



## Tuberculosis preventive treatment in eight SEAR countries – Current practices, implementation challenges and operations research priorities

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### ABSTRACT

**Objectives:** Countries in the South East Asian region face similar challenges in control of infectious diseases. There is limited access to experiences and learnings of neighboring countries. The Indian Council - of Medical Research (ICMR) has established a Regional Enabler for the South-East Asia Research Collaboration for Health (RESEARCH) Platform for South East Asian Region (SEAR) countries to address the above issues. This paper discusses about current practices, implementation challenges and operations research priorities of Tuberculosis Preventive therapy (TPT) in eight SEAR countries.

**Methods:** A three day workshop on “Capacity Building for TB Research under Programmatic Settings”. was conducted under the aegis of this RESEARCH platform jointly ICMR and the Union which was participated by eight SEAR countries. Data were collected from a semi-structured questionnaire prior to the workshop and open discussions during the workshop.

**Results:** The various challenges faced for TPT implementation were broadly categorized as poor demand and low level of acceptance by the beneficiary, low level of acceptance to provide TPT among the providers, challenges in ruling out active TB, issues with supply and supply chain management of diagnostic tests and drugs. Many operations research priorities like person centric TPT driven models, capacity building for improving cascade of care for latent TB infection, health system strengthening and effective risk communication were identified.

**Conclusion:** Full implementation of the TPT guidelines requires focused attention and coordinated action from all stakeholders of the country to attain the full benefit of TB preventive therapy and the ultimate TB elimination goal.

### 1. Introduction

Prevention of active tuberculosis by TB preventive treatment (TPT) is a critical component of the WHO End TB Strategy. UN High-Level Meeting (UNHLM) on TB set a target to offer TPT to 30 million people

in the five years between 2018 and 2022, however till 2021 TPT has reached only 12.5 million which is 42.0 % of the target [1]. In 2021, South-East Asia Region contributed to about 45.0 % of the TB cases in the world. Estimated number of TB deaths were higher in the South East Asia Region (SEAR) (+8.6 %) region in 2021 compared to 2015. To

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accelerate TB reduction, optimal implementation of TPT is a very critical in this region. A recent modelling study concludes that the annual incidence rate of TB can be potentially reduced by 8.30 % relative to 2015 in the SEAR countries by optimal implementation of TPT [1,2].

Countries in the South East Asian region face similar challenges in control of infectious diseases. There is limited access to experiences and learnings of neighboring countries. Many a times, regional problems are not addressed at the global level. The Indian Council of Medical Research (ICMR) has established a (SEAR- RRP) RESEARCH platform (Regional Enabler for the South-East Asia Research Collaboration for Health) Platform in 2019. This research platform aims to develop regional approaches to address the above problems.

A three-day workshop was conducted by (ICMR) - National institute for Research in Tuberculosis, India from February 14, 2023 to February 16, 2023 for country program managers and TB researchers of SEAR countries on 'Capacity building for TB research under programmatic settings'. The workshop was conducted under the aegis of ICMR-SEAR RRP and in collaboration with The UNION, South East Asia. Objectives of the workshop were to understand the current situation of TB in the SEAR countries, to deliberate on key strategies for accelerating TB elimination and to foster collaborations among countries for multi-country research for accelerating TB elimination. TPT was one of the priority areas considered and based on the deliberations from the workshop, we describe the current practices and key challenges faced by the country program managers to improve the TPT coverage in SEA Region.

