2018).** Tuberculosis has been affecting humans for thousands of years and is one of the leading causes of morbidity and mortality **(Hershkovitz I, 2015).** In 2019, 7.1 million people were diagnosed to have TB, which was a rise from 7.0 million reported in 2018, globally. According to Global Tuberculosis Report, a total of 1.4 million people died from TB in 2019 (including 208000 people with HIV). India had the highest estimated incidence of 2.69 million and accounted for 26% of all TB cases reported, globally (WHO, 2018). The WHO End TB Strategy 2016-2035 has aimed at 3 main targets to be achieved by 2035. They are, 1) To reduce TB deaths by 95%, 2) To cut the incidence of TB by 90% between 2015 and 2035, and 3) To ensure that no family is burdened with catastrophic expenses due to TB **(WHO End TB Strategy).** Although, efforts to reduce the TB incidence rate have resulted in a decline in disease burden both globally and in India **(Kyu et al, 2018)**. Children accounted for 12% (0.15 million) and adults for 88% (2.40 million) of people with TB infection in India from cases reported in both private and public sectors. In India, the number of people newly diagnosed with TB rose from 1.2 million to 2.2 million between 2013 and 2019 (+74%). There has been an increase seen in the number of cases reported because of increased and improved diagnostic practices.

India represents one-fourth of the global burden of tuberculosis and due to poor airborne infection control practices, the burden of Latent Tuberculosis Infection (LTBI) also increases (Nandini Sharma et al, 2020). Nearly one-third of the world's population is predicted to have Latent Tuberculosis Infection (2.3 billion individuals) **(WHO Fact sheet, 2015**).

Currently, India is facing a high TB burden and hence, the LTBI burden is estimated to be massive, approximately 33-40% of the population **(Sanjay Rajpal et al, 2020)**. A huge proportion of the Indian population is expected to progress to active TB disease from LTBI, due to the presence of multiple risk factors **(Sanjay Rajpal et al, 2020).** For instance, 1.77 million homeless people in India pose a higher risk of developing active TB from LTBI due to lack of proper housing, sanitation and low immunity. Homelessness causes spread of infectious disease due to overcrowding of shelters and negligence towards health and disease. It was reported in many developing, high TB burden countries that the TB rates were 20 times higher among homeless population. As per the NSP 2017, search for active TB cases has been initiated in the homeless population **(Nandini Sharma et al, 2019**). Globally, TB is driven by poverty, immunocompromised conditions, poor health infrastructure, undernourishment, drug abuse, HIV infection, patients on anti-tumour necrosis (TNF) treatment, dialysis and transplantation. They are recognized as target population for LTBI treatment **(Jonathon R. Campbell et al, 2015).** Health Care Workers (HCWs) too are at risk of developing occupational TB and LTBI due to regular encounter with TB symptomatic cases **(Pardeshi G.S. et al, 2017).** A total of 26 (3.9%) TB disease cases were reported among 662 medical trainees at a tertiary care centre, Pune, India with an estimated disease incidence of 3279 cases/100,000 person-years **(Basavaraj A et al, 2016)**. India has the second-highest number of diabetes patients in the world **(Sachin Atre, 2019**), 2.5 million people are exposed to silica dust and pose a high risk of silicosis, which puts them at a higher risk of progression to TB **(S.K. Jindal, 2019).** Studies have suggested that patients with latent TB and active TB have an increased risk of SARS-CoV-2 infection due to immunocompromised status. People Living with HIV (PLHIV) also have the potential of increasing this pool and there are approximately 2.1 million PLHIV in India. **(Sanjay Rajpal et al, 2020).** As India contributes for 25% of the global TB burden, the government has therefore, initiated

