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REVIEW

The paradigm shift in the approach to management of latent tuberculosis infection in high tuberculosis burden countries

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ABSTRACT

Introduction: Addressing the reservoir of Latent Tuberculosis Infection (LTBI) is critical to TB elimination because if left untreated LTBI can progress to active TB disease. This additional burden can prevent achieving the global targets of TB elimination. Management of LTBI has been a low priority target for National TB Elimination Programs (NTEP) due to various challenges in the field settings.

Areas covered: This article reviews the most recent advances in the field of LTBI management including newer diagnostics, treatments, vaccines, programmatic challenges, and gaps and suggests a way forward that can be adopted by NTEPs for LTBI. We searched the electronic databases of PubMed, Scopus, and Web of Science for studies published between 2010 to 2020 using MeSH terms: Latent TB Diagnosis, TB preventive therapy, Vaccines, LTBI, and HIV/ COVID.

Expert opinion: NTEPs of developing countries should offer a better, point-of-care diagnostic, and effective treatment for LTBI to reduce the number of new TB cases arising from people infected with M. tb. Awareness about LTBI should be increased among the health system staff and the public. More funding is needed to advance research as well as implement the newer findings in the NTEP to achieve the End TB targets by 2035.

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Latent TB infection; preventive therapy; shorter regimen; drug resistant TB; diagnosis of LTBI; vaccine

1. Introduction

World Health Organization (WHO) estimated that in 2018, globally 10.0 million people fell ill with tuberculosis (TB) with an estimated 1.5 million deaths due to TB. The burden of disease varied enormously among countries, the average being 130 new cases per 100,000 population [1]. Infection with *Mycobacterium tuberculosis (M.tb)* is the precursor to TB disease. After initial exposure, *M.tb* may be eliminated by the host immune response or persist as a latent infection called Latent TB Infection (LTBI) or progress to primary active disease [2].

LTBI is a state of a persistent immune response to stimulation by *M.tb* antigens with no evidence of clinically manifest TB disease. Following the establishment of LTBI with viable *M.tb*, progression to active TB disease depends on several factors, the most important being weakened immunological status as in HIV infection or immunosuppressive therapies. Studies have found that about 75% of people who develop the active disease after coming into contact with someone with TB do so within one year of TB diagnosis of the index patient, and 97% develop TB within two years and rarely beyond 2 years [3,4]. Though the risk of progression is highest within the first 2-years of acquiring the infection, 5–10% of persons with LTBI can progress to active disease during their lifetime [5]. It was estimated that globally in 2014, approx. one-fourth of the global population were latently infected with *M.tb*.

Addressing this LTBI reservoir is critical to TB elimination because if left untreated the current LTBI can progress to active TB disease and this LTBI burden is likely to prevent achieving the global targets for TB elimination. The target of TB elimination can only be achieved with effective treatment of active TB combined with treatment of LTBI that can progress to active TB.

2. Recent advances

The United Nations High-Level Meeting on Tuberculosis in 2018 endorsed a political declaration committing to provide 30 million individuals with TB preventive therapy (TPT) to protect them from the development of TB disease [6]. Achievement of this target requires a massive expansion of TPT services through health system strengthening and mobilization of resources. In this context, we have compiled the many recent advances that have taken place heading toward a paradigm shift in the management of LTBI.

2.1. Pathways of TB progression

One of the new paradigms in LTBI is the demonstration of a dynamic continuum of *M.tb* infection in the TB spectrum. Instead of only LTBI and active TB, now 2 additional clinical states, called incipient and subclinical TB have been proposed [7]. Although the spectra of TB infection and disease remain continuous, it is suggested that categorizing them into discrete states between latent and active TB provides an

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Article highlights

- Good point-of-care diagnostic test with high specificity is essential to scale up TPT to all high-risk groups of the population. Tests that differentiate the TB spectrum and better predict future TB risk are needed.
- Treatment of LTBI is only one component of the TB prevention effort. Airborne infection control practices at health care facilities and congregate settings, cough etiquette, etc require more attention to reduce TB transmission.
- Development and widespread use of a safe and effective TB prevention vaccine, either POD or POI, will pave way for remarkable transformation in the field of TB prevention.
- Preventive treatment can be individualized and targeted to high-risk contacts in case of contacts of MDR TB patients.
- Social factors like over-crowding and indoor air pollution, Co-morbid conditions like malnutrition, and diabetes mellitus besides immunodeficient conditions. A complete package for LTBI strategy needs to be developed with community engagement for demand generation, patient literacy, and address factors like stigma and awareness for implementing a successful plan for ending TB in the country.

opportunity to understand the disease dynamics better and may help in therapeutic intervention to prevent progression to active TB disease. However, given the limitations with the available diagnostic tools, such categorization may not currently change the clinical practice directed toward the management of individual patients. For example, persons with subclinical TB are usually asymptomatic and they may not be able to produce quality sputum. Hence novel assays may be necessary to use on non-sputum-based specimens like detecting *M.tb* proteins and metabolites in urine. Similarly in incipient TB infection, because of low bacillary load, a high-sensitivity test like peripheral blood host RNA-based signatures or cytokine levels may be required to measure the host immune response as opposed to direct pathogen detection. Also, we do not have enough evidence to show the benefit of TPT on the clinical outcome of subclinical TB.

2.2. Global burden of LTBI

As a drive toward eliminating TB, an estimate of the global burden of LTBI was recently updated using available data and modeling techniques. It has been estimated that under a quarter of the global population (approximately 1.7 billion) individuals are infected with LTBI against the earlier figure of one-third of the global population [8]. The highest prevalence was in the South East Asia region (31%). China and India show the highest-burden at the country level with the proportion of infected cases increasing with increasing age, a trend seen in many other countries also. For the first time, this estimate showed that about 1% of the global populations were recently infected within the last 2-years and around 11% of these recent infections were due to isoniazid-resistant strain of *M. tb* [7].

No direct data for the prevalence of latent MDR-TB are available, because infecting *M.tb* strains cannot be isolated nor tested for resistance. Hence, a mathematical model, using cohorts followed over time and historical annual risk of infection data, which estimated that globally 19 · 1 million people were latently infected with MDR-TB in 2014 – a global prevalence of 0 · 3% (95% UI 0 · 2–0 · 3). MDR strains accounted for 1 · 2% (95% UI 1 · 0–1 · 4) of the total latent TB burden overall, with double the burden in children younger than 15 years [9]. This has public health importance as isoniazid monotherapy may not be effective in these individuals. However, clinical data or evidence to confirm the results of this modeling exercise is lacking. More research is required to ascertain the outcome of 6–9 months of IPT in contacts of H-resistant TB.

