HTA on Latent TB Infection Tests

Assessing the Cost-effectiveness of Latent TB Infection Tests (LTBI) in India

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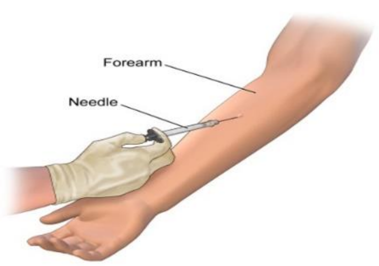

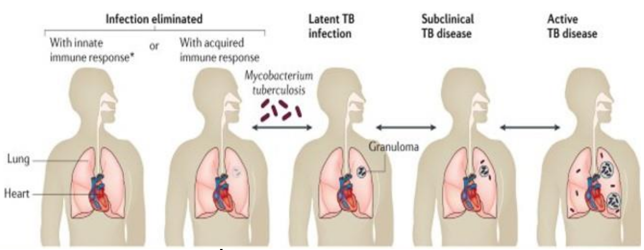

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Summary

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by Mycobaterium tuberculosis (M.tb) antigens without evidence of clinically manifested active tuberculosis (TB). Hence screening and treatment of LTBI should be an important part of global TB control activities if we want to achieve End TB strategy. WHO recommends systematic screening, identification and treatment of LTBI especially in groups at high risk for developing active TB like people living with HIV, child contacts of pulmonary TB cases, patients other immunosuppression. After ruling out active TB by a symptom screen, individual should be tested for LTBI by either interferon-gamma release assay (IGRA) or tuberculin skin test (TST). TST with purified protein derivative (PPD RT 23) is the routine diagnostic test in most tuberculosis high burden countries. C-Tb (Statens Serum Institute, Copenhagen, Denmark) is a novel specific skin test based on ESAT-6 and CFP10 antigens. A LTBI screening model was adapted to screen the cohort of household contacts. A cost effectiveness analysis was performed from an Indian healthcare perspective, taking into account the risk of isoniazid- related toxicity and post exposure TB using C-Tb test and TST screening strategy. Taking a cohort of 100000 household contacts for analysis, for true positive cases only the incremental cost effectiveness ratio per case detected (ICER) of TST vs C-Tb test is 119128, which denotes that to prevent one active TB cases by C-Tb test we have to spend additional of ₹119128. Examining the cost alone, the C-Tb screening strategy was the most expensive at ₹166 million per 100000 contacts screened. Test cost comprised a significant proportion (34%) of the total cost of the C-Tb screening strategy. Conversely the TST was less expensive but this strategy incurred the higher diagnosis costs from the total cost, resulting from the test accuracies (₹47 million), particularly the costs incurred on true positive results. However, less contacts need to be treated to prevent an active case of TB in C-Tb test screening which has prevented 25 active TB cases more compared to TST. The number adverse events are more by TST test screening compared to C-Tb test, since the number of false positive (14030) detected by TST screening are more which results in over treatment of household contacts which are LTBI negative but tested positive.

I. INTRODUCTION

Latent tuberculosis infection (LTBI) is the persistence of an immunological response to *Mycobacterium tuberculosis (M.tb)* antigen stimulation without any clinically active disease. The global prevalence of LTBI is estimated to be nearly 33%. In India, there are no estimates regarding the prevalence of LTBI in the general population; however, the WHO data indicate that around 0.35 million children below the age of 5 years were eligible for LTBI treatment.[1] A significant proportion of the Indian population is susceptible to progression to active TB disease from LTBI due to the presence of the risk factors. For instance, 1.77 million homeless people live in India, and studies have found that there is a disproportionately higher risk of TB in these population.[2] Identification and treatment of LTBI cases remain an effective strategy in the control of tuberculosis (TB). Diagnosis of LTBI can be established on the basis of Tuberculin Skin Test (TST) and/or Interferon-Gamma Release Assays (IGRAs). TST is easy to use, but false-positive reactions may occur in individuals vaccinated with Bacille Calmette–Guerin (BCG) vaccine, particularly in infants after birth, or in individuals infected with nontuberculous mycobacteria. The TST detects *M.tb* sensitization via a delayed-type hypersensitivity response to *M.tb* antigens from purified protein derivatives while IGRAs measure interferon-gamma (IFN-γ) release in response to specific *M.tb* antigens.[13] IGRAs are not recommended by the World Health Organisation (WHO) as a TST replacement, in low and middle income countries but are suggested to use in high-income countries.[16] IGRAs do not differentiate between LTBI and active TB disease. They are whole blood tests, which measure the immune response to antigens, derived from these bacteria.[2]