the TB National Strategic Plan (NSP) with the plan to eliminate TB by 2025, with the assistance of NTEP (National Tuberculosis Elimination Programme). The goal of the programme is to reduce the prevalence rate to 44 and incidence rate from 320 to 65. One of the main objectives is preventing the development of active TB in people with latent TB, especially among people in "high-risk" groups. The high-risk population, majorly consists of immunocompromised population. Due to the immunocompromised condition, a single negative test is insufficient to rule out the diagnosis of LTBI, hence a combination of TST (Tuberculin Skin Test) and IGRA (interferon-gamma release assay) is employed in order to confirm the diagnosis. In case of contact tracing, initially if TST or IGRA is negative, re testing of contacts of infectious TB cases is recommended, 8-10 weeks after the exposure has ended **(SK Sharma et al, 2012).** The initial negative result might be due to the fact that the infection was too recent to be detected the first time **(SK Sharma et al, 2012).** Contact tracing helps in quick and rapid investigation of new sources of environmental transmission **(SK Sharma et al, 2012).** Although, efforts to reduce TB incidence rate have resulted in a decline in disease burden both globally and in India. Approximately, one in ten LTBI cases are at risk of developing TB disease during their lifetimes and larger risk amongst close contacts of active TB cases **(LTBI Guidelines, Geneva, WHO 2018).** The infection remains hidden due to innate immunity, but due to any degradation in the immunity could lead to tuberculosis infection, once he/she gets exposure to the infection. To eliminate TB completely from the country, attention towards LTBI is required, so that future chances of the infection can be reduced. There is nation-wide absence of policy on LTBI treatment, where people with LTBI acts as a reservoir of bacteria. If the infection can be controlled in the latent stage, chances of it getting converted into active infection can be reduced, which will help preserve national resources. There is an absence of understanding of the disease and lack of tools to predict who will and who will not progress from LTBI to active TB. This forms a major challenge to TB control efforts to implement guidelines on how best to screen patients for LTBI **(Kim SH et al, 2015).** Through this study, the researcher decides to comment on the understanding of the disease, interventions and entire national strategy, keeping in mind the TB elimination by 2025. Results from this systematic literature review may help identify gaps in the efficient and effective management of Latent TB Infection in high burden country like India.

2. WHAT IS LTBI?

LTBI has been defined as a state of persistent immune response to *Mycobacterium tuberculosis* antigens without the presence of clinically active TB disease **(Nandini Sharma et al, 2020).** LTBI refers to a condition in which *Mycobacterium tuberculosis* is present in the body, but remains in dormancy **(S Kiazyk et al, 2017).** As the bacteria are latent, the person does not fall sick and has no symptoms of TB, although there is a high risk of developing active TB infection **(Hannah Alsdurf et al, 2016)**. LTBI is a non-communicable form of active TB disease, but without preventive treatment, it can advance to active TB disease. Once infected, the risk of developing active TB is highest within the first two years but can remain at risk for a lifetime representing a reservoir of bacteria **(Meenu Singh et al, 2011).**

3. OBJECTIVE OF THE LITERATURE REVIEW

The aim of this Literature review is to understand the disease, current strategies and interventions for the management of LTBI in India. Another objective is to understand the preparedness of NTEP to eliminate TB by 2025 from India. This literature review will also help to understand need of further research in field of LTBI management.

4. BACKGROUND

LTBI management is very new in India and no sufficient literature is available with us although barriers to LTBI management were cited in few of the studies, which includes, 1). Non-implementation of existing guidelines, 2). Perceived inability to rule out LTBI and 3). Limited local guidance on the use of preventive therapy after close contact with TB patients. Lack in diagnostic services was also found to be one of the barriers in the identification of LTBI patients Lack of awareness about the latent tuberculosis infection and its preventive therapy is also mentioned as one of the barriers towards decreased attention on LTBI. Emphasis was given in some studies on the fact that LTBI management should include extensive patient education element explaining the disease process, the significance of treatment completion, adherence support and the acknowledgement and management of the potential side effects of the treatment.

5. LITERATURE REVIEW

Current study details the research related to management of LTBI. A detailed literature survey has been conducted for articles published between the years 2011 and 2020, with specific emphasis on management of LTBI and its current strategy and interventions.

Based on the literature survey, the review focused on 5 major topics, as follows:

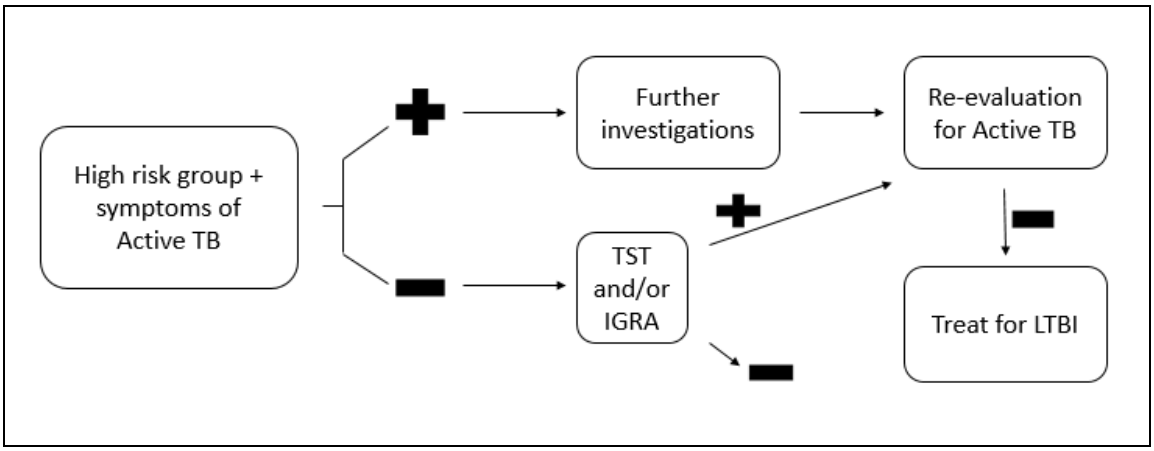
1) Diagnosis and screening.
2) Risk groups.
3) Immunocompromised patients.
4) LTBI in children.
5) Treatment of LTBI.

Details of research conducted in each of these topics have been discussed in the further sections. Research publications, books and proceedings published between 2011 and 2020 were studied and considered for this review.

5.1 Diagnosis and screening of LTBI

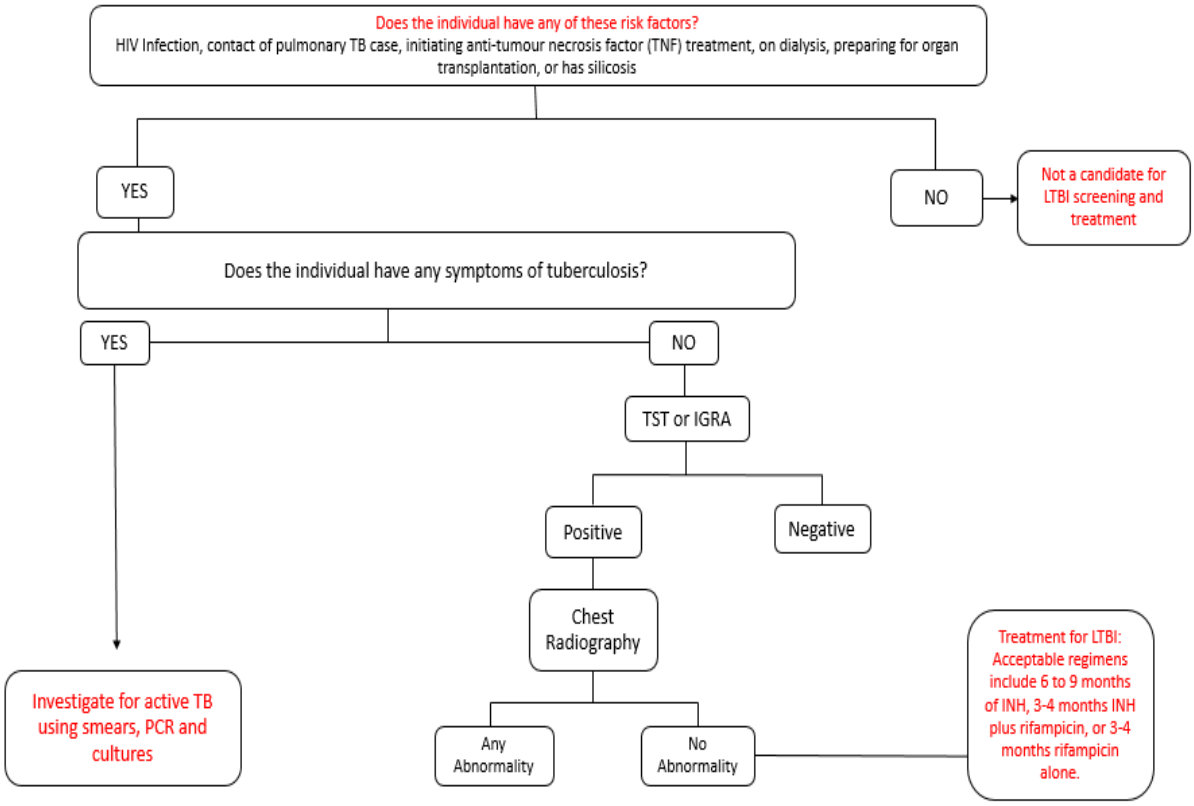
Currently, there are two tests available for the screening of LTBI: Tuberculin Skin Test (TST) and interferon-gamma release assay (IGRA). TST is done using the Montoux skin test and purified protein derivatives (PPD) is the antigen injected intra dermally. Skin induration is seen in 48-72 hours **(Hung et al, 2015).** IGRA is done in vitro, and use highly specific peptides from 2 main antigens- early secreted antigenic target (ESAT 6) and culture filtrate protein (CFP 10). Both TST and IGRA depend on memory T-cell response (cell-mediated immunity), positive test results suggest that the patient has been exposed and sensitized to MTB in the past. According to many papers published, both TST and IGRA can be used for the diagnosis of LTBI, but neither of the tests can accurately differentiate between LTBI and active TB. Both of the tests are considered somewhat imperfect tests. Both measure a cellular immune response to MTB and represent indirect markers of MTB exposure (read as mm induration with the TST, and amount of interferon-gamma released by T-cells in IGRAs). (**S. Saha et al, 2019)** suggested that there is a lack of gold standard test for the diagnosis and screening of LTBI. In terms of certainty, IGRA is more specific than TST as it utilizes antigens found only in *Mycobacterium tuberculosis*, thereby abolishing cross-reactivity with the Bacille Calmette-Guerin (BCG) vaccine **(M. Pai et al, 2014).** However, out of both IGRA and TST, TST is still considered a simple and cost-effective tool for both epidemiologic research and TB control. In a high burden, resource-limited country like India, TST is the preferred method for LTBI diagnosis due to cost and logistic constraints **(Sharma et al, 2017).** Due to the availability constraints, LTBI testing with TST is constricted only to PLHIV, HIV-infected children, and children born to HIV-positive mothers in India **(Nicholas I. Paton, 2019).** Commercially available IGRAs are Quantiferon-TB Gold In-Tube Test, Quantiferon-TB Gold In Tube (QFT-GIT) (Qiagen, Valencia, CA, USA) and T-SPOT.TB (Oxford Immunotec, UK) **(Meenu Singh et al, 2011).** They have been approved by the U.S. Food and Drug Administration (FDA) for commercial use. However, IGRAs are not much used for diagnosis and screening purposes as it requires proper laboratory setup and can be quite expensive.