2.3. Target population

Not all individuals infected with *M. tb* progress to active TB disease. It is imperative to identify the at-risk populations or the target populations for systematic testing and TB preventive treatment (TPT). The target populations will benefit from TPT when there is a high prevalence of TB infection or a high incidence of TB disease compared to the general population, indicating a high TB transmission setting. However, the benefits of TPT should outweigh the potential risk of acquiring TB or drug toxicity.

The risk of progression of LTBI to active TB is particularly increased in children and immunocompromised individuals [10]. LTBI screening tests should be offered to all HIV-infected individuals including HIV-infected infants (< 12 months of age and in contact with a person with TB) and HIV-infected children (≥ 12 months of age). If the screening tests are positive, they should be offered treatment for LTBI. Pregnant and postpartum women living with HIV should also be offered treatment for LTBI with some caution in pregnancy as a higher frequency of stillbirths and abortions have been reported with the use of isoniazid preventive therapy in pregnancy [11,12]. In cases of an anergic test or doubtful result of screening tests, LTBI treatment should be discussed with the individual and assist them in making an informed decision. Though there is not much evidence, WHO currently recommends that all children living with HIV after completion of TB treatment may receive TPT [13]. This is to reduce the risk of reinfection in children living in TB endemic settings after completion of **antituberculosis treatment** (ATT). However, there are reports of no additional benefit of isoniazid preventive therapy in reducing TB incidence in children on antiretroviral therapy (ART) [14]. Also, when a child is diagnosed with TB and started on treatment, all the household contacts of the child must be screened for TB (bottom-up approach), as there may be an adult with undiagnosed TB transmitting the disease. There is also evidence that older children with pulmonary sputum positive TB may transmit the disease as adults. Hence screening the household contacts of a child with TB is appropriate.

Another paradigm shift in the target population for TPT is in the household contact (HHC) of people with bacteriologically confirmed pulmonary TB. Earlier there was a strong recommendation for TPT for pediatric household contacts aged < 5 years and age regardless of HIV status after ruling out active TB. A meta-analysis on the risk of children after close exposure to TB showed that children not receiving preventive therapy with a positive result for TB infection had significantly higher 2-year cumulative TB incidence than children with a negative result for TB infection, and this incidence

was greatest among children below 5 years of age (19 · 0% [95% CI 8 · 4–37 · 4]). The effectiveness of preventive therapy was 63% (adjusted HR 0 · 37 [95% CI 0 · 30–0 · 47]) among all exposed children and 91% (adjusted HR 0 · 09 [0 · 05–0 · 15]) among those with a positive result for TB infection [15]. Another systematic review focusing on HHC in countries with high TB burden showed that all HHC, regardless of their age or LTBI status, are at higher risk for progression to active TB than the general population (RR: 24.7, 95% CI 24.7 (14.2–43.0)) [16]. Based on this, the current WHO guideline has been updated which recommends TPT for children > 5 years, adolescents, and even adults HHCs of bacteriologically confirmed PTB patients after ruling out active TB [13]. Compared to young child contacts, preventing TB in adolescents and adults is likely to have a far greater effect on community transmission.

Also, other risk groups that have been identified who will benefit from testing and treatment of LTBI with TPT include those on dialysis, initiating anti-TNF treatment, organ transplant, silicosis, prisoners, health workers, immigrants, homeless people, and drug users [13]. Systematic testing and treatment are not recommended for people with diabetes, alcoholics, smokers, and malnourished individuals due to a lack of evidence of the benefit of TPT. One should also remember that TPT may not always outweigh the harm. In a programmatic approach, LTBI treatment can be offered to all high-risk individuals, regardless of an immune response to TB antigens, however, the scientific approach should be to recommend testing and treatment based on the results.

2.3.1. Special situation

(a) *Infants on Breastfeeding*: Infants who are being breastfed have a high risk of infection from mothers with smear-positive pulmonary TB and of developing TB. Infants should receive six months of TPT, followed by BCG immunization. Breastfeeding may be safely continued during this period [17].

(b) *Close contacts of MDR-TB patients*: Another newer addition to the target population of TPT are the HHC of MDR-TB patients. Earlier where only observation was offered to the HHC of drug-resistant TB patients, few studies have shown a significant reduction in the risk of development of the disease (OR 0.02, 95% CI 0.00, 0.39) with tailored preventive treatment as compared to those who did not receive proper preventive treatment [18,19]. Studies are still underway and result from them may help us address the uncertainties around TPT for contacts of MDR-TB patients. Till we have more evidence, children who are close contacts of MDR-TB patients should receive careful clinical follow-up for at least two years. If the active disease develops, prompt initiation of treatment with a regimen designed to

