Discoveries Journals
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DISCOVERIES REPORTS 2022, 5(1): e27
DOI: 10.15190/drep.2022.1

Review Article

Latent Tuberculosis: Challenges and Opportunities for Diagnosis and Treatment

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Submitted: January 05, 2022; *Revised:* March 02, 2022*; Accepted:* March 03, 2022; *Published:* April, 2022
Citation: Hange N, Somagutta MR, Sharma A, Agadi K, Ngaba NN, Paikkattil N, Pormento MKLL. Latent Tuberculosis: Challenges and Opportunities for Diagnosis and Treatment. *Discoveries Reports* 2022; 5(1): e27. DOI: 10.15190/drep.2022.1

ABSTRACT

It is imperative to contain this silent epidemic of tuberculosis (TB), considering the monstrous burden of TB incident cases and deaths. As part of the WHO initiative of the end tuberculosis strategy, TB-preventive treatment (TPT) initiation to reduce TB incidence has been considered the ultimate preventive resort. This article addresses the challenges and strategies for latent TB management. Targeted LTBI Screening in the population with suspicion of TB infection with an effective contact screening strategy is an ideal preliminary step. Along with precise, short regimen treatment initiation for LTBI, the health care system ought to ensure the entire course of therapy. Effective utilization of existing infrastructure and resources for TB elimination is ideal for handling contact screening and LTBI management. Inconsistent guidelines about TB contact screening and cognizance of the population regarding attending an LTBI screening clinic are the first-line barriers hindering screening rates. Poverty, malnutrition, TB-HIV co-infection, long-term treatment, adverse effects, and associated out-of-pocket expenditure pose significant concerns for LTBI treatment. A cost-effective treatment regimen with a shorter duration and fewer adverse effects, population-specific treatment strategies with social intervention-teaching, and dedicated health care staff are crucial to ensuring the initiation and completion of LTBI treatment. Embracing LTBI strategy with active TB patient community engagement and education is essential for TB eradication across the globe. However, the most effective resort for TB elimination requires a specific LTBI management program. Until then, optimizing our current tools and strategies is essential for progress towards the TB elimination.

Abbreviations

Tuberculosis (TB); TB-preventive treatment (TPT); World Health Organization (WHO); Latent tuberculosis infection (LTBI); Mycobacterium tuberculosis (M. tuberculosis); TST (tuberculin skin test); IGRA (Interferon-gamma release assay); Information education and communication (IEC); Interferon-Gamma Release

Assays (IGRAs); Tuberculin skin test (TST); Multiple drug resistance (MDR); Directly observed treatment strategy (DOTs); Body mass Index (BMI); Bacillus Calmette-Guerin (BCG); Nontuberculous Mycobacteria (NTM); RR (rifampicin-*resistant*); Human Immunodeficiency Virus (HIV).

Keywords

Tuberculosis, TB preventive treatment, latent tuberculosis infection, adherence.

SUMMARY

1. Introduction

Globally, among 10 million individuals with active tuberculosis (TB) annually, 1.5 million patients die. TB has emerged as a serious public health threat worldwide[1]. The incidence and prevalence of TB cases remained highest in the World Health Organization (WHO) South-East Asia and African regions[1, 2]. As part of the WHO initiative of the end tuberculosis strategy, targets have been set to reduce the TB incidence by 90% and deaths by 95% by 2035[2,3]. Active TB infection is a preventable disease. Though asymptomatic, latent tuberculosis infection (LTBI) is not acutely infectious, it can later reactivate and progress to active disease[3-5]. Treatment of LTBI is one of the crucial prerequisites in TB elimination[4,5]. Hence, countries intending to tackle and eliminate TB by implementing WHO end TB strategy have opted for TB-preventive treatment (TPT) to reduce the TB incidence[1,5].

About one-third of the world's population has LTBI, indicating infection. However, it doesn't mean that they are sick and can transmit tuberculosis[2]. About 30% of individuals exposed to *Mycobacterium tuberculosis (M. tuberculosis)* will develop LTBI and, if untreated, approximately 5% to 10% of these individuals will progress to an active tuberculosis disease or a reactivation of tuberculosis[6]. Eight countries account for two-thirds of the total TB burden, with India leading the count with a TB incidence >100 per 100,000 population in 2019, followed by Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh and South Africa[1,7]. Criticality in the TB control program depends upon the extent of prevention of LTBI developing into active disease, early diagnosis, and treatment of an active disease once developed[5]. Thus, this article aims to focus on the challenges and opportunities for the diagnosis and treatment of the LTBI in the developing, high burden TB countries.