Meta analyses have shown that IGRAs have demonstrated superior specificity and sensitivity when compared with that of TST. Major disadvantages of the IGRA is that it require high relative cost and the need for an equipped laboratory. Blood samples must be processed within 12 hours with the QFT-G, and errors in collecting, transporting, or running the assay can lead to inadequate test results. Consequently, IGRA tests can be non-diagnostic, necessitating second testing. Finally, data are limited in children, recently exposed subjects, and immunocompromised individuals.[3]

C-Tb (Statens Serum Institute, Copenhagen, Denmark) is a highly specific skin test for the diagnosis of LTBI designed to address some of the drawbacks of TST and IGRAs. C-Tb is applied and read in the same way as TST, but is based on the antigens ESAT-6 and CFP-10 that are also included in the IGRAs. Due to high specificity, C-Tb uses a universal 5 mm cut-point induration irrespective of the status of BCG, HIV, or both.[4] C-Tb combines the cost-effectiveness and the ease of the TST with the specificity of the IGRAs in the diagnosis of LTBI. The C-Tb test is also unaffected by BCG vaccination. This test has fared well in Phase 3, double-blinded, and randomized trial published in 2017. It showed 94% concordance with the IGRA results with similar indurations sizes as the TST.[5]

Currently, the TST with purified protein derivative (PPD RT 23) is the routine diagnostic test in most TB high burden countries. The intermittent shortage of PPD, the low specificity of the test in BCG vaccinated population and the cumbersome training necessary for TST has highlighted the need for adoption of newer, more specific tests.[32] Nevertheless, for the incorporation of new technologies to the public health system, local assessments of feasibility, acceptability, and cost-effectiveness are necessary. We aimed to analyse the cost-effectiveness of newer LTBI diagnostic tests that is C-Tb with the TST test in diagnosing and treatment of LTBI.

II. RESEARCH QUESTION

The current Health Technology Assessment proposes to answer the research question on what is the cost- effectiveness of implementing the C–Tb test to screen and treat LTBI in India.

III. OBJECTIVE

1. To estimate the clinical-effectiveness of different LTBI tests.
2. To estimate per test cost for the detection of LTBI by different tests (TST and C- Tb).
3. To estimate cost-effectiveness of C-Tb test as compared to TST.
4. To estimate the cost and clinical outcome of screening and treating with the different LTBI tests.
5. To estimate the budget incurred by the program if C-Tb test is implemented.

IV. METHODOLOGY

Study Perspective

This cost-effectiveness modelling was conducted primarily from the health system perspective which includes costs incurred by the health system i.e. cost of screening and treating the LTBI with C-Tb test. Also estimated the expected additional cost for implementing C-Tb test for LTBI diagnosis and treatment in India and Tamil Nadu.

Study Population

The current estimate focused on all the household contacts of the index case with active TB.

PICO

Population	Household contacts of active TB patients
Intervention	C-Tb test
Comparator	TST (Tuberculin Skin Test)
Outcome	Clinical effectiveness of the test (diagnostic accuracy), cost incurred to detect and treat LTBI case, cost effectiveness and clinical outcomes (no LTBI, LTBI, TB) of different screening strategies and cost incurred on averted false positive cases.

Population

Household contacts are defined as all people who shared meals and rooms with the index case and living together for at least the previous three months. Index case is defined as smear positive pulmonary TB patient aged >18 years who had at least one household contact, with no previous history of TB or taking anti-tubercular treatment in the previous six months.[6] So household are considered for the study.

Intervention

Screening and testing the household contacts with the C-Tb test, it is applied and read in the same way as TST. C-Tb test is the next-generation skin test for detection of LTBI.

- It is a novel specific skin test based on 6-kDa early secretory antigenic target (ESAT-6) & 10-kDa culture filtrate protein (CFP-10) antigens of *M.tb*.[4]
- C-Tb test is a diagnostic test for screeening of LTBI due to its high specificity for detection of *M.tb* infection and overcome the issues of the interaction with BCG vaccine and infection with non-tuberculous mycobacteria seen with the TST.

Comparator

Screening the household contacts with the standard of care for diagnosing LTBI that is Tuberculin Skin Test (TST).

Outcome

This cost-effectiveness study will assess which strategy is effective in detecting the correctly classified infection and will be calculated by the number of true positive and false positive cohort cases of LTBI in household contacts, treating the positives cases with preventive therapy of six months isoniazid regimen and also to find out the budget impact analysis of C-Tb test over TST. The final outcome will be the number of TB cases prevented by the screening the population by C-Tb test and TST.

Model Structure

A deterministic decision tree model for cost-effectiveness analysis was developed in Microsoft Excel to compare the sensitivity and specificity of the various test of LTBI in household contacts of the active TB index patients. The model was parameterized using data from different sources such as published articles, systematic reviews and primary data sources.

