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Review

Diagnosis and management of latent tuberculosis infection in Asia: Review of current status and challenges

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ABSTRACT

Asia has the highest burden of tuberculosis (TB) and latent TB infection (LTBI) in the world. Optimizing the diagnosis and treatment of LTBI is one of the key strategies for achieving the WHO 'End TB' targets. We report the discussions from the **A**sia **L**atent **T**ub**ER**culosis (ALTER) expert panel meeting held in 2018 in Singapore. In this meeting, a group of 13 TB experts from Bangladesh, Cambodia, Hong Kong, India, Indonesia, Malaysia, Myanmar, the Philippines, Singapore, Taiwan, Thailand and Vietnam convened to review the literature, discuss the barriers and propose strategies to improve the management of LTBI in Asia. Strategies for the optimization of risk group prioritization, diagnosis, treatment, and research of LTBI are reported. The perspectives presented herein, may help national programs and professional societies of the respective countries enhance the adoption of the WHO guidelines, scale-up the implementation of national guidelines based on the regional needs, and provide optimal guidance to clinicians for the programmatic management of LTBI.

Contents

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Introduction

According to the 2018 World Health Organization (WHO) global tuberculosis (TB) report, about 10 million new cases of TB were recorded worldwide in 2017. In this report, TB was ranked as the tenth leading cause of all-cause mortality and the leading cause of death due to a single infectious agent. In 2017, approximately 300,000 and 1,270,000 TB-associated deaths were reported among HIV-positive and HIV-negative individuals, respectively. Asia is one of the highest TB-burden regions in the world. Out of the top eight high TB-burden countries, accounting for about two-thirds of the global TB cases in 2017, six countries were from Asia. Furthermore, the WHO Southeast Asian region presented the second highest incidence of TB (226 per 100,000 population) and the second highest TB-associated mortality rate (1.4 and 32 per 100,000 population HIV-positive and -negative TB deaths, respectively) in 2017 (WHO, 2018a).

The WHO 'End TB strategy' aims to reduce TB deaths by 95% and lower the incidence of new TB cases by 90% between 2015 and 2035 (WHO, 2015). Although efforts to curb the TB burden have resulted in a decline in the disease burden both globally and in Asia, progress to date has been slow and efforts need to be accelerated if the WHO targets are to be achieved (WHO, 2018a). Especially, in the high TB-burden countries in Asia, it is not only crucial to improve the diagnosis and treatment of active TB, but also to prevent the development of active TB. Various approaches could be effective, such as optimizing active contact-tracing, integrating TB and HIV control programs, addressing the key gaps in latent TB infection (LTBI) diagnosis and treatment, and improving the scale-up of LTBI treatment (Houben and Dodd, 2016; Kyu et al., 2018; WHO, 2018a, 2018b).

Overview of LTBI

Latent TB infection is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB (Getahun et al., 2015; WHO, 2018b). While about 30% of the world's population is estimated to be infected with *M. tuberculosis*, only 10% of the infected individuals develop clinically active TB disease and 90% remain in the latent phase. This constitutes a large reservoir of individuals with LTBI (WHO, 2018b).

A substantial proportion of the global LTBI reservoir is located in Asia, with the highest LTBI prevalence rate of about 31% found in Southeast Asia, and 28% in the Western Pacific region, compared to 11%–22% in the other regions of the world (Houben and Dodd, 2016). Therefore, optimizing the diagnosis and management of LTBI in Asia will be essential for achieving the WHO 'End TB' targets. It has been estimated that if we were to treat just 14% of individuals with LTBI per year, this would reduce the TB incidence from 1280 cases per million recorded in 2010 to 20 cases per million by 2050, without any additional intervention (Dye et al., 2013). Achieving $\geq$90% LTBI treatment coverage by 2025 is therefore one of the key milestones set up by WHO (WHO, 2015).

Despite the high LTBI burden and proposed targets, treatment of LTBI is currently suboptimal in Asia (WHO, 2018a), with wide regional variation in the implementation of the key WHO LTBI guideline recommendations. According to WHO, the percentage of newly diagnosed HIV-positive individuals who received preventive LTBI treatment in 2017 in Cambodia, India, Indonesia, Myanmar, the Philippines, Singapore, and Vietnam was 21%, 10%, 16%, 17%, 57%, <1%, and 31%, respectively (WHO, 2018a, 2017). Although the LTBI treatment coverage for household contacts has been noted to be improving in Taiwan (97% directly observed preventive therapy rate in 2017) (CDC-Taiwan, 2018), and the percentage of household child contacts <5 years of age on LTBI treatment in 2017 in Singapore and Malaysia has been noted to be high (WHO, 2017), low LTBI treatment coverage in child contacts <5 years old has been reported in other Asian countries such as Bangladesh, Cambodia, India, Indonesia, Myanmar, the Philippines, Thailand and Vietnam (21%, 44%, 11%, 8.5%, 2.1%, 12%, 5%, and 26%, respectively) (WHO, 2018a).

The regional importance of Asia for achieving success in global LTBI treatment and the variability in implementation of WHO LTBI treatment guidelines motivated this expert consultation to understand the unmet needs and barriers to optimization of LTBI diagnosis and treatment in the region.