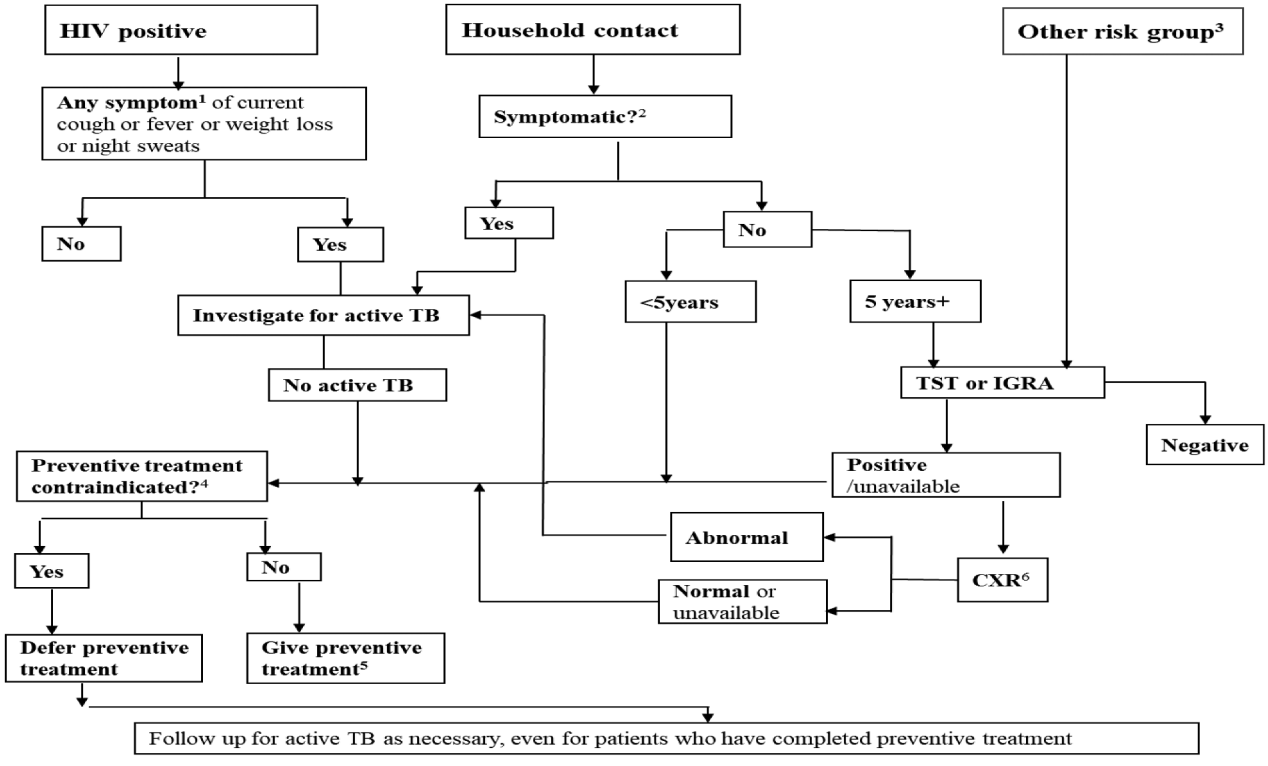

Figure 1. Algorithm for LTBI testing and TB preventive treatment in individuals at risk.

a. If < 10 years, any one of current cough or fever or history of contact with TB or reported weight loss or confirmed weight loss > 5% since last visit or growth curve flattening or weight for age <-2 Z-scores. Asymptomatic infants < 1 year with HIV are only treated for LTBI if they are household contacts of TB. TST or IGRA may identify PLHIV who will benefit most from preventive treatment. Chest radiography (CXR) may be used in PLHIV on ART, before starting LTBI treatment.

b. Any one of cough or fever or night sweats or hemoptysis or weight loss or chest pain or shortness of breath or fatigue. In children < 5 years, they should also be free of anorexia, failure to thrive, not eating well, decreased activity or playfulness to be considered asymptomatic.

c. Including silicosis, dialysis, anti-TNF agent treatment, preparation for transplantation or other risks in national guidelines. People in this category should also have TB disease ruled out if they have suggestive clinical manifestations.

d. Including acute or chronic hepatitis; peripheral neuropathy (if isoniazid is used); regular and heavy alcohol consumption. Pregnancy or a previous history of TB are not contraindications.

e. Regimen chosen based on considerations of age, strain (drug susceptible or otherwise), risk of toxicity, availability and preferences.

f. Chest radiography may have been carried out earlier or as part of intensified case finding.

treat MDR-TB is recommended. For contacts of patients with extensively drug-resistant TB, there is no specific guidance and currently, only close observation and follow-up are suggested [20]. A meta-analysis of 25 studies evaluating the household contacts of drug-resistant TB found 7.8% of active TB cases and 47.2% of LTBI [21]. In almost all of the studies that reported DST and genotyping, the majority of secondary cases had DST and/or genotyping results concordant with that of the source case [21]. This high yield of LTBI and active TB cases among the household contacts of drug-resistant TB cases warrants contact investigations for DR-TB patients also.

2.3.1.1. Algorithm to rule out TB disease before TPT. TB disease must be ruled out using available tools before initiating TPT in any group of individuals. Offering TPT to someone who has TB disease can delay the resolution of the disease and favor the emergence of drug resistance. At the same time. TPT with two effective drugs like isoniazid and rifampicin, if taken effectively, can result in the resolution of incipient TB. Various known and validated tools available to rule out TB include the following and the algorithm is also explained in Figure 1.

2.3.2. Screening for TB symptoms and signs

Absence of symptoms can be used to rule out TB disease. The standard 4-symptoms to rule out any form of TB includes current cough, fever, weight loss, and night sweats. Using a standard set of signs and symptoms to screen for TB disease has been shown to have a high sensitivity and a high negative predictive value, meaning that it can reliably rule out TB if none of the clinical manifestations are present (presence of even only one of the symptom/sign has a low specificity for TB disease and could be due to other conditions). Secondly, it is a simple and easy intervention and can be repeated as often as necessary without special equipment. The sensitivity and negative predictive value of this symptom screen in various groups are shown in Table 1. Additional tests such as chest radiography can be combined with a symptom screen to improve its accuracy. A recent meta-analysis of 18 studies showed that the pooled sensitivity of the four-symptom screening was lower for people on ART (51 · 0%, 95% CI 28 · 4–73 · 2) as compared to those not on ART (89 · 4%, 95% CI 83 · 0–93 · 5). Similarly, the pooled specificity for those on ART was 70 · 7% (95% CI 47 · 8–86 · 4) and those not on ART was 28 · 1% (95% CI 18 · 6–40 · 1). Adding any abnormal chest radiographic findings in people on ART improved the sensitivity to 84 · 6% (95% CI 69 · 7–92 · 9) but further decreased the specificity to 29 · 8% (95% CI 26 · 3–33 · 6) [22].

Table 1. Sensitivity & predictive value of symptom screen for various risk groups of LTBI.

Groups	Symptom screen	Sensitivity	NPV
PLHIV 10 years or above	Absence of current cough + fever + weight loss or night sweats	79%	97%
Infants and CLHIV	Absence of poor weight gain + fever + current cough + h/o contact with TB	90%	99%
HIV negative HHC aged 5 years or older & other high risk groups	Absence of cough of any duration + heamoptysis + fever + night sweats + (weight loss/chest pain/ shortness of breath/fatigue)	73%	99%

PLHIV – people living with HIV; CLHIV – Children living with HIV
HHC – Household Contact; LTBI – Latent TB infection
NPV – negative predictive value

2.3.3. Chest x-ray

A chest x-ray should be considered for TB screening where it is available. Chest radiography is known to have high sensitivity but low specificity for TB especially in children between 5–9 years of age with no symptoms of TB. In the absence of radiographic findings, TPT can be considered. Lack of access to chest x-ray should not be a reason to delay the initiation of TPT. Similarly, a chest x-ray can be offered to PLHIV on ART, but should not be made mandatory. Having said that, starting TPT without ruling out pulmonary TB in chest x-ray can be disastrous even leading to the emergence of drug resistance among other consequences. National TB Elimination programs should strengthen their TB prevention services so that all centers and individuals being offered TPT should have the minimum set of investigations to rule out TB before initiating TPT.