Screening strategy

Two different screening tools were investigated in this cost-effectiveness analysis such as (1) Screening by TST; and (2) Screening by C-Tb test. Since there is no gold standard test for LTBI detection, test sensitivity, specificity and prevalence of the LTBI derived from the literature review are used to calculate diagnostic accuracy using the formula. The diagnostic accuracy of each test is in terms of true positive, true negative, false positive and false negative cases. The model has been calibrated to the characteristics of the Indian population and examined in a hypothetical cohort of 100000.

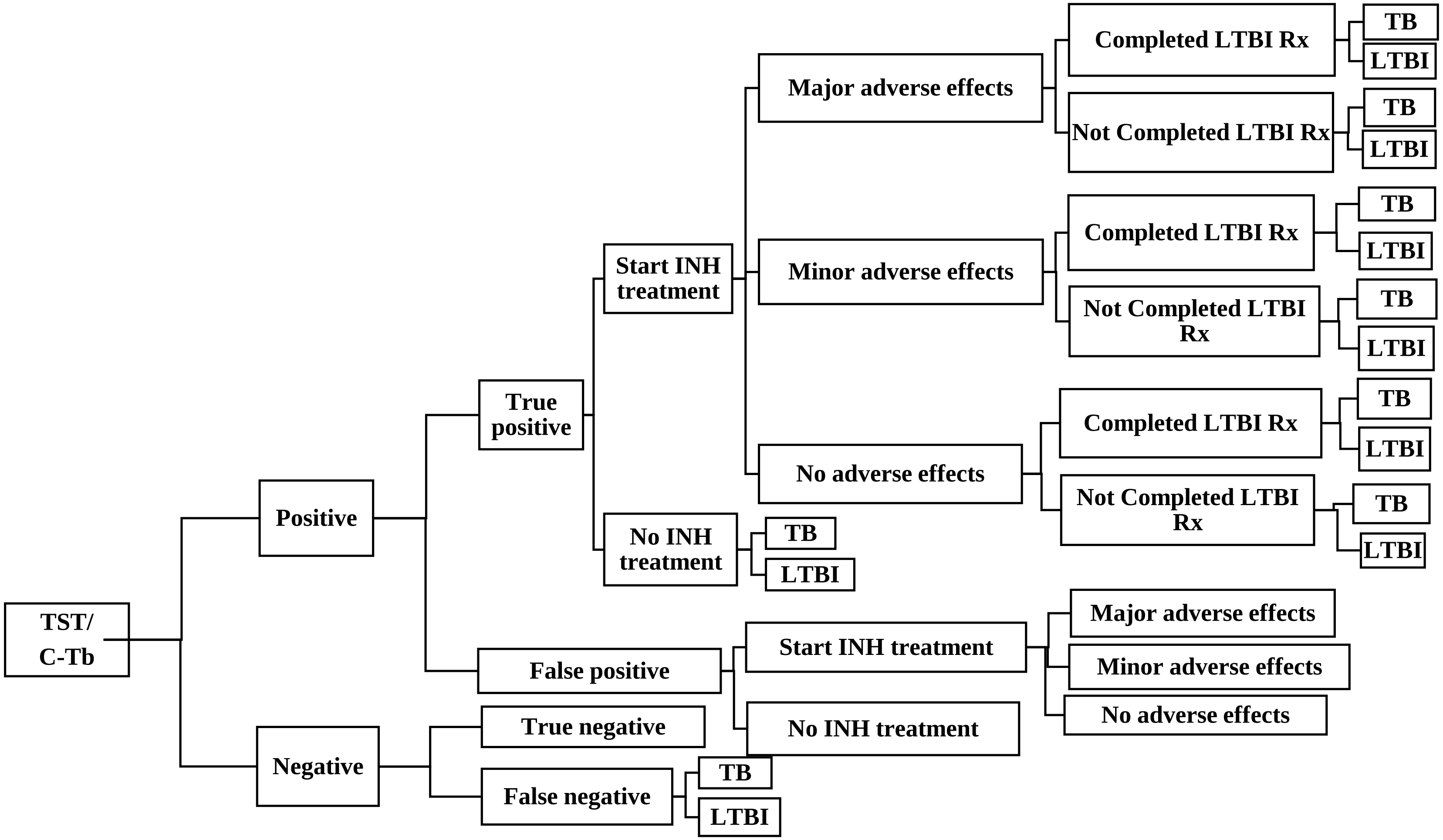
Table 1. Strategies for measuring cost-effectiveness analysis

Strategies	**Intervention**	**Implementation**	**Population**
Proposed strategy	Testing with C-Tb test	Public health facilities	Household contacts
Comparator	Testing with TST		

Decision tree

A decision tree has been used to represent the clinical pathway associated with screening close contacts of infectious TB index cases. We have modelled two testing strategies: testing with TST and C-Tb test. The branches of the decision tree captures the probability of testing positive, negative and the probability of testing true positives and false positives among the tested positives. Similarly the probability of true negative and false negative among the tested negatives. Further the positive cases are started with the preventive therapy and toxicity are been branched in to mild, moderate and severe. Breakdown of TB, remain LTBI and no LTBI state are the last three outcomes of completion or not completion of the preventive therapy.