## 2. Methods

This was a report from a workshop incorporating qualitative techniques for data collection. A team consisting of a program manager of National TB Control Program (NTP/NTP), an epidemiologist and a microbiologist associated with NTP from each of the eight SEAR countries (India, Indonesia, Bangladesh, Nepal, Bhutan, Sri Lanka, Timor-Leste, Maldives) attended a three day in-person workshop held in Chennai, India along with the faculties from ICMR, WHO and The Union. Before the in-person workshop, current status of TPT implementation were collected using a semi structured questionnaire from each country over email, a month before the workshop. Through the questionnaire, country program managers were asked to write a short description about (1) availability of national guidelines for TPT (2) target high risk groups for TPT (3) algorithms for ruling out active TB (4) test used to detect TB Infection (5) regimen used for TPT (6) mechanisms for adherence monitoring and treatment support (7) management information system for PMTPT and challenges in implementation related to each domain. All countries submitted their response in the prescribed format. A week before the workshop, an e-poster template was created and sent to the countries which consisted of three columns – current status of implementation (target high risk groups for TPT, test used to detect TB Infection, regimen used for TPT, management information system for PMTPT), challenges in implementation of TPT and operations research priority for the country. During the workshop each country program manager presented the status of TPT implementation in their countries using the e-posters template. Each presentation was followed by clarification and discussion session where other members and faculty sought additional information from the countries. Each presentation lasted for approximately 10 min followed by additional 10 min of discussion. This was followed by a 40-min open discussion consolidating all the challenges in implementation of TPT and identifying research priorities for the SEAR region. The open discussion was moderated by two experts who ensured equal participations by all the participants to express their views and had effective probing questions asked to explore specific areas of interest and additional questions to find out more about relevant country specific issues. An independent researcher prepared the 'workshop notes' and the entire discussions were video recorded too. The workshop happened in an environment where the participants could

collaborate and interact without any hesitation. Deliberations were in English.

A team of researchers comprising of Scientist from ICMR- National Institute for research in Tuberculosis, and experts from the UNION, South East Asia compiled the results. All of them had experience in working in the field of TB and were epidemiologist and public health experts by training. They looked at (1) responses to the questionnaires filled by the country program managers (2) e –poster presented by the countries and (3) workshop notes and compiled the report under the following themes- (1) high risk groups eligible for TPT for when TPT services are provided as on Feb 15, 2023 (2) practice on testing for LTBI and ruling out active TB (3) TPT regimens used by countries for various groups and (4) TPT information system. Major challenges in implementation as reported by the countries and those emerged during the discussions were listed out. Individual country program managers were contacted again over email post workshop to discuss any discrepancy in the observations from the three sources or for seeking any missing information. The results tables were sent to the participants from all countries for final review and approval.

## 3. Results

Information on TPT as available from all eight countries are shown below.

**High risk groups for TPT:** The high risk groups for which TPT are provided in the countries are as shown in [Table 1](#). All eight countries that have expanded the target groups as recommended by WHO.

Seven out of eight countries are currently providing TPT services to household contacts above 5 years of age and five countries are providing TPT to all other high-risk clinical groups also. In addition to the high risk groups mentioned above, Indonesia and Maldives are offering TPT services to prisoners and Timor –Leste is extending services to people who are undernourished and are having diabetes.

Definition of index TB patients for all countries except Sri Lanka were 'bacteriologically confirmed pulmonary TB'. For Sri Lanka, 'all' pulmonary TB is considered and only contacts below 15 years and more than 50 years were currently being provided TPT services. Sri Lanka has also included non-household close contacts.

**Assessment for eligibility:** None of the countries in the SEA Region recommend Latent TB infection [LTBI] testing for household contacts of bacteriologically confirmed TB patients who are less than 5 years of age and for PLHIV. Current practices regarding assessment for eligibility for TPT among household contacts above 5 years is as shown in [Table 2](#).

By policy, in all countries, the eligibility for TPT among household contacts above 5 years is assessed based on absence of TB symptoms and positive LTBI tests (only in those places where facilities are available.) However, the countries are practicing a 'test and treat' approach for household contacts above 5 years. Chest radiography to rule out abnormalities suggestive of TB is a mandatory practice before initiation of TPT among household contacts above 5 years in Sri Lanka and Bhutan.

**TPT Regimens:** All the countries are using at least one of the four shorter TPT regimens recommended by WHO guidelines in their national guidelines. The regimens currently in practice among the high risk groups are shown in [Table 3](#).