The combined use of chest radiography and TB symptom screening will increase the confidence of health providers as there is less chance of missing TB disease. WHO recommends that chest radiography may be considered in TB screening algorithms Figure 1 where it is available and should not be considered as a mandatory requirement and become a barrier to starting TPT [13].

2.3.4. Tuberculin skin test (TST)

has been widely used for detecting LTBI for almost a century now. The important advantages of the TST include its low cost and convenience. But it has several biologic and operational limitations including false-positive results due to prior Bacillus Calmette-Guerin (BCG) vaccination or non-tuberculous mycobacteria, false-negative results due to immunosuppression or malnutrition, or the type of purified protein derivative used for TST [23,24]. Also, the intradermal injection must be administered properly, the patient must return for the TST reading, and the measurement of the induration must be done correctly. However globally there is a limited supply of PPD as listed here. (PPD-S (JHP Pharmaceuticals USA), PPD RT23 2 TU (AJ vaccines Denmark), PPD RT23, 5 TU (Arkay Healthcare, Mumbai), PPD RT23, 5TU (Bulbio) Bulgaria, Tuberculin T* (Institute of Virology), Serbia, Tuberculin PPD-S (Tubersol) Sanofi Pasteur (Canada).

2.4. Newer tests to diagnose LTBI

Identifying persons with LTBI at the highest risk for progression of LTBI to active TB remains challenging. Tools for reliable identification of patients with LTBI are required for the rational use of TBT. There are no 'gold standard' tests for accurately diagnosing LTBI. Only three tests are currently available and approved by the WHO for the diagnosis of LTBI: the tuberculin skin test (TST), and the two interferon-gamma release assays (IGRAs) the QuantiFERON (Qiagen, Germany) and T-SPOT.TB (Oxford Immunotec, United Kingdom) tests [25].

2.4.1. Interferon-gamma release assays (IGRAs)

IGRA is a whole-blood test that can help in diagnosing *M.tb* infection. IGRA test measures the release of gamma interferon by white blood cells when the cells are exposed to specific TB antigens. *IGRA*s do not differentiate between LTBI and active disease and they should not be used as diagnostic tests for active TB. The IGRAs and their newer generation variants have some limitations in terms of interpretation since they are based on the immune response to *M.tb* and thus are only indirect tests of LTBI [26]. Does a positive IGRA mean persistent infection with *M.tb* for life or is this only immunological memory of a past infection? [27]. Also, IGRAs used on immunocompromised patients appear less sensitive and give false-negative and indeterminate results. We need more sensitive and specific LTBI tests that can distinguish between true infection and immunological memory.

2.4.2. Newer IGRAs

The *IGRA test LIOFeron TB*/LTBI was introduced in 2019 by Lionex GmbH (Braunschweig, Germany) and contains the alanine dehydrogenase (Ala-DH) of *M.tb*. This test differs from the QuantiFERON-TB Gold Plus test in that the first antigen tube (TB-A) contains full-length ESAT-6, CFP-10, and TB7.7, and the highly purified recombinant Ala-DH is included in the second antigen tube (TB-B). A recent study reported that the LIOFeron TB/LTBI assay may have higher sensitivity than the QuantiFERON-TB Gold Plus test [28]. Chemiluminescence immunoassays (CLIA) have also been studied in comparison to the QuantiFERON-TB Gold test [29].

2.4.3. C-Tb test

The C-Tb test, a novel skin test having an inoculating device for precise testing (Statens Serum Institute, Copenhagen, Denmark) that uses ESAT-6 and CFP-10 instead of purified protein derivative (PPD). The test aims to combine the operational advantages of the TST with the performance characteristics of IGRAs. This test performed better than the TST in BCG-vaccinated people, had a high concordance with the QuantiFERON-TB Gold In-Tube test, and positivity was correlated with the exposure risk [30]. C-Tb was found to be safe in people living with HIV and children less than 5 years of age, giving a positivity rate similar to the QuantiFERON test.

2.4.4. Blood biomarkers

Whole blood biomarkers that can better predict the risk of TB progression are being studied using RNA sequencing of blood from cohorts; these studies identify gene signatures for the risk of progression to active TB [31–34]. Investigators have tried to identify the characteristic biomarker signature associated with treatment failure and pulmonary inflammatory states [35–37]. *M.tb*-specific CD4 + T-cell activation markers in blood may discriminate pulmonary and extrapulmonary TB from LTBI [38].

2.4.5. Whole-genome sequencing (WGS)

WGS of bone marrow specimens from LTBI patients may show the presence of *M.tb* with rpo-gene mutations in stem cell CD34 populations. This is still in research mode and its utility in high burden countries or its translational value is still not very clear.

Despite these advances, no diagnostic tests are currently available that can accurately detect LTBI, distinguish subclinical or early clinical disease from LTBI, and identify LTBI due to drug-resistant strains of M.tb. The prevalence of LTBI due to MDR-*M.tb* strains continues to increase in high MDR-TB countries, while progress in the development of diagnostic tests to detect these individuals has not been forthcoming, raising concerns about who and when to treat in light of the risk of treating subclinical or early TB disease [39]. Thus, there is an urgent need for a point-of-care, easy to use, affordable diagnostic tests for LTBI.

2.5. TB preventive therapy regimens

An ideal TPT should be short, effective, nontoxic, easily deliverable in the community, and avoid drug-resistance in those with undetected early disease. Courtney Yuen and colleagues, using a decision tree model predicted that a 'Treat-all' approach in household contacts will lead to 13 fewer incident TB cases compared to an approach whereby only contacts with positive TST were treated [40]. But in countries with a high incidence of TB, reactivation of LTBI may account for a higher incidence of new TB cases rather than the household contacts breaking down with incident TB. Whatever the scenario may be, one potential benefit of TPT is on further transmission by reducing incident TB in contacts. Several regimens are recommended for treating LTBI that includes drugs like isoniazid (INH), rifampicin (RMP), rifapentine. Drugs like fluoroquinolones have also been suggested for treating LTBI.