2. Epidemiology of LTBI in high burden TB countries

A meta-analysis found that the global prevalence of LTBI was 24.8% and 21.2%, based on Interferon-Gamma Release Assays (IGRAs) and a 10-mm Mantoux tuberculin skin test (TST) cut-off, respectively. Furthermore, the highest LTBI prevalence was found in Southeast Asia[8]. Similarly, another author suggested that WHO South-East Asia, Western-Pacific, and Africa regions had the highest prevalence and accounted for around 80% of those with LTBI[9]. Knight et al. has calculated LTBI burden using a new mathematical model that follows cohorts over time, applying the historical annual infection risk to estimate risk trends of new infections with MDR strains and related prevalence of LTBI. The study has come with an estimation of 19.1 million people with LTBI, due to multiple drug resistance (MDR)-*M. tuberculosis* strains globally[10]. According to WHO, countries with an incidence of >10, 000 TB cases per year are given the highest priority for TB elimination and are labeled as "High Burden TB countries"[7]. Along with higher incidence, the fatality of TB cases and related population size of a country determines TB burden. The latest list of nations that was released by WHO based on the high TB burden and MDR (TB bacteria resistant to at least isoniazid and rifampin)/RR (TB bacteria resistant to rifampin). TB burden can be seen in Table 1.

3. Screening and diagnosis of LTBI

LTBI is "a state of persistent immune response to stimulation by *M. tuberculosis* antigens without any evidence of clinically manifested active TB"[12]. However, LTBI carries a 5–15% risk of progression to active TB in the first 2 years from the infection.

Table 1: List of High TB burden Countries[11]

WHO-regions	High TB burden countries	High MDR/RR- TB burden countries
Southeast-Asia region	India, Bangladesh, Indonesia, Nepal, Thailand, Democratic people's Republic of Korea	India, Bangladesh, Indonesia, Nepal, Thailand, Democratic people's Republic of Korea
Western-Pacific region	China, Philippines, Vietnam, Papua New Guinea, Mongolia	China, Philippines, Vietnam, Papua New Guinea, Mongolia
African region	Angola, Central African Republic, Democratic Republic of Congo, Ethiopia, Gabon, Kenya, Liberia, Mozambique, Namibia, Nigeria, Lesotho, South Africa, Uganda, United Republic of Tanzania, Sierra Leone, Zambia, Zimbabwe	Angola, Democratic Republic of Congo, Mozambique, Nigeria, South Africa, Zambia, Zimbabwe
East-Mediterranean region	Pakistan	Pakistan, Somalia
European region	-	Republic of Moldova, Ukraine, Belarus, Russian Federation, Ukraine
Region of Americas	Brazil	Peru

Additionally, there is a 5% risk of developing active TB after, mostly due to decreased immunity while aging or other diseases[13]. Sloot and colleagues have reported 75% of active TB cases took place in the first one year from the diagnosis and 97% within two years[14]. Individuals with LTBI have negative test results for active TB while having a positive specific diagnosis based on either a skin (tuberculin skin test) or a blood (interferon-gamma release assay) test, pointing out to an immune response to *M. Tuberculosis*[15-17].

Targeted testing of LTBI screening should be used to identify and treat people who are at high risk (Figure 1) for exposure to or infection with *M. tuberculosis* and for developing TB disease once infected with *M. tuberculosis*[1,27].

The IGRA is the preferred test for adolescents and adults who have received Bacillus Calmette-Guerin (BCG) vaccination, while the TST is the preferred test for the diagnosis of LTBI in children <5 years of age[15]. In immunocompromised individuals, especially those with HIV/AIDS, T-SPOT.TB test is preferred instead of the tuberculin skin test and QuantiFERON-TB Gold In-Tube (QFT-GIT) for the diagnosis of LTBI, due to a lower incidence of nonconclusive results[18].

Testing algorithm

Screening for LTBI shall be performed in the population with suspicion of TB infection. All high-risk TB contacts and old TB patients shall be systematically investigated for active TB with an intention of treatment initiation for positive TST or IGRA[5]. TB contact screening process and the testing algorithm are explained in Figure 2.