In India, TPT among household contacts of MDR-TB index patients (in whom FQ resistance has been ruled out) and among household contacts of INH resistant index patients (in whom R resistance has been ruled out), are 6Lfx and 4R respectively. Indonesia also provide TPT for household contacts of DR-TB patients.

**Treatment Support:** All eight countries use the same adherence supporting mechanism used for index TB cases for TPT adherence also. TPT is either self-administered or given by a caregiver Adherence to TPT is assessed by healthcare staff during their routine supervisory visits. The TPT for PLHIV is administered during their ART medication refills. There is no financial incentives proposed for TPT completion in any of the eight countries.

**Table 1**

High Risk Groups for which TPT services are provided in the SEAR countries as on February 15, 2023.

High risk groups recommended by WHO 2020	India	Indonesia	Bangladesh	Nepal	Timor-Leste	Sri Lanka	Bhutan	Maldives
PLHIV (without TsB)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Household contacts children less than 5 years of index TB patients	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Household contacts children aged more than 5 years, adolescents and adults of index TB patients	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Persons on anti-TNF (tumor necrosis factor) treatment	Yes	Yes	Yes	No	No	No	Yes	Yes
Persons receiving dialysis	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Persons preparing for an organ or hematological transplant	Yes	Yes	Yes	No	No	No	Yes	Yes
Persons with silicosis	Yes	Yes	Yes	No	No	No	Yes	Yes

**Table 2**

Current practices regarding assessment for eligibility for TPT among household contacts above 5 years in SEAR countries.

	India	Indonesia	Bangladesh	Nepal	Timor-Leste	Sri Lanka	Bhutan	Maldives
<b>Testing for Latent TB Infection before initiation of TPT</b>	Optional	Optional	Optional	No testing	Optional	Optional	Optional	Optional
<b>Test to diagnose LTBI</b>	TST or IGRA	TST	TST	NA	TST or IGRA	TST or IGRA	TST	TST or IGRA
<b>Chest radiography to rule out active TB before initiation of TBI</b>	Optional	Optional	Optional	Optional	Optional	Mandatory	Mandatory	Optional

**Table 3**

TPT regimens currently in practice among the high risk groups.

High Risk Groups	India	Indonesia	Bangladesh	Nepal	Timor-Leste	Sri Lanka	Bhutan	Maldives
PLHIV	6H	6H		6H	3HP	6H	3HP	NA
Children (without HIV)	3HR/6H	3HR	3HR	3HR	3HR	6H	3HR	3HR
Adults (without HIV)	3HP/6H	3HP	3HP	NA	3HP	6H	3HP/6H	3HP
TPT regimen when index case is DR-TB	Lfx/4R	Lfx + Eto	NA	NA	NA	NA	NA	NA

**Management Information System:** The routine TB surveillance systems in most all countries captures the TPT related recording and reporting. Five countries (India, Indonesia, Nepal, Bhutan, Timor Leste, and Maldives) use a mix of paper based and digital systems to record TPT information, the rest of the three countries use paper based information. In future, Bangladesh intends to incorporate digital reporting for TPT soon. However, there are gaps in terms of data completeness and accuracy in TPT recording and reporting.

**4. Challenges in implementation of TPT**

In all countries, the coverage of TPT is sub-optimal in terms of geography covered and inclusion of all eligible people. Major challenges in scaling up of TPT services as reported by the countries were as follows.

**1. Poor demand and low level of acceptance by the beneficiary:**

Due to various factors including stigma and lack of awareness, there is poor demand and a low level of acceptance to the TPT among the beneficiaries especially adult household contacts. Providers also found it difficult to convince beneficiaries for taking TPT.

*“Beneficiaries are not convinced and we found it very difficult to convince them at each step”*

**2. Low level of acceptance to provide TPT among the providers:**

Low level of confidence among the providers was reported as another important challenge. Various reasons for the same were reported as lack of systematic training to the providers, concerns regarding effectiveness of TPT and risk of developing drug resistance in future.