Longer regimens include 6-month or 9-months of isoniazid monotherapy (IPT), with 6-month therapy being more cost-effective with better compliance. In high TB and HIV prevalence settings, continuous use of IPT in PLHIV for 36 months or longer seems to be beneficial and outweighs the risk of increased adverse effects as compared to 6-months IPT [41]. It has been suggested that in high TB burden countries, a longer duration of INH therapy not only continues to treat any existing LTBI but also prevents the acquisition of new *M.tb* infection [42].

Short course regimens include – 3 months of once-weekly INH plus Rifapentine; 4 months of daily RMP; 1 month and 3 months of daily INH plus RMP. A range of TPT options includes rifamycin-based regimens for high-risk groups where the benefit outweighs the risk.

a. Rifampicin Monotherapy: A multi-country clinical trial demonstrated that the 4-month regimen of RMP was not inferior to the 9-month regimen of INH for treating LTBI and also had a higher rate of treatment completion and lesser adverse events [43,44].

b. INH plus Rifampicin: A network meta-analysis showed that 3 months of INH and RMP was an effective regimen along with 3 months of RMP or 4 months of RMP regimens [45]. Based on this result, many guidelines like WHO, NICE, etc. have recommended 3INH and RMP as a standard regimen. In children, the use of 3–4 months of INH with RMP is dependent on the availability of dispersible pediatric fixed-dose formulations.

c. INH plus Rifapentine (3HP): Studies have shown that 3HP is non-inferior to 9 INH in preventing active TB in nearly 3-years of follow-up; has a higher treatment completion rate, a lower rate of clinically relevant hepatotoxicity than 9INH regimen, and is more cost-effective when given by direct observation [46–48]. Thus weekly use of 3HP seems to be a safe alternative to the daily use of 9 months of INH for LTBI treatment. A 1-month regimen of rifapentine plus isoniazid (1HP) has also been shown to be non-inferior to 9-months of INH alone for preventing TB in HIV-infected individuals, with a significantly higher percentage of participants completing a 1-month of treatment [49].

d. Other regimens: Earlier regimen with 2 month RMP with Pyrazinamide was recommended for treatment of LTBI in HIV infected individuals, but with caution owing to its high rate of serious hepatotoxicity, especially more in non-HIV people.

2.5.1. Special situation

(a) TPT for People living with HIV: Evidence shows that TPT reduces TB incidence and also mortality in PLHIV up to 37% independent of ART and is a cost-effective intervention even using shorter regimens [50]. After thorough screening to rule out active TB at every consultation with a health care worker, TPT has to be started for PLHIV. The most commonly used TPT contains classically one drug, INH, administered for six to nine months and can be co-administered with any ART regimen. The new TPT regimens are safe and effective and can be used with current ART with monitoring for drug-drug interactions. The 3HP regimen has been shown to be safe and effective in PLHIV and can be co-administered with dolutegravir without dose adjustment [51]. As far as co-administration of TPT with ART is concerned more evidence is required for the administration of rifamycins-based TPT in PLHIV on tenofovir-based ART or for the use of 1HP with dolutegravir. Recent evidence favors the use of 600 mg of efavirenz in patients using rifampicin, given similar efficacy and safety when compared to a higher dosage of efavirenz of 800 mg [52].

(b) Treatment for MDR-TB Contacts: Quality of evidence to support the treatment of contacts of the MDR-TB patient remains low. Close clinical and radiological follow-up should be considered. The decision to treat MDR-TB contacts must be based on individual risk assessment for each patient and drug susceptibility profile of suspected source organisms. Few regimens are under evaluation for the effectiveness of LTBI treatment for contacts of DR-TB patients Table 2. Fluoroquinolone based regimens with or without ethionamide or ethambutol for 6–12 months has been suggested [19,53]. A meta-analysis revealed that treating LTBI in MDR-TB contacts lead to reduced incidence of active TB, thus preventing progression to MDR-TB [54]. Confirmation of LTBI is required in the HHC and individualized preventive treatment can be offered to high-risk contacts like HIV infected and children.

(c) TPT after Solid Organ transplantation: Reactivation of latent infection due to opportunistic pathogens such as *M.tb* is common after solid organ transplants, leading to significant morbidity and mortality. The ideal approach is to treat LTBI before transplant. INH with vitamin B6 supplementation is the treatment of choice [55]. Rifampicin containing regimen may be used only in the pre-transplant period given drug-drug interaction later. Data concerning the use of Fluoroquinolones for LTBI treatment are scarce but have been shown to exhibit a lower risk of drug-induced liver injury than INH when used in liver transplant recipients [56–58]. Unacceptably high incidences of tenosynovitis were reported in liver transplant recipients receiving fluoroquinolones preventive therapy [57]. It seems reasonable to consider therapy with isoniazid only in patients with compensated cirrhosis or good liver allograft function and in whom hepatotoxicity can be closely monitored and fluoroquinolones can be suggested as an alternative for LTBI treatment. More studies are necessary to determine the patient profile and the real efficacy of fluoroquinolones in preventing LTBI in solid organ transplant recipients.

2.5.2. Adverse events with TPT

It is imperative to monitor for adverse reactions during the treatment of LTBI. The risk of significant adverse events, namely grade 3 to grade 5, during LTBI treatment was reported to be approximately 1 in 30 in a multi-country trial comparing four-month of rifampicin to 9-months of isoniazid [59].

a. Isoniazid: Major adverse event of INH is hepatotoxicity, which may range from asymptomatic liver enzyme raise to severe liver toxicity and increases with older age, preexisting liver disease, regular alcohol consumption, pregnancy, and puerperium. Another potential adverse reaction with INH is

Table 2. Trials to evaluate the effectiveness of LTBI treatment in HHC of MDR-TB patients.

Name	Regimen	Site	Population	Outcome
V-QUIN trial (Double-blind placebo-controlled parallel group RCT)	Levofloxacin Vs Placebo	10 provinces of Vietnam	Contacts of Patients with MDR-TB	Incidence of bacteriologically confirmed TB within 30 months after randomization
TB-CHAMP (Double-blind placebo-controlled parallel group RCT)	Levofloxacin Vs Placebo	Four clinical sites in South Africa	Children aged five and under who live with adults who with MDR-TB	Reduce their risk of developing TB compared to treatment with a placebo
PHOENIX Trial (Ranodomized parallel arm trial)	Delamanid Vs Isoniazid	Multicountry	High-risk HHCs of adults with MDR-TB	Confirmed or probable active TB at end of 24 months

HHC – Household Contact; LTBI – Latent TB infection
MDR-TB – multi-drug resistant tuberculosis
RCT – randomized clinical trial

peripheral neuropathy aggravated in the background of malnutrition, alcoholism, and other comorbid conditions like diabetes mellitus and HIV. Serious adverse events could be minimized by following close monitoring and good counseling or if necessary then using a non-isoniazid containing the TPT regimen in adult contacts.

b. Rifamycin containing regimen may cause many adverse reactions like cutaneous reactions, hepatotoxicity, gastrointestinal intolerance, pancytopenia, etc. Also one should watch out for drug-drug interactions with other drugs like oral contraceptive pills, anti-epileptic drugs, anti-diabetic drugs, etc [60].