Methodology

A group of 13 TB experts from Bangladesh, Cambodia, Hong Kong, India, Indonesia, Malaysia, Myanmar, the Philippines, Singapore, Taiwan, Thailand and Vietnam (**A**sia **L**atent **T**ub**ER**culosis [ALTER] Expert panel) convened three times (in August, September and November 2018), with the following objectives: (1) to discuss the barriers to the scale up of LTBI diagnosis and treatment in Asia; (2) to discuss strategies to improve the LTBI management in Asia; and (3) to write an evidence-based review and expert opinion article on the diagnosis and treatment of LTBI in Asia.

This article is a combined summary of the literature evidence and the expert opinion offered by the panel regarding: (1) LTBI awareness; (2) reporting systems for LTBI; (3) prioritization of at-risk groups for LTBI; (4) unmet needs in LTBI diagnosis and management; (5) implementation of the WHO LTBI 2018 guidelines; and (6) plausible strategies for optimizing the risk-group prioritization, diagnosis, management and research of LTBI in Asia.

LTBI awareness in Asia

Experts from most countries cited a lack of awareness among healthcare workers of the WHO/national LTBI recommendations, and the importance of detecting and treating LTBI in relevant risk groups. Even in countries with improving awareness, clinicians were reported to be reluctant to implement LTBI treatment due to the fear of development of resistance or side-effects. Some participants cited examples of initiatives being undertaken in their regions for improving LTBI awareness; experts from Bangladesh, Indonesia, Taiwan, and Vietnam cited the existence of training programs for healthcare workers in their countries for enhancing the awareness on LTBI and its management in children, household contacts, PLHIV and certain high-risk groups. The expert from Bangladesh also opined that the increase in LTBI awareness among clinicians in Bangladesh was partly attributed to a high incidence of patients on hemodialysis and increased use of immunosuppressive therapy for connective tissue diseases. In line with these observations, the 2016 Global LTBI Consultation Meeting report has also highlighted the need for clearing the misconceptions and enhancing the awareness of LTBI management among healthcare workers, to help increase their involvement in optimizing the treatment of LTBI (WHO, 2016).

Reporting system for LTBI in Asia

Based on the expert panel views and published literature, well-designed reporting systems for LTBI treatment are currently in place only in Singapore and Taiwan (Chan et al., 2014; Chan, 2018; Chee and James, 2003). In Bangladesh, Cambodia and Indonesia, reporting of LTBI treatment is done only for PLHIV and child contacts below 5 years of age. In Vietnam, paper-based reporting of LTBI treatment is done in children, based on the instructions from the national tuberculosis program (NTP) and reporting of LTBI treatment in PLHIV cases is done under the HIV program. There are plans to initiate an electronic reporting system for LTBI treatment in the future in Vietnam. In India, although reporting of LTBI treatment is recommended for: (1) child contacts below 6 years of age; (2) HIV-infected child contacts; and (3) children on immunosuppressive therapies, considerable regional variation in reporting is noted, in part due to the lack of adequate infrastructure and resources. Of the total PLHIV on active care in India, only an estimated 3% are reported to be receiving LTBI treatment. In Myanmar, reporting of LTBI treatment occurs only as a part of HIV-reporting, where it is included in the reporting forms. In Hong Kong, Malaysia, the Philippines, and Thailand, there are currently no existing systems for reporting of LTBI cases although electronic reporting of LTBI cases is under consideration in Malaysia (for only patients with LTBI, who are close contacts of active TB cases), the Philippines and Thailand.

Because of the paucity of nationally standardized LTBI reporting, there is currently a lack of robust region-specific epidemiology data in most of the Asian countries. This unmet need was highlighted in the 2016 Global LTBI Consultation Meeting report (WHO, 2016). Furthermore, most of the national reporting systems have been noted to be designed for reporting active TB, and, therefore, may be inappropriate for recording LTBI cases (Jagger et al., 2018). Despite these challenges, some countries in Asia such as Japan and Taiwan have mandated programmatic reporting of LTBI cases through electronic surveillance systems (Chan, 2018; Kawatsu et al., 2017), thus serving as a potential model for adoption by other countries.

Prioritization of high-risk groups for LTBI testing and treatment in Asia

The 2018 WHO LTBI guidelines suggest selecting at-risk populations for programmatic management of LTBI based on the epidemiology and TB transmission patterns in the region, to ensure lasting protection with tuberculosis preventive therapy (WHO, 2018b). The status of adoption of the 2018 WHO LTBI guidelines into national guidelines by the participating Asian countries, regarding risk group prioritization for LTBI testing and/or treatment, is shown in Table 1. In Taiwan, most of the WHO-recommended risk groups have been incorporated into the national guidelines and are being prioritized for LTBI treatment. In countries such as Indonesia, Malaysia, the Philippines, and Vietnam, although most of the WHO recommended at-risk groups were included in the local guidelines, systematic national implementation of LTBI treatment was reported to be occurring only in few key at-risk groups. While Indonesia, the Philippines and Vietnam prioritized PLHIV and child contacts below 5 years of age, Malaysia prioritized patients receiving anti-tumor necrosis factor therapy, in addition to these two at-risk groups, for LTBI treatment. Other participants cited prioritization of LTBI risk groups based on their regional epidemiology and availability of resources, as described below.