*“We are unable to convince our own doctors, especially specialists. They have serious doubts about the effectiveness of TPT. They all raise the*

*concern of increase in drug resistance. We don’t have a solid answer for all these.”*

**3. Challenges in ruling out active TB:** Ruling out active TB was found as one of the most challenging tasks to offer TPT among household contacts. Participants reported limited capacity and skill of doctor in periphery to rule out active TB. Access to chest radiography is very limited.

*“Doctors at periphery are not confident to rule out TB”*

**4. Issues with supply and supply chain management of diagnostic tests and drugs:** Inadequate TPT drugs supply especially 3HP, issues related to short expiry of reagents for IGRA and frequent stock outs of TST/IGRA due to the inability to determine targets and logistic needs precisely were cited as important challenges hindering the scale up of TPT.

*“Many found it difficult to estimate the requirement of tests as it is new to them. As a result, there are excess stocks in some area and stock out in other areas”*

*“Mostly we get very short expiry reagents- from the manufacturer. This leads to stock outs”*

**5. Difficulty in organising support systems for beneficiaries:**

Countries felt that without a strong support system and treatment adherence support, there is currently a significant gap in the TPT cascade of care. Beneficiaries found it difficult to reach the health facility multiple times (1) due to geographical distance (2) indirect

costs and (3) difficulty in accessing chest radiography and tests for LTBI. Health system found it difficult to organise the support to door steps because of (1) workload of NTP staff and (2) limited availability of treatment supporters.

*“Contacts will never come back to health facility”*

*“There is no system to ensure treatment adherence. Our staff are overburdened”*

## 5. Operations research priorities

Based on the current situation and challenges for implementing TPT, following were identified as the operations research priorities in SEAR, through discussions in the workshop.

- 1) Comprehensive intervention strategy including capacity building for providers and structured counselling to beneficiaries to improve retention in Latent TB infection cascade of care.
- 2) Demonstration to improve access to X-ray for contact investigation and ruling out active TB disease.
- 3) Conceptualize and demonstrate person centric TPT delivery models suitable to local contexts.
- 4) Determining appropriate interventions for community mobilisation for accessing TPT services.
- 5) Demonstration of TPT as a continuum of active case finding and contact investigations.
- 6) Effective methods to communicate risk of TB to the beneficiaries eligible for TPT in specific contexts.
- 7) Effective methods for providing treatment adherence support for people on TPT.
- 8) Integration of TPT care cascade to real time case based TB management information system.
- 9) Strategies to strengthen health systems for providing decentralized TPT services

## 6. Discussion

TPT is a cost-effective strategy which reduces the risk of progression of LTBI into TB disease. This manuscript describes the practices regarding TPT service and challenges faced by the National TB Control Programs in SEAR countries. Though there is a progress related to adoption of policy for TPT implementation based on latest WHO guidelines in all the eight countries assessed, the implementation pace is very slow. COVID-19 pandemic had impacted scaling up of TPT services [3]. It is felt that, due to various factors including stigma and lack of awareness, there is poor demand and a low level of acceptance to the TPT among the beneficiaries especially adult household contacts. Low level of confidence among the providers due to doubtfulness regarding sensitivity of tests used and effectiveness of the drugs coupled with concerns of developing drug resistance were some of the important challenges reported. The TPT eligibility criteria is in line with the recommendation suggested by WHO Though LTBI tests are optional in all countries to assess the eligibility for TPT, due to poor acceptance among the health care providers and beneficiaries, countries are insisting on testing by either TST/IGRA. Inadequate TPT drug supply, especially 3HP, issues related to short expiry of reagents for IGRA and frequent stock outs of TST/IGRA due to the inability to determine targets and logistic needs were cited as important challenges hindering the scale up of TPT. Countries also felt that without a strong programmatic support system and treatment adherence support, there is currently a significant gap in the TPT cascade of care. Gaps in the completeness and accuracy of the data recorded and reported were apparent due to poor integration of TPT data into digital management information systems.