Evidence point that in comparison with the INH monotherapy, the adverse event profile of the 3HP regimen generally appears favorable with an overall low frequency of adverse events and a higher completion rate [45]. Flu-like reactions were reported with an increased frequency while hepatotoxicity was reported at a lower frequency than standard treatment [61].

c. Fluoroquinolones: FQ is less hepatotoxic and is suggested as a good alternative for LTBI treatment. The toxicity profile with FQ ranges from musculoskeletal including joint pains and tendinopathy, gastrointestinal (vomiting, diarrhea), fatigue, malaise, and hepatotoxicity. The rate of permanent withdrawal of the FQ due to side effects ranges from 6% to 33% of all treated patients [57]. Drug-induced fulminant hepatitis has been reported in a child for LTBI with pyrazinamide and levofloxacin, after contact with an adult with multidrug-resistant TB [62].

2.5.3. Cost-effectiveness of TPT

Testing for and treating LTBI among individuals with and without selected comorbidities are cost-effective in low TB-burden countries [63]. However, in countries with a large population of migrants, weak care cascade, and longer regimens, the effectiveness of treating LTBI is limited [64]. Cost-effectiveness strongly depends on the prevalence of LTBI, the price of the drug or regimen, and the completion of treatment. 3HP has been shown as a cost-effective alternative to IPT in high burden countries but this depends largely on the price of Rifapentine, willingness to pay, and a completion rate of >85% [65]. In endemic countries, IPT for HIV-infected pregnant women also seems to be highly cost-effective for TB prevention, irrespective of CD4 stratification, or TST usage [66]. Recent mathematical modeling has shown that in high-incidence settings, post-treatment follow-up and secondary IPT can accelerate declines in TB incidence and also be cost-effective by potentially saving resources of TB control [67].

A systematic review estimated a 90% reduction in the incidence of MDR-TB with the treatment of MDR-LTBI, suggesting effectiveness in the prevention of progression to MDR-TB. Cost-effectiveness was greatest using a fluoroquinolone/ethambutol combination regimen [68]. Similarly, a decision analysis model demonstrated that fluoroquinolone preventive therapy resulted in substantial health system savings, reduced mortality, the incidence of drug-resistant TB, and improved quality of life than no treatment [69].

2.6. TPT in high TB burden countries

Countries with high TB prevalence will also have a high burden of LTBI given the transmission dynamics. Unfortunately, many of the TB high-burden countries remain resource-constrained, and hence early diagnosis and treatment of active TB remain their main priority. The high cost of newer diagnostics, high level of isoniazid resistance, and lack of newer drugs make the implementation of TPT more challenging in these countries [70]. Focus on air-borne infection control, targeted screening, and TPT to high-risk individuals may be an alternative approach in high-burden settings. A recently conducted survey, using country-level information, to understand the challenges faced by TB high burden countries in implementing newer LTBI tests and TPT revealed several factors as barriers to implementing TPT guidelines. Many of them prioritized the identification and control of active TB over LTBI management. Non-availability or shortage of diagnostics methods, high cost, and labor-intensive newer diagnostic techniques, non-availability of newer drugs or regimens for TPT were identified as common problems to implementing TPT in high burden countries [71]. Another systematic review on child contact management in high TB burden countries identified additional challenges to TB preventive therapy like knowledge gap among index cases as well as health care workers on the need for contact screening, the stigma associated with the revelation of TB diagnosis of the index case while screening of contacts, competing priorities of the family over TB preventive therapy, besides the above-mentioned barriers in the contact management cascade [72].

2.7. Newer research

Numbers of research studies are ongoing in the field of TPT both with drugs and vaccines. Recently, a multicountry study conducted to evaluate the efficacy of a new TB vaccine M72/AS01E to prevent active pulmonary TB disease showed vaccine efficacy of 49.7% (95% CI, 2.1 to 74.2) at 36 months of follow-up. Vaccination with M72/AS01$_E$ elicited the immune response and protected against progression to pulmonary TB disease for at least 3 years [73]. There are many other vaccines and drug candidates in the pipeline that are being tried for TB prevention. We have compiled below a list of all clinical trials registered at clinicaltrials.gov that are either recruiting or yet to begin recruitment as of 10 September 2020.

2.7.1. Ongoing drug trials

a. Multicenter, randomized, open-label, phase III clinical trial comparing a 4-week daily INH/RPT regimen (1HP) to a 12-weekly INH/RPT (3HP) for the treatment of LTBI in HIV-infected participants without evidence of active TB (NCT03785106)

b. Multicenter randomized control trial comparing the risk of Systemic Drug Reactions under conventional 3HP regimen (Arm 1: 3HP), and a new regimen of 1HP consisting of daily rifapentine (10 mg/kg) plus isoniazid (5 mg/kg) for 1 month (Arm 2: 1HP).

c. Open-label, non-randomized clinical trial to evaluate the efficacy and safety of the 1RPT/INH to prevent TB compared with those who do not receive preventive treatment among silicosis patients (NCT03900858)

d. Multicentric, randomized, parallel-arm trial to evaluate the efficacy and safety of 26 weeks of delamanid (DLM) versus 26 weeks of INH for preventing confirmed or probable active TB among high-risk household contact of adults with MDR-TB (NCT03568383)

e. Evaluate the relationship between vitamin D status and active MDR-TB disease among adult outpatient pulmonary MDR-TB cases, household contact controls, and matched controls from the general population (non-household controls) (NCT04342598)