In 2018, an algorithm was issued by the World Health Organization (WHO) for the testing and treatment of LTBI, as shown in Fig 1.



5.2 Risk Groups

For the methodical and systematic management of LTBI, the WHO in 2018 recommended selecting at-risk population, based on the epidemiology and TB transmission pattern in the region (WHO, 2018). Due to the high population of India, there are several groups of at-risk population, which are prone to develop LTBI or progress to active TB from prior LTBI infection (Nicholas I. Paton, 2019). Reactivation of latent infection into active TB disease can occur, often within the first 2 to 5 years following the infection. The reasons for LTBI reactivation are still unknown, but host and environmental factors play a major role **(Getahun H et al, 2015; Shea KM et al, 2014)**. People living with HIV, injection drug abusers, people with poor standards of living, undernourished, low body weight (10% below ideal), medical conditions like diabetes mellitus, silicosis, chronic renal failure or on haemodialysis, gastrectomy, organ transplantation, head and neck cancer conditions that require prolonged use of corticosteroids or other immunosuppressive agents such as TNF-alpha antagonists are referred as risk groups and risk factors associated with the progression of LTBI to TB disease **(S Kiazyk et al, 2017**). For high TB burden countries, the WHO in 2014 published its first comprehensive guidelines on the management of latent TB infection (Figure 2). These guidelines provide clear and crisp recommendation for LTBI management in resource constrained, high burden countries (WHO, 2014).



According to the 2018 WHO LTBI guidelines, systematic testing for LTBI in diabetics was not recommended due to lack of good quality evidence (WHO, 2018). However, the experts suggested that diabetics may represent an important risk group to progress from LTBI to active TB. Various studies reveal a high prevalence of LTBI among diabetics (Barron et al, 2018; Martinez-Aguilar et al, 2015). In a meta-analysis of 13 studies, involving 38, 263 participants, it was seen that diabetes was associated with high risk of LTBI (Lee et al, 2017).