There is a need for a robust social mobilization plans which could increase community engagement and create a demand for TPT.

Engagement with the TB affected community for TPT scale up could help in demand generation for TPT. There is a need to involve people from different target population who have taken TPT to formulate appropriate communication strategies. Communication resources should be available freely to help individuals and communities to be to make informed decisions regarding TPT.

There is an urgent need of a strong advocacy plan to gain confidence of the providers. All countries need to enhance capacity building of health system staff is necessary to optimize TPT delivery services. This need to be done meticulously and periodically. Tools for training for all categories of health personnel need to be developed that will bring a sustained behavior change. The clinicians and academicians are not confident enough to rule out active TB without a chest radiography, because of poor sensitivity of screening using symptom complex alone. National TB Prevalence survey in India reported that nearly half of the diagnosed TB cases would have been missed if chest X-ray was not used for screening [4]. To gain the confidence of providers and to alleviate their concerns regarding accelerating drug resistance due to inadvertent treatment of TB disease with a TPT regimen, offering chest radiography to rule out TB can be considered. However, access to radiography remains a major challenge in all the countries. Even with chest radiography the ability to read the same is also deficient at the periphery. This is identified as an important bottle neck for TPT scale up, as proper delineation of active and LTBI is not achieved. Demonstration of use of hand-held X-ray devices or mobile X-ray vans with artificial intelligence emerged as a potential operational research question during the workshop.

Ensuring availability of adequate quantities of drugs and diagnostics through appropriate quantification and robust supply chains is the need of the hour. Ready to use simple planning tools could help the countries in proper estimation about the requirements. A study and dedicated supply chain management for TB care could ensure use of available stocks in a timely manner. National programme's capacity for contact investigation has to be strengthened to improve access to TPT for contacts. An operational research study from India and Thailand report that contact tracing and can be improved by providing invitation cards and covering transport costs [5]. This will enhance their access to TPT. The study from Thailand also concluded that additional assistance is required for TB screening among the contacts. Similar models with support systems for contact investigations could enhance the TPT acceptance and prevent leakages in cascade of care.

To conclude, it is essential that investing in health system capacity building like laboratory for IGRA, train human resources, maintain uninterrupted logistics and supply chain for TST, IGRAs and newer tests like Cy-Tb reagents and consumables. Having these LTBI testing facilities in the country can ensure correct TPT candidate selection and also gain trust and confidence in diagnostics. It can potentially prevent unwanted TPT provision, related adverse events and will enhance the TPT acceptance. Optimal implementation the TPT guidelines requires focused efforts and action from all stakeholders in the country if we have to attain the full benefit of TB preventive therapy and ultimate TB goal.

## 7. Limitations

The study has various limitations. The results were collated by a group of public health experts from the workshop and measures to mitigate bias like inter-rater reliability were not adopted. Also a semi-structured questionnaire and a template for poster presentation was used to collect data which could have missed certain information, but this was overcome to some extent by open discussions during the workshop. There would be certain sensitive information which the participants would not have discussed in the open forum which could have been overcome by in-depth interviews country wise.

## 8. Key findings

In all countries, the coverage of TPT is sub-optimal in terms of geography covered and inclusion of all eligible people.

## 9. Key implications

Full implementation of the TPT guidelines requires focused attention and coordinated action from all stakeholders to attain complete full benefits of TB preventive therapy and the ultimate TB elimination goal.

## Author contribution

PG,RPS, BV,MM,LSG, NG, - Idea and Conceptualization, Methodology, Data acquisition, Data analysis, Interpretation, Writing – original draft preparation, review and editing.

TZ,RBJ,MC,FI,FNR,ACS,NP- Data acquisition, Data analysis, Interpretation, Writing – original draft preparation, review and editing.

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## Declaration of competing interest

None to declare.

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