2.7.2. Ongoing vaccine trials

a. Phase III, double-blind, multicenter, randomized, single administration, active-controlled, parallel-group design of VPM1002 versus BCG SII (1:1 allocation) to assess the efficacy, safety, and immunogenicity of VPM1002 against Mtb infection (NCT04351685)

b. Phase III, double-blind, multi-center, randomized, active-Controlled Study to Investigate the Efficacy and Safety of 'GC3107(BCG Vaccine)' after Intradermal Administration in Healthy Infants (NCT03947138)

c. Multicenter Phase II/III Double-Blind, Randomized, Placebo-Controlled Study To Evaluate The Efficacy And Safety Of VPM1002 In The Prevention Of TB Recurrence In Pulmonary TB Patients After Successful TB Treatment (NCT03152903)

d. Phase IIb, Randomized, Placebo-Controlled, Observer-Blind, Phase IIb Study to Evaluate the Efficacy, Safety, and Immunogenicity of BCG Revaccination in Healthy Adolescents for the Prevention of Sustained Infection With Mycobacterium Tuberculosis (NCT04152161).

e. Phase IIa, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Safety and Explore the Immunogenicity and Efficacy of ID93+ GLA-SE Vaccine in BCG-Vaccinated Healthy Healthcare Workers (NCT03806686).

f. Multi-center, prospective, randomized, placebo-controlled, participant, and laboratory-blinded clinical trial to evaluate a single pre-travel vaccination with investigational freeze-dried glutamate BCG (Japan) to prevent Mycobacterium tuberculosis complex (*Mtb*) infection in healthy adult travelers (NCT04453293).

g. Phase Ib Clinical Trial Evaluating the Safety and Immunogenicity of Freeze-dried Recombinant Tuberculosis Vaccine (AEC/BC02) in Healthy Adults (NCT04239313).

h. Phase 1, open-label study to evaluate the safety and immunogenicity of a single administration of one of two doses of a recombinant replication-deficient human adenoviral (Ad5) TB vaccine containing the immunodominant antigen Ag85A delivered to the respiratory tract by aerosol in healthy volunteers with a history of BCG immunization. (NCT02337270).

i. Phase 1, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Safety and Explore the Immunogenicity of ID93+ GLA-SE Vaccine in BCG-Vaccinated Healthy Adolescent (NCT03806699).

j. Phase I, open-label, clinical trial of the Therapeutic TB H56: IC31 Vaccine and Cyclooxygenase-inhibitors in MDR-TB (NCT02503839).

k. Phase I Clinical Trial to Compare the Safety and Immunogenicity of Candidate TB Vaccine ChAdOx1 85A Administered by the Aerosol Inhaled Route and the Intramuscular Route in Healthy Adult Subjects (NCT04121494).

Another large multicenter randomized trial is being conducted by the Indian Council of Medical Research to evaluate the safety and efficacy of two potential vaccine candidates – VPM 1002 and *Mycobacterium Indicus Pranii* (MIP) – to prevent the occurrence of TB among healthy household contacts of sputum smear-positive TB patients.

2.8. Programmatic challenges

2.8.1. Challenges in screening for LTBI

Optimizing the various screening approachesand making them accessible and available to participants to effectively and efficiently rule out active TB is one of the biggest challenges to implementing TPT. A positive test diagnostic of LTBI identifies people most likely to benefit from TPT [11]. There are many logistical challenges for scaling up the implementation of diagnostic tests in high burden settings. Tests needed to confirm LTBI may not be feasible in resource-limited settings due to the non-availability of a good test with high sensitivity & specificity and trained staff, hence deciding when to start TPT is a big challenge. In the absence of a good test to 'rule in' LTBI, WHO suggests the combination of the absence of any chest x-ray abnormality and absence of TB related symptoms to have the highest sensitivity and negative predictive value for 'ruling out' TB [74].

2.8.2. Challenges in treating LTBI

Implementation of TPT, though improved in many countries, still has not reached the desired levels to achieve TB elimination targets. Various challenges have been identified both for initiation and completion of TPT, a few of which are identified –

(a) Drug stock out or Access-related issues: In resource constraint TB endemic settings, all the focus is more on TB treatment than TB prevention. Fear of drug stock-outs, especially at the peripheral centers has been identified as the major cause for not initiating IPT [75]. To overcome this, the program managers should estimate the required quantity of TPT much ahead of stock-out and not only procure them on time but distribute it to all peripheral centers. They have to ensure the supply chain management is robust to prevent frequent drug stock-outs.

(b)Lack of Training/awareness among health care workers: Lack of awareness about the need for TPT in asymptomatic individuals resulted in not many PLHIVs being initiated on TPT. Similarly, lack of risk perception of adverse events by

individuals related to TPT can lead to reducing adherence as well as dropouts of participants from TPT due to adverse events.

(c)Provider reluctance to prescribe LTBI treatment mainly due to

i. Fear of development of drug resistance with monotherapy

ii. Doubts about the benefits of LTBI treatment

iii. Fear of adverse events

iv. inability to convince asymptomatic patients to take treatment

(d) Model of Care: Identify the best model of care that can deliver high coverage, high uptake or initiation, and high completion of TPT. Compared to the number of individuals eligible for LTBI treatment, those who start and complete the treatment is small [76]. Completion rates of longer TPT like IPT under programmatic settings are likely to be lower than under research or study conditions [77]. Routine screening of LTBI and a positive TST/IGRA may unnecessarily create anxiety and prejudice against an individual resulting in stigmatization as they may later develop TB.

(e) TPT options for communities with high isoniazid or fluoroquinolones resistant TB: Lack of regimens for contacts of patients with isoniazid, rifampicin, or fluoroquinolones resistant TB patients. As the testing for the drug susceptibility pattern of the above drugs are being increasingly used in the treatment of TB, the National programs must design TPT for such contacts.

The above issues can be overcome by training and increasing awareness of the community as well as health care workers. Securing a stable medication supply to effectively deliver this intervention is also very crucial for TB elimination.

2.8.3. Recording and reporting

Many countries especially the high-burden TB countries do not have a system of recording and reporting diagnosis or treatment of LTBI in various risk groups. Recording and reporting of TPT for LTBI has to improve from high-burden countries both for people living with HIV and non-HIV high-risk LTBI groups.

2.9. TB services and COVID-19 pandemic

Considering the global prevalence of TB, it is likely that patients with TB may get exposed to COVID-19, the new epidemic now spreading across countries worldwide. As both the conditions affect the lungs and have almost similar symptoms, COVID-19 may unmask TB especially when they approach the hospital for superimposed COVID-19 infection. This may help in the timely diagnosis of TB if the health system can also investigate them for active TB at the time they come for COVID testing [78,79]. National TB elimination programs have to actively engage in ensuring an effective and rapid response to COVID-19 while ensuring that TB services are maintained. Measures must be put in place to limit transmission of TB and COVID-19 in congregate settings and health care facilities, as per WHO guidelines. Accurate diagnostic tests are essential for both TB and COVID-19 in these settings. As there are a lot of common grounds between the two conditions, efforts to curb these diseases can also be combined. Chest x-ray and Cartridge based nucleic acid testing have been suggested for diagnosing COVID-19 which are also being used to diagnose TB in many regions. Hence while investigating a patient with symptoms akin to COVID-19, they can also be investigated for TB. Contact tracing for COVID-19 can help in tracking the TB close contacts and household contacts thus sharing the workload of health care workers. The preventive measures required for TB are very similar to what is required for COVID-19. Counseling on cough etiquette and wearing masks to prevent air-borne transmission for COVID-19 will play a significant role in TB transmission too, and we hope will have a positive effect on LTBI too.