Prioritization of specific at-risk groups

Diabetics

The 2018 WHO LTBI guidelines do not recommend systematic testing for LTBI in diabetics because of the lack of good-quality evidence (WHO, 2018b). However, the expert panel opined that diabetics may represent an important group at risk of progression from LTBI to active TB. Countries such as Myanmar and the Philippines have included diabetics as an at-risk group for LTBI testing and treatment in their national guidelines. Several 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 revealed that diabetes was associated with a significant risk for LTBI (Lee et al., 2017). Furthermore, poorly controlled diabetes has also been reported as an important risk factor (Martinez-Aguilar et al., 2015). Therefore, the ALTER panel considered that LTBI at-risk groups should be

routinely screened for diabetes and diabetes patients should be considered for preventive TB therapy, based on the epidemiology, TB transmission patterns, and effectiveness and availability of resources in the region. These views are also supported by recent literature (Barron et al., 2018; Koesoemadinata et al., 2017; Shivakumar et al., 2018).

Healthcare workers in high TB burden countries

In the 2018 WHO LTBI guidelines, a *conditional recommendation* has been provided for systematic testing and treatment of LTBI in healthcare workers in countries with low TB incidence (WHO, 2018b). However, the ALTER panel opined that healthcare workers may be considered as an important at-risk group for LTBI testing and treatment even in high TB-burden countries. Studies conducted in Asia and other meta-analyses have reported a high prevalence of LTBI among healthcare workers (Hung et al., 2015; Nasreen et al., 2016; Ratnawati et al., 2017; Uden et al., 2017). In a cohort study conducted by Benedicto et al. among healthcare workers (n = 337) in 10 tertiary hospitals in the Philippines for about two years, the prevalence of LTBI among healthcare workers was noted to be 84.87% (95% CI, 80.59%–88.52%) (Benedicto et al., 2012). Collectively, these data may suggest that healthcare workers represent an important at-risk group for LTBI testing and treatment.

Prisoners

The 2018 WHO guidelines recommend LTBI testing and treatment in prisoners in countries with low TB burden, with no

Table 1
Status of adoption of the 2018 WHO LTBI recommendations into the national guidelines by the participating Asian countries.

WHO LTBI recommendations (2018)	Adoption of WHO LTBI guidelines into the regional recommendations[q]											
	BD[s]	CAM	HK	IN	ID	MY	MM	PH	SG	TW	TH	VT
Identification of at-risk groups												
PLHIV for LTBI treatment based on symptomatic screening and/or LTBI testing	√	√	√	√[c]	√[f,g,h]	√	√	√[m,n]	√	√	√	√
HIV-negative household contacts for LTBI treatment based on appropriate clinical evaluation												
1. Children <5 years	√	√	√	√[d]	√[f,g,h]	√	√	√[m,n]	√	√	√	√
2. Children ≥5 years			√					√[m,n,o]	√	√	√	√
3. Adolescents and adults			√					√[m,n,o]	√	√		√
Other HIV-negative at-risk groups for systematic testing and treatment for LTBI												
1. Patients initiating anti-TNF therapy	√[a]		√	√[e]	√[g,h,i]	√		√[n,o]		√		√
2. Patients receiving dialysis	√[a]							√[n,o]		√		√
3. Patients preparing for an organ or haematological transplant	√[a]				√[g]	√		√[n,o]		√		√
4. Patients with silicosis	√[a]		√									√
5. Prisoners					√[g]	√	√			√	√	
6. Healthcare workers					√[g]	√	√			√	√	√
7. Immigrants from countries with a high TB burden						√						
8. Homeless people					√[g]	√				√		
9. People who use illicit drugs					√[g]	√				√		
10. Diabetics[r]							√	√[n,o]				
11. People with harmful alcohol use[r]					√[g]							
12. Tobacco smokers[r]					√[g]							
13. Underweight people[r]					√[g,h]							
Algorithms to rule out active TB												
PLHIV should be screened for TB according to a clinical algorithm.		√			√[f]					√	√	√
Preventive TB therapy should be offered to asymptomatic PLHIV, regardless of ART status.		√			√[f]					√	√	√
Chest radiography may be offered to PLHIV on ART, and preventive therapy given in case of no abnormal findings.		√[b]								√		√
PLHIV with symptoms of active TB should be evaluated for TB and other diseases that cause such symptoms.		√			√[f]					√	√	√
Infants and children living with HIV with poor weight gain, fever or current cough, or history of contact with active TB case should be evaluated for TB and other diseases that cause such symptoms. If active TB is not detected, preventive therapy should be provided, regardless of age.		√			√[f]					√		√
The absence of any TB symptoms or abnormal chest radiographic findings may be used to rule out active TB among HIV-negative household contacts aged ≥5 years and other at-risk groups before preventive treatment.		√								√		√
Testing for LTBI												
Either TST or IGRA can be used for LTBI testing.			√		√[g,h,j,k]	√			√	√[p]	√	√
LTBI testing by TST or IGRA is not a requirement for initiating preventive treatment in PLHIV or child household contacts aged <5 years	√	√		√	√[f]	√	√	√[m,n]			√	√
Treatment options for LTBI												
IPT for 6 months is recommended for treatment of LTBI in both adults and children.	√	√	√	√	√[f]	√	√		√	√	√	

Table 1 (*Continued*)