Figure 1. Decision Tree



Source: Pooran A, et al. Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost effectiveness analysis. BMC Pulm Med 2010; 10:7.

The decision tree is for the diagnosis of LTBI using the TST or C-Tb test alone in a single test strategy. It was adapted from the publication on a LTBI screening model directed at screening contacts. It was used to perform a cost-effectiveness analysis from a UK healthcare perspective. We used the same decision tree.

Table 2. Summary of methodology

Study Area	**India**
Design	Model based study
Perspective	Health system's perspective
Target population	Household contacts of active TB patients
Intervention	C-Tb Test
Comparator-1	Tuberculin Skin Test (TST)
Outcomes	1. True positive and false positive cases detected and treated by the various test 2. Cost incurred to detect and to treat true positive and false positive cases 3. Number of active TB cases prevented
Model	Decision Tree
Data	Primary data and Secondary data from published literature

Model input parameter

Cost data

The economic analysis will include only the health system perspective. Using resource based costing methodology in which quantities of resources were multiplied by their respective unit costs to obtain total costs. We derived the unit costs of each screening strategy. The direct costs for screening include the cost of the test kit, consumables (vial, syringe, and needle), and human resource time. Human resource's time for testing the patient will be converted to cost utilised for the procedure and was collected from ICMR-NIRT. All the other costs were collected from current market value. The vial cost of C-Tb was taken from company's quotation. Preventive therapy cost, toxicity treatment cost, TB diagnosis cost, TB treatment cost are taken from the published literature. There was no discounting of future costs as the time period of the model is only for a year

Effectiveness parameters

The effectiveness parameters includes the adverse effects by the isoniazid preventive therapy which was categorized in to minor, major and no adverse effect and was collected from the published literature. Efficacy of the isoniazid preventive therapy was measured in terms of number of LTBI cases remaining latent and the breakdown of active TB cases after the completion or non-completion of the isoniazid preventive therapy, was also collected by the published literature.

Cost-effectiveness ratio

The primary measure of cost-effectiveness used in our analysis is the incremental cost per active cases prevented by the proposed strategy (C-Tb testing). This was calculated using incremental costs, defined as the additional costs of the proposed strategy over the cost spent over TST, divided by the difference of the number of active TB cases by the proposed strategy with the TST screening strategy.

Incremental cost per active TB case prevented =

$$\frac{\text{Cost of C−Tb screening strategy} - \text{Cost of TST screening strategy}}{\text{Active Tb cases by C−Tb screening strategy} - \text{Active TB cases by TST screening strategy}}$$

Table 3. Input parameters on prevalence and diagnostic accuracy of three different LTBI tests

	Parameter	Base case	Lower	Upper	Source
	Cohort population	1,00,000	800	1,200	Assumption
Prevalence	LTBI in India	0.390	0.312	0.468	M Singh et al.,[18]
	LTBI in Tamil Nadu	0.530	0.424	0.636	Krishnamoorthy Y, et al.,[7]
Diagnostic accuracy	C-Tb Positive	0.292	0.234	0.351	Estimated [45, 18]
	C-Tb Negative	0.708	0.566	0.849	
	C-Tb True Positive	0.985	0.788	1.182	
	C-Tb False Positive	0.015	0.012	0.018	
	C-Tb True Negative	0.856	0.685	1.027	
	C-Tb False Negative	0.144	0.115	0.173	
	TST Positive	0.437	0.349	0.524	Estimated [18,19]
	TST Negative	0.563	0.451	0.676	
	TST True Positive	0.679	0.543	0.814	
	TST False Positive	0.321	0.257	0.386	
	TST True Negative	0.834	0.667	1.001	
	TST False Negative	0.166	0.133	0.199	
INH treatment outcomes	No toxicity	0.956	0.765	1.147	Mai T Pho, et al., [15]
	Minor toxicity	0.030	0.024	0.036	
	Major toxicity	0.014	0.011	0.017	
	Start INH treatment	0.307	0.246	0.368	Estimated[8]
	No INH treatment	0.693	0.554	0.832	
	Treatment Completed	0.188	0.150	0.226	
	Treatment not Completed	0.812	0.650	0.974	
	Developed TB	0.100	0.080	0.120	P K Moonan et al.,[9]
	Remain LTBI	0.900	0.720	1.080	
Mortality	All Causes Mortality of India	0.074	0.059	0.089	United Nations - World Population Prospects
	All Causes Mortality of Tamil Nadu	0.077	0.062	0.092	NITI Aayog, Government of India
C-Tb	Sensitivity of C-Tb	0.739	0.591	0.887	Soren T Hoff, et al., [45]
	Specificity of C-Tb	0.993	0.794	1.192	