4. Treatment options and availabilities for LTBI[1,5]

Management of LTBI

Treatment of LTBI is essential for controlling and eliminating tuberculosis all over the world. Successful therapy of latent TB reduces the risk of activation of dormant infection and subsequent progression to active TB disease. Every effort should be made to start appropriate treatment and to ensure that individuals at the higher risk of reactivation complete the entire course of therapy[17]. The LTBI is managed by a cocktail of drugs that include the following: isoniazid, rifapentine, rifampin except for MDR TB. As per WHO's 2020 guidelines, regimens are described below, and supported by available

Figure 1: High risk group for LTBI screening[9,16] (adapted from references [9] and [16])

evidence[19]. The details of the different regimens and doses can be seen in Table 2.

4.1. Six- or nine-months daily isoniazid monotherapy

Six months of daily monotherapy with isoniazid, active against both intracellular and extracellular *M. Tuberculosis,* is the standard treatment for adults and children living in high burden countries[20, 21]. A recent systematic review showed a significantly greater reduction in TB incidence among participants given the six-month regimen than in those given a placebo (odds ratio [OR] 0.65; 95% CI 0.50; 0.83)[21]. Re-analysis and modeling of the United States Public Health Service trials of isoniazid conducted in the 1950s and 1960s showed that the benefit of isoniazid increases when it is given for up to 9–10 months and stabilizes thereafter[22]. Some studies showed an excellent safety profile for isoniazid[21,23, 24]. Considering hepatotoxicity, isoniazid is used cautiously in elderly, pregnant women and contraindicated in patients with acute hepatic impairment. Another common side effect of peripheral neuropathy is managed with pyridoxine supplements[25, 26].

4.2 Three months daily rifampicin plus isoniazid

The regimen of isoniazid plus rifampin was introduced to the United Kingdom in 1981 for the prophylaxis of children with exposure history and immigrants with LTBI, especially from India. The reason for including rifampin as a combination was the high incidence of isoniazid resistance in index cases (6%) from India consistent with WHO guidelines [27,28]. Initial treatment (1981) duration was of 9 months and was gradually shortened to three months (1989) of rifampin together with isoniazid (3HR) in combination. Combined treatment of isoniazid and rifampin successfully reduced the TB burden of the community, with only a few cases of adverse events[29]. The radiographic findings of a randomized study conducted over 11-years (1995-2005) concluded that the short-course treatment with isoniazid and rifampin for three months is safe and superior to an isoniazid monotherapy responsible for active disease in 24% of population[30].

4.3. Three months weekly rifapentine plus isoniazid

The results from systematic review and meta-analysis showed that the effectiveness of three-