WHO LTBI recommendations (2018)	Adoption of WHO LTBI guidelines into the regional recommendations[q]											
	BD[s]	CAM	HK	IN	ID	MY	MM	PH	SG	TW	TH	VT
								√[m,n]				
Rifampicin plus isoniazid daily for 3 months should be off ;ered as an alternative to 6 months of IPT as preventive treatment for children and adolescents aged <15 years.			√		√[g,h]	√				√	√	
Rifapentine and isoniazid weekly for 3 months may be off ;ered as an alternative to 6 months of IPT as preventive treatment for both adults and children.			√		√[g,h]	√				√	√	√
PLHIV (adults and adolescents) with unknown or a positive TST and unlikely to have active TB disease should receive 36 months of IPT, regardless of ART, degree of immunosuppression, history of previous TB, or pregnancy.												
Preventive treatment for contacts of patients with MDR-TB												
In selected high-risk household contacts of patients with MDR-TB, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification.			√		√[l]	√				√		

BD: Bangladesh; CAM: Cambodia; HK: Hong Kong; IN: India; ID: Indonesia; MY: Malaysia; MM: Myanmar; PH: Philippines; SG: Singapore; TW: Taiwan; TH: Thailand; VT: Vietnam.
WHO: World Health Organization; LTBI: Latent tuberculosis infection; PLHIV: People living with HIV; HIV: Human immunodeficiency virus; TST: Tuberculin skin test; IGRA: Interferon Gamma Release Assay; TB: Tuberculosis; ART: Antiretroviral therapy; IPT: Isoniazid preventive therapy; MDR-TB: Multi-drug resistant tuberculosis; NTP: National Tuberculosis Program.
[a] LTBI testing and treatment is limited to only specific clinical settings.
[b] Chest radiography is offered in case of suspicion before LTBI treatment.
[c] Only HIV-infected children.
[d] Children <6 years, and children born to a mother who was diagnosed with TB during pregnancy.
[e] TST-positive children receiving immunosuppressive therapy.
[f] According to the Indonesia NTP.
[g] According to the Indonesian Society of Respirology guidelines (2016).
[h] According to the Indonesian Paediatric Society guidelines.
[i] Including children on long-term immunosuppressants.
[j] Only TST as per Indonesia NTP.
[k] IGRA, TST and contact tracing are mentioned in g and h.
[l] Prophylaxis with levofloxacin and ethambutol for 6 months in HIV-positive children and children under 5 years of age.
[m] According to the Philippines NTP.
[n] According to Philippines Clinical Practice guidelines (2016).
[o] tested and treated for LTBI.
[p] TST is used in individuals less than 5 years old and IGRA is used in individuals aged above 5 years.
[q] Based on the national TB/LTBI guidelines; relevant professional pulmonary, pediatric, or respiratory society guidelines; national TB programs; national annual TB reports; and/or expert opinion.
[r] Systematic testing and treatment for LTBI is not recommended by WHO in these individuals.
[s] National LTBI guidelines are not available in Bangladesh; recommendations are based on expert opinion.

mention of any recommendations for prisoners in countries with high or intermediate TB burden (WHO, 2018b). A review of the literature reveals a high prevalence of LTBI in prisoners in countries with high and intermediate TB burden (Al-Darraji et al., 2014; Martinez-Aguilar et al., 2015; Navarro et al., 2016). Considering their regional epidemiology and the available evidence, the ALTER panel opined that prisoners may also be an important at-risk group for LTBI testing and treatment.

Others

The other at-risk groups evaluated by the expert panel included–(1) individuals with low body mass index and chronic kidney disease, and (2) immunocompetent workers who have moved from a high TB burden region to a low TB burden region (representing a high risk group in the host region). However, due to lack of quality evidence, no recommendation was made by the ALTER panel regarding LTBI testing and treatment in these at-risk groups.

Diagnosis of LTBI in Asia

The 2018 WHO guidelines for LTBI testing, and the status of their adoption in the national guidelines of various participant countries, are detailed in Table 1 (WHO, 2018b).

Unmet needs in the diagnosis of LTBI in Asia

Regional unmet needs

Unavailability of Tests

The expert panel opined that accessibility of tuberculin skin test (TST)/interferon-gamma release assay (IGRA) was not an issue for treating PLHIV and child contacts <5 years of age for LTBI, as the new WHO guidelines recommend that LTBI treatment may be initiated without prior LTBI testing in these at-risk groups (Table 1) (WHO, 2018b). However, unavailability of TST/IGRA was cited as an unmet need for the other WHO recommended at-risk groups. Among the participating nations, Cambodia, India and Myanmar reported that only TST was available for LTBI testing. In India, the use of TST is restricted only to HIV-infected children, and children born to HIV-positive mothers, due to availability constraints. Both TST and IGRA were reported to be available for LTBI testing in Bangladesh, Hong Kong, Indonesia, Malaysia, the Philippines, Singapore, Taiwan, and Thailand. However, in Bangladesh, Indonesia, Malaysia, and the Philippines, because of cost constraints, only TST is being used in the public sector; IGRA is used in Bangladesh, Indonesia, and the Philippines in some private settings only, and pilot use of IGRA to screen close contacts of TB patients has been initiated only in Kelantan state in Malaysia from 2019. In Vietnam, neither TST nor IGRA is being used currently for LTBI

testing; TST is used only in some national projects such as Zero TB Vietnam, and IGRA is used for research purposes. Considering the cost and logistic constraints, currently, in high TB-burden and resource-limited settings, the use of TST may be a preferred method for LTBI testing when compared to IGRA (Sharma et al., 2017).

Lack of scale-up of LTBI testing

Testing for LTBI in most of the WHO-specified at-risk groups is currently being followed only in Singapore and Taiwan. Prioritization of at-risk groups for LTBI testing in the other countries was found to differ based on the local epidemiology and availability of resources (Table 1).