	Parameter	Base case	Lower	Upper	Source
TST	Sensitivity of TST	0.760	0.608	0.912	C. Padmapriyadarshini, et al., [19]
	Specificity of TST	0.770	0.616	0.924	
Cost data	INH treatment	1657	1326	1988	Mai T Pho, et al., [10]
	Major AE	8287	6630	9944	S Kapoor, et [11]
	Minor AE	2961	2369	3553	
	Diagnosis Cost of TB	1594	1275	1913	
	Treatment of active TB	7873	6298	9447	
	Willingness to pay threshold (GDP per capita) (in INR)	116000	92800	139200	

Table 4. Input parameters on costs (in ₹)

Parameter	Base case	Lower	Upper	Distribution
TST_HR	270	216.00	324.00	Gamma
TST_kit	124	99.20	148.80	Gamma
C-Tb_HR	270	216.00	324.00	Gamma
C-Tb_kit	304	243.20	364.80	Gamma

One Way Sensitivity Analysis (OWSA)

The robustness of model results was tested through a sensitivity analysis by varying input parameters between 20% above or below the estimated values. Excel was used to perform OWSA by taking the parameters like C-Tb vial cost, TST kit cost, and number of true positive cases by each test, number of individuals completing treatment, sensitivity and specificity of both the test. The sources of uncertainty especially parameter uncertainties which would influence cost-effectiveness outcome has been evaluated by OWSA. Uncertainty in outcome variables and their effect on ICER is tested by Tornado diagram.

One Way Sensitivity Analysis (OWSA) for Price Threshold for the C-Tb test

The price at which C-Tb test is procured plays a crucial role in determining the overall cost of screening, therefore, one way sensitivity analysis (OWSA) was performed. ICER per case detection was analysed by changing the cost of the kit and evaluated at which cost the ICER is cost-effective.

Budget Impact Analysis

Budget impact analysis (BIA) is an economic assessment that will estimate the financial consequences of adopting a C-Tb test over TST for the period of the next five years. BIA is used to make informed decisions as a supplement to cost-effectiveness analyses (CEAs).

V. RESULTS

Diagnostic Accuracy

Sensitivity and Specificity of LTBI diagnostic tools

Sensitivity and specificity were collected from the literature, and it is observed that TST test sensitivity is higher than the C-Tb test, but when we compare the specificity, C-Tb test is more accurate in identifying people without the disease.

Table 5. Diagnostic Accuracy

Test	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
C-Tb	73.90	99.30	98.54	85.61
TST	76.00	77.00	67.87	73.99

Qualitative analysis

We assessed qualitatively comparing these three test in terms of cost, accuracy, specificity, ease of administration, ease for patient, turnaround time, loss-to-follow-up, infrastructure and the level of implementation at community. The score was given based on the expert opinion. The overall score was high for IGRA flowed by C-Tb test and TST (Table-6).

Table 6. Qualitative Analysis

	C-Tb	**TST**	**IGRA**
Cost	+	+	+++
Accuracy	++	+	+++
Specificity	++	+	+++
Ease of administration	++	++	+
Ease for patient	+	+	+++
Turnaround time	++	+	+++
Loss-to-follow-up	+	+	++++

	C-Tb	TST	IGRA
Infrastructure	+++	+++	+
Level of implementation at community	+++	+++	+
Overall score	17	14	22

Table 7. Likelihood ratio of C-Tb test and TST test

Test	Likelihood ratio	Likelihood ratio	95% confidence interval	Posterior probability (odds)	95% confidence interval:	Test Accuracy
C-Tb	Likelihood ratio +	106	[96, 116]	99%	[98%,99%]	1 in 1.0 with positive test are sick
C-Tb	Likelihood ratio -	0.26	[0.26,0.27]	14%	[14%,15%]	1 in 1.2 with negative test are well
TST	Likelihood ratio +	3.3	[3.25,3.36]	68%	[68%,68%]	1 in 1.5 with positive test are sick
TST	Likelihood ratio -	0.31	[0.31,0.32]	17%	[17%,17%]	1 in 1.2 with negative test are well

Likelihood ratios compare the probability that someone with the disease has a particular test result as compared to someone without the disease. The C-Tb test positive likelihood ratio (LR+) is 106 [CI = 95%, (96%-116%)] which denotes that individuals with LTBI is 106 times more likely to have a positive C-Tb test than someone without LTBI. Negative likelihood ratio (LR-) is 0.26 denotes that someone with LTBI is 0.26 times as likely to have a negative C-Tb test as someone without LTBI. Whereas for TST the LR+ is 3.3 and LR- is 0.31 which is significantly lesser than C-Tb test.