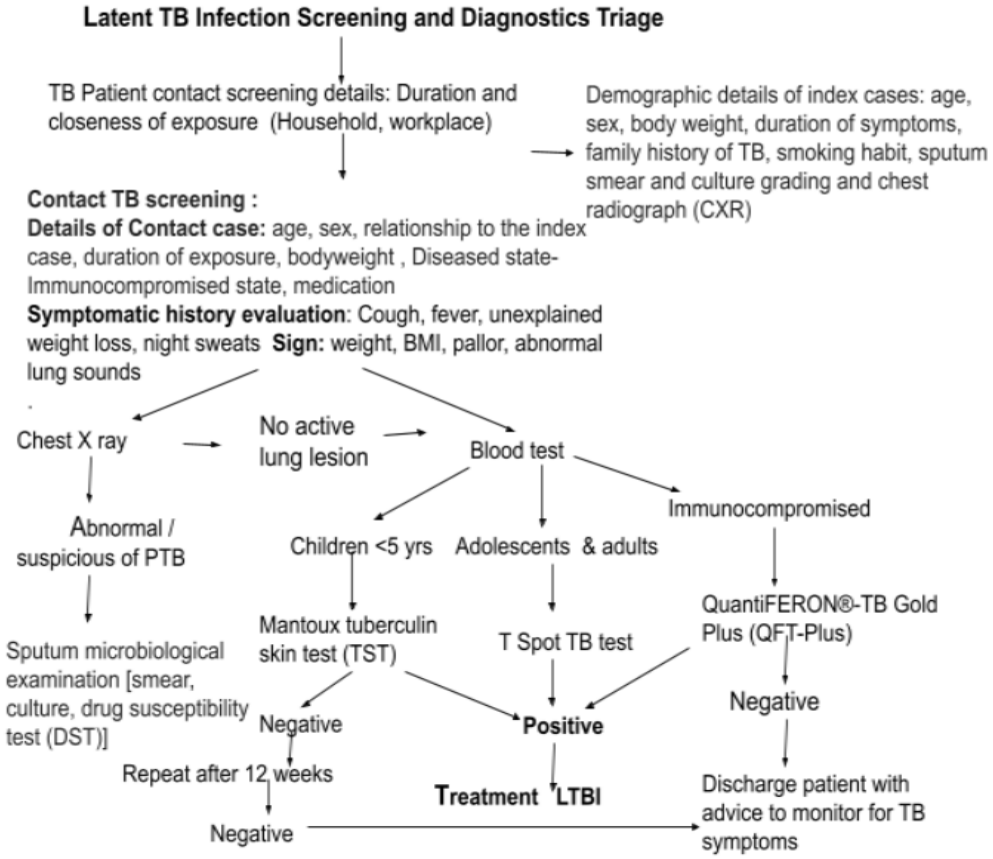

Figure 2: Screening and testing algorithm for LTBI (adapted from reference[5])
TST cut off >=5 mm in high-risk patients, >= 10 mm high TB burden population/ patients in congregate setting and 15 in population with no risk; A Quantiferon Gold test positive if the result is ≥0.35 IU·mL^{-1}; T Spot TB positive if (Panel A-Nil) and/or (Panel B-Nil) ≥ 8 spots.

month isoniazid- rifapentine was non-inferior to other LTBI regimens (OR=0.89, 95% CI=0.46, 1.70), while reported higher treatment completion and similar risk for adverse events (relative risk=0.59, 95% CI=0.23, 1.52)[31]. Moreover, a large randomized clinical trial of 3HP (three months of rifapentine plus isoniazid) administered by directly observed treatment strategy (DOTs) including children aged 2–17 years, demonstrated that 3HP was as well-tolerated and equally effective as a regimen of 9 months of daily isoniazid (9H) for preventing TB [32].

4.4. One-month daily rifapentine plus isoniazid or four months daily rifampicin

A randomized trial comparing the efficacy and safety of one month of rifapentine plus isoniazid daily to nine months of isoniazid alone in people living with HIV concluded non-inferiority of one-month rifapentine plus isoniazid therapy to nine months isoniazid regimen[19]. A previous systematic review of LTBI guidelines found similar efficacy for 3-4 months daily rifampin and six months of isoniazid (OR 0.78; 95% CI, 0.41; 1.46)[33]. The review also noted that individuals given rifampin daily for 3-4 months had a lower risk for hepatotoxicity than those treated with isoniazid monotherapy (OR 0.03; 95% CI 0.00;0.48). A shorter (4-month) course of rifampin has been evaluated as a viable alternative to isoniazid in LTBI, given its low toxicity and high efficacy profile. Furthermore, an open-label trial conducted in nine countries, comparing the 4-month regimen of rifampin with a 9-month regimen of isoniazid for the prevention of latent TB concluded that the 4-month regimen of rifampin was not inferior to the 9-month

Table 2*:* Recommended regimen and dose for LTBI treatment[2]

Regimen	Dose recommended
6 or 9 months of daily isoniazid (6H or 9H)	Age 10 years and above: 5 mg/kg/day Age <10 years:10 mg/kg/day
4 months of daily rifampin (4R)	Age 10 years and older: 10 mg/kg/day Age <10 years: 15 mg/kg/day
3 months of daily rifampicin plus isoniazid (3HR)	Isoniazid: Age 10 years & above: 5 mg/kg/day Age <10 years: 10 mg/kg/day Rifampin: Age 10 years & above: 10 mg/kg/day Age Age <10 years: 15 mg/kg/day
3 months of rifapentine plus isoniazid weekly (12 doses) (3HP)	Age 2-14 years: isoniazid, 100 mg rifapentine, 150 mg Age >14 years: isoniazid, 300 mg rifapentine, 150 mg
1 month of rifapentine plus isoniazid daily (28 doses) (1HP)	Age ≥13 years: isoniazid, 300 mg rifapentine, 600 mg
MDR-TB: 6 months of levofloxacin daily	Age ≥14 years, by body weight: < 46 kg, 750 mg/day; >45 kg, 1g/day Age <15 years: 15-20 mg/kg/day

regimen of isoniazid and was associated with a higher rate of treatment completion and better safety[34].