Health Care Workers (HCWs) also represent high chances of getting infected, especially in the regions of high burden (Nasreen et al). In 2018, WHO LTBI Guidelines, *a conditional recommendation*, has been provided for systematic testing and treatment of LTBI in HCWs, in countries with low TB burden. However, systematic testing and treatment of HCWs should be considered in high TB burden countries as well. According to a study conducted among post graduate medical residents and nursing students at a medical college and general hospital in Pune, Maharashtra, it was seen that the prevalence of LTBI among medical residents and nursing students was 30% and 35% respectively **(Arti Kinikar et al, 2019).**

According to WHO guidelines 2018, LTBI testing and treatment is advised among prisoners in countries with low TB burden. However, no such instructions or recommendations are given for prisoners in countries with high or intermediate TB burden (WHO, 2018)

5.3 *Immunocompromised patients*

Patients with compromised immunity or on immunosuppressant drugs like steroids, DMT (Disease-Modified Treatment) and anti-rheumatic drugs have a greater risk of developing TB than the general population **(Lobue P, Menzies D, 2010).**

Although, a large number of people suffer from rheumatic diseases in India, but there is a lack of clear guidelines for LTBI testing and treatment for them. Because of the immunocompromised conditions, the value of TST remains sceptical, due to false negativity in immunocompromised patients and false positivity due to BCG vaccination.

Patients with multiple sclerosis (MS) have compromised immunity. Therefore, they pose a high risk of developing active TB from LTBI. The prevalence of LTBI in MS patients is not well established. However, a German study suggests the prevalence of 3.85% (95% CI) of LTBI among MS patients. Although, these results cannot be generalised, as the MS population with LTBI is not known in India. Therefore, it is important to check LTBI status in the MS patient population, because MS treatment could place patients at a greater risk for reactivation of their LTBI **(Graf J et al, 2017).**

For HIV (Human Immunodeficiency Virus Infection) patients in resource-limited countries, the WHO has recommended some guidelines for LTBI testing and treatment. According to these guidelines, isoniazid preventive therapy (IPT) should be initiated in all

individuals with HIV, irrespective of age (children > 1 year age, adolescents, adults and pregnant women). TST is not mandatory to initiate IPT. TB patients those were previously treated, those on ART (Antiretroviral Therapy) and pregnant women should also receive IPT. The NSP, 2017 aims to increase IPT to all PLHIV across India. For children less than 1 year of age and are HIV positive, IPT should be initiated only in those in close contact of active TB cases. People with HIV and latent TB co-infection have more than 100 times increased risk of developing active TB disease **(Selwyn et al, 1989).**

5.4 LTBI in Children.

Infants and children less than 5 years of age, are more prone to progress to active TB disease after acquiring LTBI infection. Children after acquiring LTBI become adults who act as the reservoir of bacteria. Therefore, screening of children in contact with TB cases is recommended for the best interest of the child and public health in general for disease control **(Meenu Singh et al, 2011).**

5.5 Treatment of LTBI

Prior to starting the preventive therapy for LTBI, accurate assessment to rule out active TB is necessary, otherwise the patient might develop complications in the form of drug-resistant strains **(Menzies D et al, 2011).**

According to the 2018 WHO LTBI guidelines, isoniazid monotherapy is recommended for LTBI treatment in both children and adults for 6 months. Moreover, two new short duration regimens have been proposed by the 2018 WHO LTBI guidelines as adherence to isoniazid monotherapy is low in most of the Asian countries with high TB burden. These includes:-

1. Rifampicin plus isoniazid daily for 3 months in children and adolescents aged <15 years (3RH regimen).
2. Rifapentine plus isoniazid weekly for 3 months in both adults and children (3HP regimen).

6. RESULT

One of the studies highlighted that health care workers are at increased risk of contracting occupational TB due to regular encounters with symptomatic TB and LTBI cases. Other medical conditions mentioned in most of the studies include silicosis, diabetes mellitus, chronic renal failure, organ transplant and head and neck cancer conditions. It was highlighted in few of the studies that the Indian population is vulnerable to progression to active TB disease from LTBI due to the presence of risk factors. One of the studies revealed that poverty, malnutrition, tropical infection, addiction, illiteracy, poorly functioning health-care systems and political imbalance act as important contributors to the development of risk factors. It was noted in one of the studies that a large proportion of the Indian population with low BMI and latent TB infection is at risk of developing TB disease.