Figure 2. Nomogram showing post-test probabilities for a positive and negative diagnostic test result. (C-Tb test)

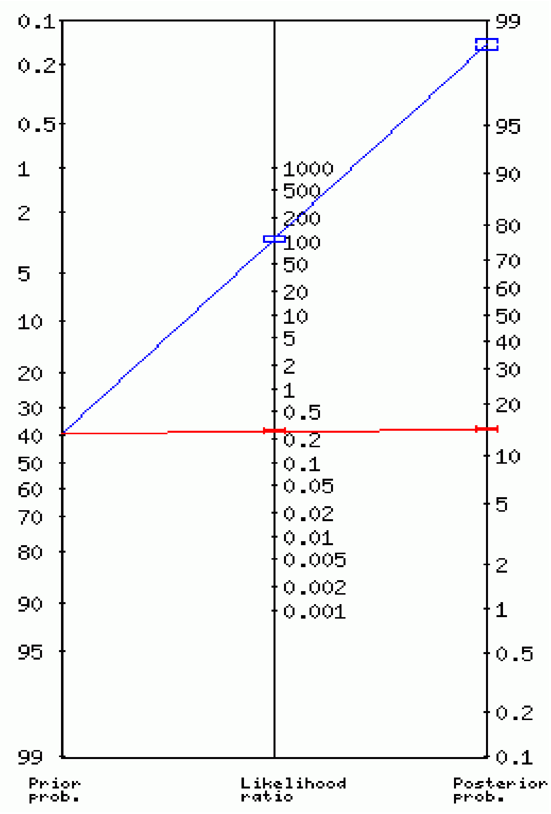
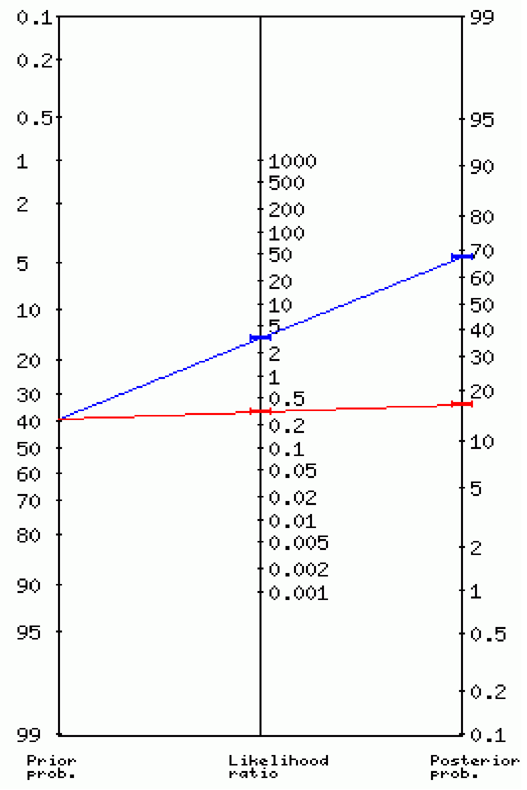


Figure 3. Nomogram showing post-test probabilities for a positive and negative diagnostic test result. (TST)



Cost

Table 8. Unit cost per test (in ₹)

Component of Cost	C-Tb	TST
HR	270	270
Kit	304	124
Total Cost	574	394

Human resource's time for testing the patient was converted into cost. Kit cost includes the cost of syringe, needle, vial when screened by TST and C-Tb test. HR cost for C-Tb test and TST was ₹270 per test, it was similar for both tests. All the component cost of kit was collected from the current market value (IndiaMart website) and C-Tb vial cost was collected from the company market price. It was ₹304 for C-Tb and ₹124 for TST. C-Tb test cost was ₹180 higher as compare to TST.

Base Case Analysis

Cost and probability estimates were inputted into the decision tree model to determine associated costs and effectiveness measures of each screening strategy. In cost terms alone, the C-Tb screening strategy was the most expensive at ₹166 million per 100000 contacts screened, respectively. Test cost comprised a significant proportion (34%) of the total cost of the C-Tb screening strategy. Conversely the TST was less expensive but this strategy incurred the higher diagnosis costs from the total cost, resulting from the test accuracies (₹47 million), particularly the costs incurred on true positive results.