5. Challenges in Screening and treating LTBI in developing nations

Various issues may arise during the management of LTBI. This section discusses concerns regarding screening, treatment, and economic barriers to LTBI management in developing countries.

5.1 Challenges in screening LTBI

There is no gold standard test for LTBI, and the diagnostic tests used are TST and IGRA. However, TST is rarely used in developing countries for LTBI, primarily due to erroneous belief that the BCG vaccine will cause a false positive test result[35-37]. IGRA has higher specificity over TST but also shows variable results with repeated testing in low-risk populations[36]. Furthermore, both tests are less sensitive in children less than two years old despite this age group having a higher risk of progression to active TB and overall poor positive predictive value[35-38]. Screening guidelines for the use of TST or IGRA vary per country and are inconsistently implemented[35, 36, 39]. A lack of awareness of health care providers regarding LTBI management guidelines may contribute to the discrepancies. However, along with this, the tests themselves are unavailable in most countries[39]. Financial constraints may lead to limited testing even in high-risk groups. Another consequence of cost may be the type of test offered. TST is more cost-effective but requires patients to return for the result, leading to probable drop-out[39].

5.2 Challenges in treating LTBI

5.2.1 Drug adherence

Non-adherence to anti-tuberculosis (anti-TB) medication is a significant risk factor for poor treatment outcomes. The reasons for drug non-adherence mainly include adverse drug reactions, longer duration of treatment, long-distance from the health facility, history of incarceration, absence of perception of risk, presence of stigma, alcohol and drug use, unemployment, time lag between diagnosis and treatment, etc[40]. A systematic review of randomized controlled trials concluded that in

LTBI patients, shorter regimens and DOTs effectively improved treatment completion[41]. In addition, it is essential to monitor adverse drug reactions during treatment. For individuals taking self-administered therapy, monthly or more frequent assessments by a health care provider is required[42]. Hence, to increase adherence to LTBI treatment, treatment-related interventions, such as case management, education, and counseling, should be accompanied. Appropriate recording, reporting, and monitoring systems should be established[40-42].

5.2.2 TB-HIV co-infection and drug resistance

It is known that the concomitant use of antiretroviral therapy (ART) with the treatment of drug-susceptible pulmonary TB improves survival rates in HIV-infected individuals. However, TB therapy for such patients is complicated by the risk of developing "immune reconstitution inflammatory syndrome" and expected drug interactions[43]. Such critical drug interactions can occur between the rifampicin and the protease inhibitors and non-nucleoside reverse transcriptase inhibitor drugs. It is known that rifamycin derivatives (rifampin and rifapentine) induce liver enzymes and reduce serum concentrations of protease inhibitors, such as indinavir, ritonavir etc. In HIV-infected individuals, rifapentine is not recommended due to the development of acquired rifamycin resistance[44]. Patients infected with strains resistant to isoniazid and rifampin, called multidrug-resistant (MDR) TB, are practically incurable by standard first-line treatment. Apart from drug interactions, drug resistance can also be developed due to poor adherence, repeated use of short-course therapy, community or facility-based transmission, respectively[45,46]. Program-based surveillance systems and clinical studies are needed to monitor the risk of resistance to the medicines used in TB preventive treatment, particularly rifamycin-containing regimens[1, 2,46].