A study highlighted that some Mtb bacilli may remain viable (latent) and "reactivate" later to cause active TB disease. One of the studies stated that the pathogenic state of bacterial infection and the likelihood of reactivation depends on the balance between host immunity and the impact of exogenous factors. Most of the studies said that continuous environmental exposure to Mtb increases the risk of TB reactivation by increasing the total host mycobacterial load. One of the studies highlighted that IPT was found to reduce the risk of reactivation by 82%, among people with immunocompromised conditions like HIV. Children of the ages 1-2 years were observed with reactivation rates up to 40% in high burden settings like India. It was mentioned in few of the studies that the probable risk of TB reinfection is higher among high burden countries, which could reduce the overall public health impact of mass LTBI treatment. As per a study, the risk of TB reactivation was maximum with 9 months of INH alone and minimum with 6 months of Rifampicin. However, it was mentioned in some of the studies that the combination of INH and Rifampicin is the most effective with no chances of reactivation. It was interpreted from one of the studies that for the elimination of TB, it is necessary to decrease the burden of LTBI in the community to prevent reactivation in the future. Most of the studies said that, the lifetime risk of reactivation of TB disease is estimated to be around 5-10%. It was mentioned in one of the studies that preference of LTBI treatment should be given to those at high risk of reactivation, especially due to short term reversible predisposing factors. Therefore, the decision to treat LTBI should be taken by considering the possibility of reactivation versus re-infection. It was noted in one of the studies that without the elimination of latent TB, India's efforts to eliminate TB by 2025 will not be fruitful. Therefore, on practical grounds, India must actively treat LTBI patients who are at risk of progression to active TB.

According to many studies, there is a lack of gold standard test for the screening and diagnosis of LTBI as neither of the present diagnostic tests (IGRAs, TST) can completely differentiate between LTBI and active TB. These tests are immunological tests that provide indirect evidence of sensitization of the host to TB antigens. As suggested by various studies, in high burden countries, neither IGRAs nor TST accurately identify people who will benefit from the treatment. At present, there is no diagnostic test that can identify an individual with LTBI who will progress to develop active disease or remain asymptomatic.

Various studies suggest that IGRAs are not preferably used in high burden settings due to its expensive and sophisticated laboratory dependency. Rather, TST is mentioned in several studies as more-valuable and cost-effective tool for LTBI diagnosis, regardless of BCG status. It was noted from few studies that IGRAs perform poorly in terms of sensitivity and provides more

intermediate results in terms of children. However, one of the studies said that IGRAs seem to be significantly more accurate than the skin test. As per few studies, routine testing with both TST and IGRA is not recommended. In high burden countries like India, with limited resources, TST is considered as the mainstay for LTBI testing in view of its low cost and minimal logistic requirements.

One of the studies said that the goal of testing for LTBI is to identify individuals who are at an increased risk for the development of active TB. It was highlighted in one of the studies that LTBI screening must be restricted to specific high-risk populations in India. One of the studies mentioned that a single active TB case often infects several others prior to receiving anti-tubercular treatment due to delayed diagnosis in densely populated regions in high burden countries, creating a never-ending reservoir of latent TB cases. Many studies highlighted that diagnosis of LTBI are hindered by the cost implication of testing and lack of consensus on the tests recommended. It was noted in few of the studies that in countries with limitation of resources and high burden like India, testing is recommended only in HIV and children <5 years of age. It was suggested in few studies that in resource limited settings, TST should remain as the pillar for LTBI testing before we have a considerably improved test due to low reagent cost, ease of applicability, no requirement of technical expertise, standardized labs and venipuncture. One of the studies revealed that the available data on testing for LTBI as well as treatment outcomes in India are sadly lacking. This data is very relevant for a high burden country like India. We also need to identify other high-risk subgroups for whom the LTBI treatment may be validated. The complex nature of the disease and various socio-economic factors require further research in this area.