Lack of scale-up of LTBI testing in community settings

The testing for LTBI was noted to be mainly in hospital settings in most participating Asian countries, except for Hong Kong, Malaysia, Singapore and Taiwan, where LTBI testing is also being conducted in community settings. In Vietnam, testing in community settings is done only in Zero TB cities.

Limitations of current diagnostic tests

The expert panel identified a number of local challenges with TST, including: (1) shortage of reagents, (2) need for a second visit resulting in drop-outs, and (3) low specificity for detecting those at risk of progression to active disease. The challenges with IGRA included: (1) high cost, (2) limited availability, (3) timing of the test, (4) technical complexity, (5) lack of adequate infrastructure and resources, (6) indeterminate results, and (7) lack of specificity. Furthermore, the inability to differentiate between LTBI and active TB, and the reduced sensitivity in immunocompromised patients, were also cited as some of the major drawbacks of the current LTBI tests by the expert panel. Most of the aforementioned unmet needs in the diagnosis of LTBI have been highlighted in the 2016 Global LTBI Consultation Meeting report (WHO, 2016) and other published literature (Fox et al., 2017; Trajman et al., 2013). Therefore, the panel emphasized the importance of research to develop better point-of-care diagnostic tests and novel biomarkers able to predict the progression from LTBI to active TB.

Management of LTBI in Asia

WHO recommendations on LTBI treatment

The 2018 WHO LTBI guidelines recommend isoniazid monotherapy for 6 months for LTBI treatment in both adults and children (WHO, 2018b). However, adherence to isoniazid therapy has been noted to be low in most Asian countries (Huang et al., 2016; Rutherford et al., 2012). Hence, two new short-duration regimens have been proposed by the 2018 WHO LTBI guidelines, as an alternative to 6 months isoniazid monotherapy, for scaling up LTBI treatment in countries with high TB burden including: (1) rifampicin plus isoniazid daily for 3 months in children and adolescents aged <15 years (3RH regimen), and (2) rifapentine plus isoniazid weekly for 3 months (3HP regimen) in adults and children (Table 1) (WHO, 2018b).

Clinical efficacy and safety of shorter-duration LTBI regimens (3RH and 3HP)

Clinical studies have proven the efficacy and safety of the 3–4RH regimen versus isoniazid monotherapy for the treatment of LTBI (Spyridis et al., 2007). The 3HP regimen has also been clinically proven to be as effective as isoniazid monotherapy, but with significantly higher treatment completion rates, better safety with lower risk of hepatotoxicity, and higher cost-effectiveness, in global and Asian clinical studies, systematic reviews and meta-analyses, and routine healthcare settings, and is recommended for LTBI treatment in both high and low TB burden countries (Bliven-Sizemore et al., 2015; Chen et al., 2018; Doan et al., 2019; Hamada et al., 2018; Huang et al., 2016; Njie et al., 2018; Sterling et al., 2011; Sun et al., 2018; Wang et al., 2018; Sandul et al., 2017; WHO, 2018b). Currently, there is no evidence comparing the efficacy and safety of 3RH versus 3HP regimens for the treatment of LTBI.

Regional unmet needs in the treatment of LTBI

Several unmet needs hinder the optimal management of LTBI in Asia. Some of the unmet needs identified by the expert panel included the following:

Reluctance of clinicians to prescribe LTBI treatment

The expert panel unanimously agreed that one of the major barriers for scaling up LTBI treatment in most of the Asian countries is the reluctance of the clinicians to prescribe treatment for LTBI due to fear of resistance, side effects, or drug-drug interactions. Indeed, clinicians are notably concerned about inducing resistance by administering isoniazid monotherapy to an undiagnosed active TB case.

Management of HIV-negative household contacts

Achieving treatment for all HIV-negative household contacts, as per the updated 2018 WHO LTBI guidelines (WHO, 2018b), was cited as a major challenge by most of the participants, due to the lack of adequate resources and the high cost of tests. Poor implementation of LTBI treatment in close contacts of patients with TB has also been noted in previous expert meetings (WHO, 2016).

Limited access to drugs

An important barrier to optimization of LTBI treatment in Asia is the limited access to drugs (Fox et al., 2017; WHO, 2016). Shortages of stocks of isoniazid therapy were cited by most participants. The shorter-duration, 3HP regimen is approved for LTBI treatment in the following Asian countries: Hong Kong, Indonesia, the Philippines, Taiwan, and Thailand. However, this regimen is currently available and is being used only in Hong Kong and Taiwan. In Vietnam, the 3HP regimen is available only via the NTP; the NTP of Vietnam is planning to initiate a pilot program for implementation of this regimen in 8 provinces of the country, based on the availability. In Malaysia, the use of the 3HP regimen is limited to research settings.

Other unmet needs

The other unmet needs identified by the expert panel included: (1) lack of data on toxicity of drugs in Asians; (2) lack of adequate data on drug-drug interactions between LTBI regimens and antiretroviral therapies (ARTs) or anti-hypertensive drugs; (3) lack of co-formulated pills, with the high pill burden of existing regimens, contributing to the lack of adherence to LTBI treatment; (4) lack of local guidance on LTBI treatment; and (5) ineffective systems to link homeless people and people living in TB hotspots to existing healthcare facilities. In addition, studies have highlighted other unmet needs such as: (1) poor implementation of LTBI treatment for child contacts (WHO, 2016); (2) reluctance of individuals with LTBI to undergo a prolonged course of treatment for an asymptomatic condition (Blumberg and Ernst, 2016; Fox et al.,

2017); and (3) poor treatment completion rates (Blumberg and Ernst, 2016).