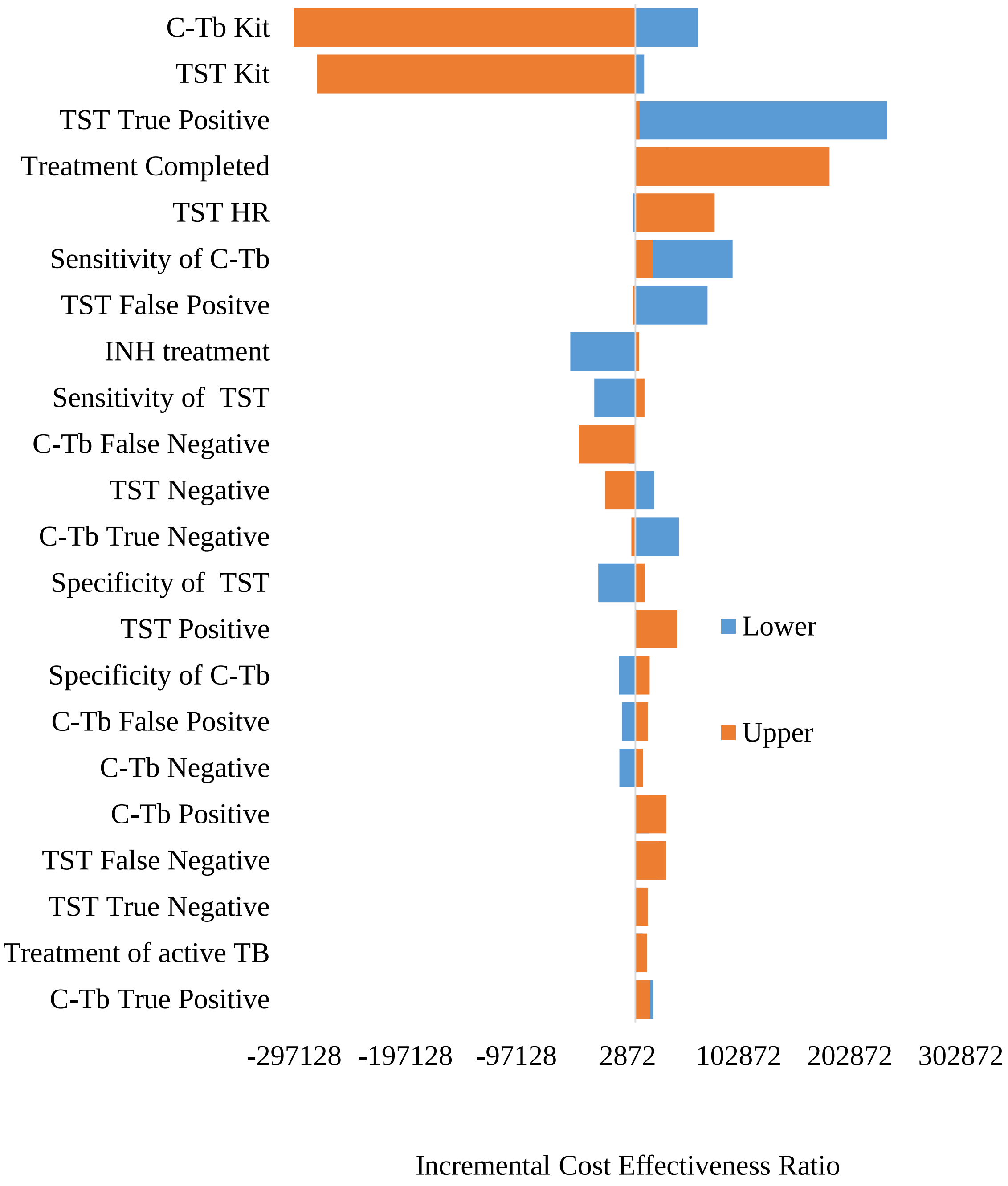
Table 9. Incremental Cost Effectiveness Ratio per case detection

Test	Total Cost	TB cases	Incremental		ICER
			Cost	TB cases	Cost/TB
C-Tb	₹16,69,87,121	2882	₹9756567	- 82	119128
TST	₹15,72,30,554	2964			

Screening the cohort of 100000 household contacts by C-Tb test at ₹304 results in identification of 2882 TB case with the cost of ₹166.9 million. Whereas screening by TST test results in identification of 2964 cases with the cost of ₹157 million. It was estimated that when we use C-Tb test, less TB cases are arising as compared to TST. It may be due to less false positive cases and more true negative cases diagnosed by C-Tb test. The incremental cost effectiveness ratio per case detected (ICER) of TST vs C-Tb is 119128, which denotes that to prevent one active TB case by C-Tb test we have to spend additional of ₹119128 which includes LTBI screening, preventive therapy, adverse effect cost, diagnosis and treatment of active TB.