5.2.3 Economic domains of LTBI

Poverty and undernourishment

In developing countries, LTBI management is a challenge due to poverty and poor quality of living. The World Bank defines international poverty as people living below US$ 1.90 per day [47]. The top30 high TB burden countries accounted for 86% of all estimated incident cases worldwide, and eight of these countries accounted for two-thirds of the global total: India (26%), Indonesia (8.5%), China (8.4%), Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%)[19]. India's poverty rate was estimated to range from 8.1 to 11.3 percent at the international poverty line between 2011-12 and 2017[20,48]. Poverty amplifies the risk of, and risks from, malnutrition. Poor people are more likely to be affected by different forms of malnutrition[49]. Data suggests that ~800 million people are undernourished, out of which 780 million reside in low-to-middle income countries, especially in Sub-Saharan Africa and South Asia[50]. TB leads to the loss of weight, while being underweight is considered a risk factor for developing TB, whether through reactivation of latent TB or developing progressive primary disease upon infection[51]. Thus, it is considered that TB and nutrition have a bidirectional relationship. Under-nutrition is also associated with poor therapy outcomes in TB patients. A log-linear association between Body Mass Index (BMI) and TB incidence was previous described, across a wide range of settings with various levels of TB burden. Thus, it is estimated that, the TB risk increases with approximately 14% for each unit reduction in BMI. Moreover, undernourished patients have been shown to have poor bioavailability of essential drugs like rifampin, which can contribute to treatment failure and the development of MDR[52]. Poverty elimination is the best way to fight this challenge. A study published in Lancet Global Health has revealed that poverty reduction efforts effectively reduce TB with medicines and vaccines. It also concluded that, with the reduction in poverty and expanding social protection coverage, an 84.3% drop in the incidence of TB could be achieved by 2035[53].

Cost-effectiveness of Latent TB

Budgetary constraints are a vital consideration that has affected diagnostic assay and treatment plans in developing countries. The TST is a standard method commonly used for diagnosing LTBI, has a low cost. However, because of to false-positive results in individuals vaccinated with Bacillus Calmette-Guerin (BCG) or infected with *Nontuberculous Mycobacteria* (NTM), it is limited by low specificity[54]. Thus, new diagnostic strategies have been developed as tests for LTBI, such as the IGRA. However, expensive requirements for laboratory infrastructure, equipment, and supplies to perform

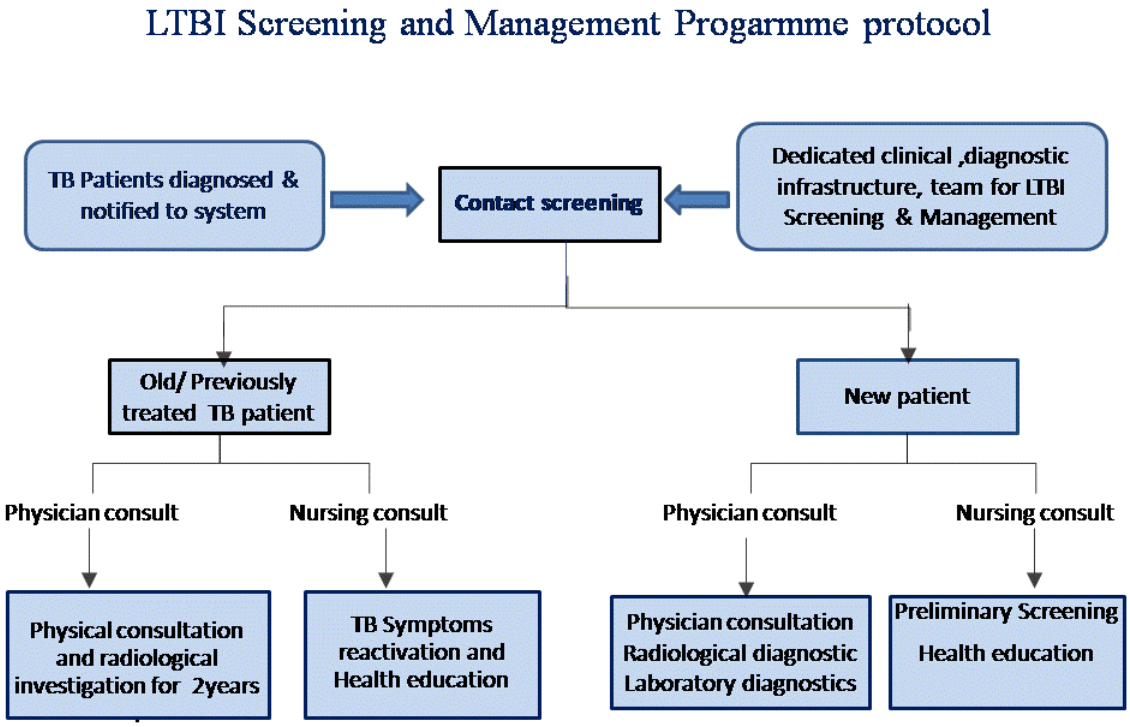

Figure 3: LTBI Screening and management programme protocol (adapted from reference[59])