Regional perspectives on the implementation of the 2018 WHO LTBI guidelines

The 2018 WHO LTBI guideline recommendations along with the status of their adoption into the national guidelines of the respective participating countries are summarized in Table 1. The adoption of the updated WHO recommendations into the national guidelines and implementation of these recommendations was noted to be variable among the participant Asian countries because of one or more of the following reasons: (1) shortage of adequate infrastructure, diagnostic tools, drug regimens, lack of awareness, and limited number of well-trained healthcare providers; (2) high cost of the LTBI testing methods; (3) variable degree of political commitment and effective government stewardship; (4) lack of adequate national LTBI guidelines that can adapt the WHO 2018 guidelines in a pragmatic manner; and (5) lack of WHO recommendations specific to intermediate-burden settings, such as Hong Kong.

Strategies to optimize the diagnosis, risk group prioritization, treatment, and research of LTBI in Asia

Several strategies were proposed by the ALTER panel for scaling up the risk group prioritization, diagnosis, management, and research of LTBI in Asia (Table 2). Some of the *general* strategies suggested by the expert panel for optimization of LTBI management included: (1) enhancing the involvement of national professional societies for the development of clear local policies for screening, testing, and treatment of LTBI; (2) developing programs to enhance the awareness of LTBI and comorbidities associated with LTBI, among clinicians and patients; (3) providing training to healthcare workers for optimizing the management of LTBI; (4) promoting center of excellence programs, or development of LTBI expert teams; (5) standardizing the cascade of LTBI diagnosis and treatment, and linking it to TB case diagnosis and active TB treatment; and (6) prompting the international community and regional governments for support and mobilization of adequate budget and resources for LTBI testing and treatment.

Table 2
Strategies to optimize the risk-group prioritization, diagnosis, management, and research of LTBI in Asia, and the applicability of these strategies to public and/or private settings.

Category	Optimization strategies	Public settings	Private settings
Risk group prioritization (Scaling-up the prioritization of the following at-risk groups for LTBI testing and treatment–)	All PLHIV and HIV-negative household contacts aged <5 years, who are contacts of individuals with active TB, and who are not found to have active TB	√	√
	Diabetic patients with ongoing risk of exposure to active TB cases	√	√
	Healthcare workers	√	√
	Other HIV-negative at-risk groups (patients initiating anti-TNF therapy, patients on dialysis, patients preparing for an organ/haematological transplant, patients with silicosis, prisoners)		√
Diagnosis	Integrating HIV and childcare programs with LTBI testing	√	√
	Reduction in cost of tests, and inclusion of LTBI testing under national insurance program	√	
	Increasing the breadth of the tests to be able to detect active TB		√
	Promoting active case finding and contact tracing through national programs	√	
	Enhancing the involvement of private sector, and improving public–private partnerships for scaling up LTBI testing	√	√
Treatment	Enhancing the availability of drugs through the national insurance program	√	
	Encouraging public-private partnerships to enhance LTBI treatment	√	√
	Encouraging SAT with periodic monitoring	√	√
	Use of community DOTS, video DOTS, and web-based monitoring platforms to improve treatment adherence	√	√
	Experience sharing on the value of shorter-duration regimens		√
	Scaling up of the use of 3HP regimen to improve treatment completion rates	√	√
	Scale-up of treatment in high TB burden regions within countries with intermediate TB burden	√	√
Research (Encouraging research in the following areas–)	Novel point-of-care tests, such as dipstick IGRA	√	√
	Research to identify better tools and algorithms to be able to rule out active TB in prioritized risk groups	√	√
	Novel biomarkers such as blood RNA signature for differentiating individuals with LTBI at high risk of developing active TB		√
	Research on kinetics, drug–drug interactions, and safety of LTBI treatment regimens	√	√
	Studies to determine the rate of progression to active TB in vulnerable groups		√
	Studies to estimate the true burden of drop outs and to assess outcomes in individuals receiving LTBI therapy	√	√
	Research to elucidate the mechanism and incidence of drug resistance after LTBI treatment		√
	Research on reduction in dose/treatment duration of LTBI drug regimens	√	√
	Systematic meta-analyses to evaluate the best treatment options for LTBI according to comorbidities		√
	Studies on effectiveness and safety of LTBI treatment in children aged 2–12 years	√	√
	Research on the impact of LTBI testing and treatment in healthcare workers	√	
	Research on the cost-effectiveness of various LTBI treatment strategies	√	√

LTBI: Latent tuberculosis infection; HIV: Human immunodeficiency syndrome; PLHIV: People living with HIV; DNA: Deoxy ribonucleic acid; IGRA: Interferon-gamma release assay; DOT: directly observed therapy; SAT: self-administered therapy.

Regarding optimization of LTBI diagnosis, the expert panel emphasized on the need for research in the development of novel biomarkers that can differentiate individuals with LTBI at a high risk of progression to active TB. Recently, new biomarkers such as blood RNA signature and T-cell activation markers have been found to be sensitive and specific for differentiating individuals at a high risk of developing active TB (Petruccioli et al., 2016; Zak et al., 2016). For optimizing the management of LTBI, the panel highlighted the need for – (1) research on diagnostics, efficacy, safety and cost-effectiveness of LTBI regimens; (2) strategies to enhance the availability of and adherence to LTBI regimens; and (3) strategies to broaden the implementation of shorter duration LTBI regimens.