Nearly all of the studies have described the most popular LTBI regimens, which developed in the past 2 decades. They were Isoniazid Preventive Therapy (IPT) and shortcourse rifamycin-containing regimens. It was pointed out in few of the studies that the overall efficiency of various regimens is baffled by issues concerning adherence, duration of protection and drug toxicity. Studies have majorly described the current WHO guidelines for resource-limited and high burden countries of at least 6-month INH therapy for both adults and children, regardless of TST, after excluding active TB. Based on multiple studies, it has been mentioned that moxifloxacin, from the fluoroquinolones class of drugs is effective drug for the treatment of both active TB infection and LTBI. As per the guidelines of The Revised National TB Control Program (RNTCP), the recommended treatment of all close household contacts aged 6 years is 6 months of IPT (5 mg/kg daily) regardless of BCG vaccination status.

It is being noted in several studies that LTBI can be safely and effectively treated through preventive therapy. It was highlighted in one of the studies that INH preventive therapy is approximated to reduce the lifetime risk of morbidity and mortality due to TB. For this, the duration of 9 months is recommended for the maximal beneficial effect, and some additional benefit is gained by extending the therapy to 10 months. In adolescents, rifampicin therapy (10 mg/kg/day for 6 months) is approved based on the safety and acceptability.

Based on a randomized controlled trial (RCT) comparing 4 months rifampicin vs. 9 months isoniazid, found the two therapies to be similar in efficiency and side-effects profile, however rifampicin arm had better adherence rates. As mentioned in one of the studies, the IAP (Indian Academy of Pediatrics) has recommended isoniazid for the treatment of LTBI in the dose of 10 mg/kg/day for 6 months. It was highlighted in one of the studies that the WHO has given an algorithm recommending the treatment options for LTBI stating, 6-9 months of isoniazid, 3 month regimen of weekly rifapentine plus isoniazid, or 3-4 months of rifampicin alone. As per one of the studies, IPT was found to be relatively safer than the combination regimens. Considerable pharmacokinetic drug interaction and additive toxicities with ART prohibits the use of rifamycin-containing combination regimens as the first choice for LTBI treatment.

Recent studies in adults using shorter regimens of rifampicin plus pyrazinamide for 2 months were anxious with unexpected high rates of hepatotoxicity including fatalities from liver failure. Isoniazid Preventive Treatment for LTBI treatment increases the risk of hepatotoxic reaction, the cumulative risk of side-effects from four-drug first-line anti TB regimen used for the treatment of TB is much higher especially with increasing age and among women. Therefore, it was pointed out in one of the studies that newer LTBI drug regimens, like the once weekly twelve-dose INH Rifapentine regimen (3HP) are considerably less likely to cause adverse effects compared to IPT. According to a study, children are found to be more tolerant to INH as compared to adults and have minimal risk of drug-related hepatitis. It was noted in several studies that isoniazid can lead to hepatotoxicity and peripheral neuropathy. Rifamycin leads to gastrointestinal intolerance and hepatotoxicity, though there is no significant difference in adverse effects between rifampicin and rifapentine. One of the studies pointed out that the risk of toxicity is highest with isoniazid, especially in older individuals, and those who consume alcohol. It was noted in one of the studies that the differential approach to the management of LTBI is advocated due to the limited diagnostic accuracy of the screening tests, the significant risk of side-effects from LTBI treatment and the threat of INH resistance.

7. CONCLUSION AND RECOMMENDATIONS

Latent tuberculosis infection (LTBI) is defined as a consistent immune response to *Mycobacterium*

tuberculosis antigens without evidence of clinically evident active tuberculosis (TB). Early identification and treatment of individuals with LTBI is an important priority for TB control in specific groups at risk within the population: this is of crucial meaning in recently infected cases both at the community level and in some occupational settings**. (Zellweger et al, 2020)** Tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) are used to diagnose LTBI. Therefore an unequivocal policy /of diagnosis and treatment of LTBI will serve to ameliorate the standards of the Indian health scenario and bring the TB infection to the propinquity of its ultimate elimination. **(Rajpal S et al, 2020)**

LTBI management is important to help identify and tackle the reservoir of TB infection, as an effort to prevent and control TB incidence, with the aim of achieving the milestones of eliminating TB epidemic in India by 2025. As there are very limited studies available on the treatment adherence of the LTBI across the world and India is just step in LTBI management there is a huge scope to conduct research studies to access effectiveness current strategy adopted by NTEP to eliminate TB from India.

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