Having said this, one also has to remember that the COVID-19 pandemic has severely affected the routine TB services secondary to the diversion of health care workers to COVID-19 activities. Implementation of country-wide lockdowns and strict quarantine measures have delayed TB diagnosis, initiation of treatment, and follow-up investigations. Having to stay indoors in close quarters with the infected patient has also increased the risk of TB transmission among household contacts. Contact tracing and initiation of TPT have also been severely disrupted by this restricted movement. Diversion of healthcare workers including TB workers to tackle COVID-19 emergencies has further delayed these contact tracing. Many TB patients have lost livelihood in-turn affecting their socio-economic conditions and their buying capacity especially nutritious diet. Achievements toward TB elimination by 2035 have suffered a major set-back.

Post COVID-19 pandemic, National TB Elimination Programmes (NTEP) have to be strengthened and have to function to their fullest capacity to hasten the battle against TB and to compensate for the time lost during this pandemic. Countries also have to revisit their TB Elimination targets and timelines in the post-COVID era. Health system strengthening has to be revisited as responding to threats like COVID-19 in the future should not be at the expense of services to other diseases. Optimal and country-specific methods have to be planned by the policymakers and technical partners to enhance coverage of TPT services – like making available better diagnostics, newer and shorter regimens of TPT, specific training tools, etc. Adequate priority has to be given to TPT in existing national HIV and TB programs. Advocacy, social mobilization, and better engagement with TB affected community for scale-up of TPT services should be considered.

3. Conclusion

Prevention of TB is a key component of a comprehensive TB elimination strategy. Although the management of active TB is the foremost priority for all TB Control programs, TB elimination requires one step more – Identification and Treatment of LTBI.

Diagnostic tests for LTBI are most effective when targeted at individuals at high risk for LTBI. Besides focusing on people living with HIV, national TB programs should also focus on

household contacts and high-risk groups for initiation and follow-up of treatment for LTBI. Treatment of LTBI must balance the risk of adverse drug reactions and the benefits of preventing progression to active TB. The shorter regimen is likely to be more effective given the increased uptake and better adherence. While treating with shorter, newer regimens one should also watch for adverse reactions. An effective vaccine to prevent pulmonary TB will make a major contribution to the End TB strategy goal of reducing TB morbidity and mortality.

New tools alone are not sufficient. Advances must be made in identifying patient characteristics who will progress to active TB from LTBI, greater engagement with the community to ensure better adherence, early identification of adverse reactions and avoid the unnecessary stigma attached with the diagnosis of TB infection thus providing high-quality, people-centered care for LTBI. Reducing the cost of TPT should be one of the priorities of the National programs for successful scaling up of TPT. The possibility of diversion of human and budgetary resources from treatment to prevention of active TB should be taken into consideration. Renewed political will, coupled with improved access to quality care can reduce the morbidity, mortality, and stigma long associated with TB.

4. Expert opinion

To get the National TB Elimination programs ready for scaling up of TPT in a country, certain changes are inevitable.

(i) Views of the program managers and policymakers toward LTBI must change drastically. It is essential to understand that treating LTBI is as important as treating TB disease if one reaches the global SDG goal of ending TB by the year 2030 and the goal for India in 2025.

(ii) Country-specific operation plans with adequate resources have to be specifically earmarked for LTBI and TPT activities especially in high TB burden countries.

(iii) Target populations who will benefit most from TPT should be identified and diagnostic tests with high sensitivity and specificity should be made easily available to the target population to diagnose LTBI once an active case of TB is diagnosed. We may have more easy, feasible, and less cumbersome point-of-care diagnostic tests for LTBI. Molecular diagnostic tests may be used to identify the resistance pattern of LTBI. The use of RNA biosignatures to identify groups at the highest risk of progression from latent infection to active TB may become the focus of research.

(iv) Availability of Ultra-short course and safe TPT regimens to all high-risk individuals. Plan the requirement of the country along with buffer stock, much ahead of time to avoid drug stock-outs.

(v) Optimizing TPT adherence: TB elimination program should support patients to achieve optimal adherence. Various strategies like directly observed therapy, regular patient review for adverse events, mobile phone-based contact, MERM or pill-boxes, etc can be used to monitor drug compliance. Expansion of operational research in countries, with high-risk populations, will bring to light new models of TPT delivery – single or multiple rounds of ultra-short regimens.

(vi) Appropriately manage adverse events secondary to TPT. Training of health care workers and increasing awareness about early signs of toxicity among the key population should be an ongoing process. Programs should facilitate the management of toxicity from TPT at the same center where the individuals receive TPT. Staff should be trained to identify and manage AE early and properly.

(vii) Recording and reporting of LTBI and TPT need to improve both at national and international levels.

WHO needs to update the guidelines as and when evidence becomes available for better strategies for scaling up of TPT in both high- and low-TB burden countries to contribute to elimination goals.

In the next five years, most of the trials on preventive therapy will be completed and with results becoming available, countries can plan for up-scaling TPT. Country guidelines are expected to change with respect to the diagnosis and treatment of LTBI. This will require the countries to plan much ahead in terms of logistics and supply chain management, training and tool kits, advocacy, and community engagement. Many countries require the generation of in-country data to get regulatory approval to implement newer drugs and regimens in their NTEP. Such countries should start planning clinical or operational research to generate in-country data also focusing on health economics, field effectiveness, and implementation plan, etc. However, such restrictions may further delay the adoption of effective regimens in clinical practice. Program managers may face many challenges like inadequate data, training, resources, community involvement for TPT implementation. These can be overcome with proper planning and collaboration with other technical partners, both governmental and non-governmental. To reach the End TB Strategy targets by 2030 should be the ultimate goal. So all research and implementation concerning TPT services should work toward attaining this target in collaboration with all technical partners, program managers, policymakers, and the community.

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Declaration of interest

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