Summary

The effective implementation of 'End TB strategy' and achieving the WHO pre-defined LTBI targets for TB elimination in Asia may sound like 'a daunting task'. The current article provides an overarching view of the present situation of LTBI diagnosis and management, and highlights the regional unmet needs, along with the challenges in implementing the 2018 WHO LTBI guidelines in Asia. Prioritization of certain at-risk groups, in addition to those recommended by WHO, such as diabetics and healthcare workers, based on the regional epidemiology, TB transmission patterns and effectiveness and availability of resources, has been highlighted by the expert panel. Furthermore, several strategies are proposed for the optimization of diagnosis, risk group prioritization, and treatment and research in LTBI in Asia. An urgent need for commitment from national stakeholders and research in the field of LTBI has also been outlined through this paper. As treatment of LTBI is an important pre-requisite to achieving the TB elimination goals, the regional data and strategies elaborated in this paper may act as guidance for the development and improvement of national guidelines and regional strategies, thus paving way for the programmatic management of LTBI in Asia.

Author contributions

All authors have contributed equally in the preparation and reviewing of the manuscript.

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Ethical approval

It is not applicable.

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References

Al-Darraji HA, Tan C, Kamarulzaman A, Altice FL. Latent tuberculosis infection in a Malaysian prison: Implications for a comprehensive integrated control program in prisons. BMC Public Health 2014;14:22.

Barron MM, Shaw KM, Bullard KM, Ali MK, Magee MJ. Diabetes is associated with increased prevalence of latent tuberculosis infection: findings from the National Health and Nutrition Examination Survey, 2011-2012. Diabetes Res Clin Pract 2018;139:366–79.

Benedicto JP, Solante R, Benedicto MT. The incidence of active tuberculosis among health workers with latent tuberculosis infection in tertiary hospital settings. Phil J Chest Dis 2012;15(1):3–12.

Bliven-Sizemore EE, Sterling TR, Shang N, Benator D, Schwartzman K, Reves R, et al. Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of dailyisoniazid for LTBI. Int J Tuberc Lung Dis. 2015;19(9):1039–44.

Blumberg HM, Ernst JD. The challenge of latent TB infection. JAMA 2016;316(9):931–3.

Centers for Disease Control. Taiwan Centre for Disease Control annual report. 2018. . , [accessed 22 October 2018] https://www.cdc.gov.tw/uploads/files/201810/4c56b467-8b27-4540-acca-6fe90389a8a6.pdf.

Chan PC, Peng SSF, Chiou MY, Ling DL, Chang LY, Wang KF, et al. Risk for tuberculosis in child contacts: Development and validation of a predictive score. Am J Respir Crit Care Med 2014;189(2):203–13.

Chan PC. Experience from Taiwan: Political commitment for LTBI diagnosis and treatment. Invited talk of 6th annual TB experts community meeting: getting to zero by addressing latent TB in Asia 2018;.

Chee CBE, James L. The Singapore tuberculosis elimination programme: the first five years. Bull World Health Organ 2003;81:217–21.

Chen AJ, Tsai SH, Ko CF, Huang YW, Huang CL, Huang SH, et al. First screening and treatment campaign for latent tuberculosis infections in a mountainous township, Taiwan, 2016–2017. Taiwan EB 2018;34(6):35–6.

Doan TN, Fox GJ, Meehan MT, Scott N, Ragonnet R, Viney K, et al. Cost-effectiveness of 3 months of weekly rifapentine and isoniazid compared with other standard treatment regimens for latent tuberculosis infection: a decision analysis study. J Antimicrob Chemother 2019;74(1):218–27.

Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. Annu Rev Public Health 2013;34:271–86.

Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection—the promise and the challenges. Int J Infect Dis 2017;56:68–76.

Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent mycobacterium tuberculosis infection. N Engl J Med 2015;372:2127–35.

Hamada Y, Ford K, Schenkel K, Getahun H. Three-month weekly rifapentine plus isoniazid for tuberculosis preventive treatment: a systematic review. Int J Tuberc Lung Dis 2018;22(12):1422–8.

Houben RMGJ, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med 2016;13(10)e1002152.

Huang YW, Yang SF, Yeh YP, Tsao TCY, Tsao SM. Impact of 12-dose regimen for latent tuberculosis infection: Treatment completion rate and cost-effectiveness in Taiwan. Medicine (Baltimore) 2016;95(34)e4126.

Hung WT, Lee SSJ, Sy CL, Wu SK, Chen KJ, Tsai HC, et al. Prevalence of latent tuberculosis infection in BCG-vaccinated healthcare workers by using an interferon-gamma release assay and the tuberculin skin test in an intermediate tuberculosis burden country. J Microbiol Immunol Infect 2015;48(2):147–52.

Jagger A, Reiter-Karam S, Hamada Y, Getahun H. National policies on the management of latent tuberculosis infection: Review of 98 countries. Bull World Health Organ 2018;96:173–84.

Kawatsu L, Uchimura K, Ohkado A. Trend and treatment status of latent tuberculosis infection patients in Japan – analysis of Japan TB surveillance data. PLoS One 2017;12(11)e0186588.