this test make it difficult for low-resource high-burden countries[55]. A cost-effective analysis conducted in a high-burden country, comparing strategies for LTBI diagnosis in primary health care workers. It was concluded that the most cost-effective approach was the tuberculin skin test, while "the isolated use of the Quantiferon®-TB Gold In-Tube revealed the strategy of lower efficiency with incremental cost-effectiveness ratio (ICER) of US$ 146.05 for each HCW correctly classified by the test"[56]. Moreover, in the low- and middle-income countries where the global tuberculosis burden is concentrated, six months of isoniazid (6H) have long been the only preventive treatment regimen available. Policymakers and stakeholders hesitate to adopt the shortened regiments, due to high cost. For example, the 2020 Global Drug Facility (GDF) price for one course of a 12-dose weekly isoniazid and rifapentine regimen (3HP) is 5-15 times the price for one course of 6H[57]. In the base-case analysis, rifampin is the winner of all other regimens, except isoniazid plus rifapentine, which was more effective at $48,997 per quality-adjusted life-year gained. Combined treatment of isoniazid and rifapentine "dominated all regimens at a relative risk of disease 5.2 times the baseline estimate, with completion rates less than 34% for isoniazid or 37% for rifampin. Rifampin could be 17% less efficacious than self-administered isoniazid and still be more cost-saving" than this regimen to overcome the costly treatment. There is a need for cost-effective analysis using parameters from different resource settings to allow better planning for the LTBI management at the national or local level[1,2].

6. Lessons to be learned from successful nations[58]

Brazil has started surveillance on LTBI in 2018 and is scaling up the online system. People living with HIV, clinical risk groups, and all household contacts have been advised for LTBI screening and treatment since 2011. For screening, TST and X-ray have been recommended with fourth months' treatment of isoniazid and rifampin. LTBI guidelines for contact

investigation and Surveillance guidelines for health care workers have helped in the effective rollout and implementation of the program. Still, a decentralized health care system and TB not being a notifiable disease is a challenge for this program implementation. People living with HIV, child contacts aged under five years, health care workers are screened for LTBI in Kenya. Isoniazid therapy for six months, rifapentine plus isoniazid for 12 weekly doses, rifampicin plus isoniazid for three months daily doses, isoniazid 36+ months for adults and adolescents were considered treatment options for people living with HIV in high incidence settings are. LTBI screening slowed down due to fears of drug resistance, stock-outs, and instances of hepatotoxicity during the rapid response initiatives.

7. Latent TB treatment adherence strategies

Adherence to the complete course and completion of treatment determines the program's success and are important determinants of clinical benefit to patients[59]. A shorter regimen with fewer adverse effects, personalized approach with social intervention, education, counseling is key to the success of completion of LTBI treatment. Effective and innovative education strategies along with incentives possibly might help in treatment adherence. These strategies need to address misconceptions about LTBI, population-specific targeted messages, convenient drug treatment, and quality follow-up. Regular clinical monitoring of individuals receiving treatment for latent TB through a monthly visit to the healthcare provider would help in patients with adverse effects. Determining and planning regular follow-up consultations for LTBI treatment, medication supply, and blood tests will ensure patients adhere to the treatment. This article tries to formulate an LTBI program in high burden countries, as shown in Figure 3.

8. Conclusion

Screening and treatment of LTBI is a crucial primordial preventive intervention for TB eradication. Major challenges in screening and LTBI treatment in developing nations are comprised by the inconsistent LTBI guidelines, poverty, malnutrition, co-morbidities and out-of-pocket costs. Countries shall define LTBI contact screening protocol and work on training, capacity building of health care staff. Hence, policymakers should consider an effective, integrated, multidisciplinary program addressing LTBI for TB eradication. Futuristic dedicated policies with augmented research and innovation strategies would be necessary to establish a successful LTBI program.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

NH, MRS, AS collected the data, performed the background literature review for the manuscript, drafted and revised the manuscript. NH, MRS, AS, KA, NNN, NP, MKP contributed equally to this work. NH, MRS, MKP supervised the project. All authors significantly contributed to the design and/or writing and approved the final version of the manuscript.

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