Koesoemadinata RC, McAllister SM, Soetedio NNM, Ratnaningsih FD, Ruslami R, Kerry S, et al. Latent TB infection and pulmonary TB disease among patients with diabetes mellitus in Bandung, Indonesia. Trans R Soc Trop Med Hyg 2017;111(2):81–9.

Kyu HH, Maddison ER, Henry NJ, Ledesma JR, Wiens KE, Reiner Jr. R, et al. Global, regional, and national burden of tuberculosis, 1990–2016: results from the global burden of diseases, injuries, and risk factors 2016 study. Lancet Infect Dis 2018;18:1329–49.

Lee MR, Huang YP, Kuo YT, Luo CH, Shih YJ, Shu CC, et al. Diabetes mellitus and latent tuberculosis infection: a systemic review and metaanalysis. Clin Infect Dis 2017;64(6):719–27.

Martinez-Aguilar G, Serrano CJ, Castaneda-Delgado JE, Macias-Segura N, Hernandez-Delgadillo N, Enciso-Moreno L, et al. Associated risk factors for latent tuberculosis infection in subjects with diabetes. Arch Med Res 2015;46(3):221–7.

Nasreen S, Shokoohi M, Malvankar-Mehta MS. Prevalence of latent tuberculosis among health care workers in high burden countries: a systematic review and meta-analysis. PLoS One 2016;11(10)e0164034.

Navarro PD, Almeida IN, Kritski AL, Ceccato MG, Maciel MMD, Carvalho WS, et al. Prevalence of latent Mycobacterium tuberculosis infection in prisoners. J Bras Pneumol 2016;42(5):348–55.

Njie GJ, Morris SB, Woodruff RY, Moro RN, Vernon AA, Borisov MD. Isoniazid-rifapentine for latent tuberculosis infection: a systematic review and meta-analysis. Am J Prev Med 2018;55(2):244–52.

Petruccioli E, Scriba TJ, Petrone L, Hatherill M, Cirillo DM, Joosten SA, et al. Correlates of tuberculosis risk: predictive biomarkers for progression to active tuberculosis. Eur Respir J 2016;48(6):1751–63.

Ratnawati R, Burhan E, Intani CN. Latent tuberculosis infection screening in health care workers in community lung health center in Bandung, Indonesia. Am J Respir Crit Care Med 2017;195:A3989.

Rutherford ME, Ruslami R, Maharani W, Yulita I, Lovell S, Crevel VR, et al. Adherence to isoniazid preventive therapy in Indonesian children: a quantitative and qualitative investigation. BMC Res Notes 2012;5:7.

Sandul AL, Nwana N, Holcombe JM, Lobato MN, Marks S, Webb R, et al. High rate of treatment completion in program settings with 12-dose weekly isoniazid and

rifapentine (3HP) for latent Mycobacterium tuberculosis infection. Clin Infect Dis 2017;65(7):1085–93.
Sharma SK, Vashishtha R, Chauhan LS, Sreenivas V, Seth D. Comparison of TST and IGRA in diagnosis of latent tuberculosis infection in a high TB-burden setting. PLoS One 2017;12(1)e0169539.
Shivakumar SVBY, Chandrasekaran P, Kumar AMV, Paradkar M, Dhanasekaran K, Suryavarshini N, et al. Diabetes and pre-diabetes among household contacts of tuberculosis patients in India: is it time to screen them all?. Int J Tuberc Lung Dis 2018;22(6):686–94.
Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis 2007;45(6):715–22.
Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Sizemore EB, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011;365(23):2155–66.
Sun HY, Huang YW, Huang WC, Chang LY, Chan PC, Chuang YC, et al. Twelve-dose weekly rifapentine plus isoniazid for latent tuberculosis infection: a multicentre randomised controlled trial in Taiwan. Tuberculosis (Edinb). 2018;111:121–6.
Trajman A, Steffen RE, Menzies D. Interferon-gamma release assays versus tuberculin skin testing for the diagnosis of latent tuberculosis infection: An overview of the evidence. Pulm Med 2013;2013:601737.
Uden L, Barber E, Ford N, Cooke GS. Risk of tuberculosis infection and disease for health care workers: an updated meta-analysis. Open Forum Infect Dis 2017;4(3)ofx137.
Wang JY, Huang YW, Chang LY. Toward safe and reachable preventive therapy for latent tuberculosis infection: a multicentre randomised controlled trial I Taiwan. OA01-206-25. Int J Tuberc Lung Dis 2018;22(11):S65.
World Health Organization. The End TB Strategy. 2015. . , [accessed 19 September 2018] http://www.who.int/tb/End_TB_brochure.pdf.
World Health Organization. Report of the Global Consultation on the Programmatic Management of Latent Tuberculosis Infection. 2016. . , [accessed 10 September 2018] http://www.who.int/tb/publications/korea_consultation_report_apr2016/en/.
World Health Organization. Country TB profile. 2017. . , [accessed 22 October 2018] http://www.who.int/tb/country/data/profiles/en/.
World Health Organization. Global Tuberculosis Report. 2018. . , [accessed 19 September 2018] http://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf?ua=1.
World Health Organization. Latent tuberculosis infection. Updated and consolidated guidelines for programmatic management. 2018. . , [accessed 10 September 2018] http://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf;jsessionid=FE3630AA178803C05D7977171D5DB904?sequence=1.
Zak DE, Penn-Nicholson A, Scriba TJ, Thompson E, Suliman Sara, Amon LM, et al. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. Lancet 2016;387(10035):2312–22.