One Way Sensitivity Analysis

Figure 5. OWSA of different parameters affecting the ICER



One Way Sensitivity Analysis was performed to know which parameter affects the ICER and it was found that C-Tb kit cost was influencing the ICER significantly by 5 times in base case value.

Cost threshold analysis (CTA)

The price at which the C-Tb vial are procured plays an important role in determining the overall cost of screening LTBI, therefore one way sensitivity cost threshold analysis was performed. ICER per case detected suggests that, if the C-Tb vial can be procured with the reduction of ₹100 (at price of ₹204) it will be the cost saving strategy (Figure 6).

Figure 6. OWSA for Cost threshold analysis of C-Tb test

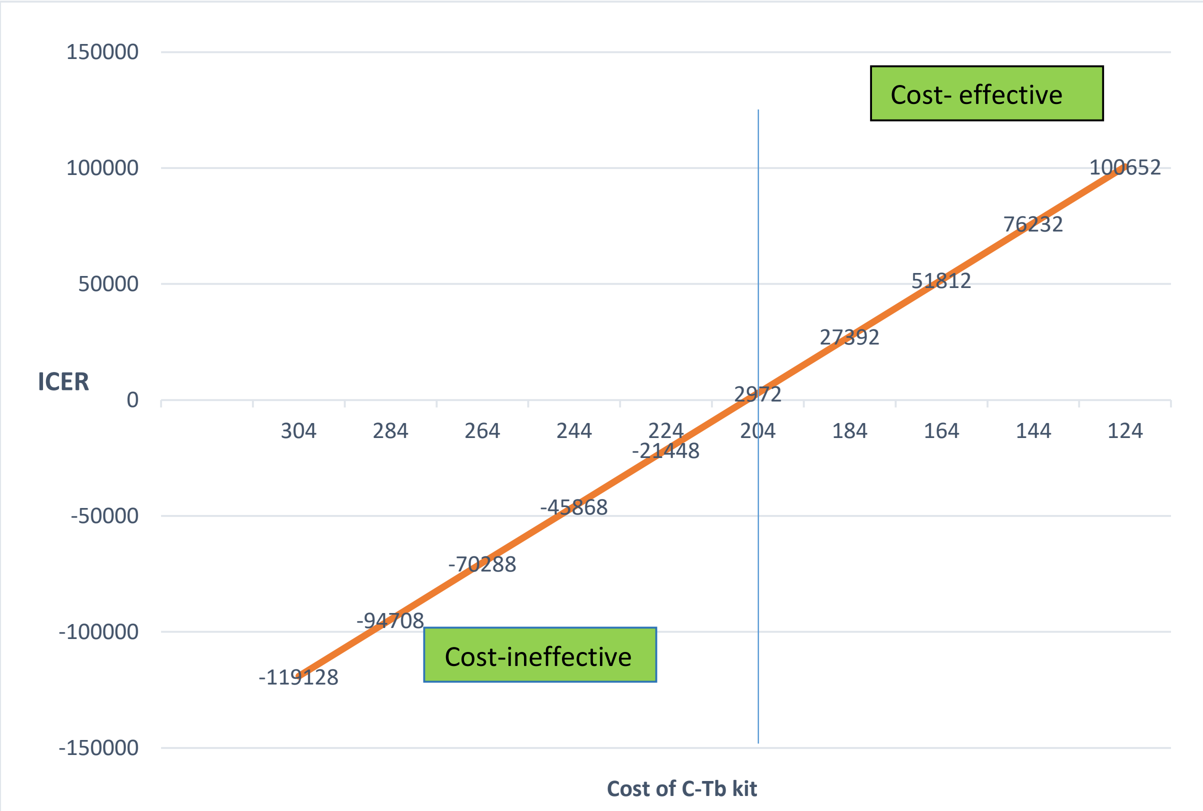


Table 10. Budget Impact Analysis for India

Year / Test	BIA with the cost of ₹ 304 for C-Tb (Number of household contacts = 11.35 million)					
	2022	**2023**	**2024**	**2025**	**2026**	**2027**
C-Tb	16,174,221,839	14,946,598,402	13,812,151,583	12,763,809,278	11,795,036,154	10,899,792,910
TST	14,405,708,658	13,312,315,371	12,301,910,634	11,368,195,617	10,505,349,569	9,707,993,537
Budget Impact (C-Tb vs TST)	1,768,513,182	1,634,283,031	1,510,240,949	1,395,613,661	1,289,686,584	1,191,799,373

Table-10 shows the budget impact of C-Tb and TST tests for total predicted household contacts in India for the five years. For the year 2023, it is expected that 3 million of true positive LTBI cases will be yielded by screening 11.35 million household contacts and it will cost ₹6020 million, by C-Tb at the unit cost of ₹304. It was also estimated that to treat by the preventive therapy the cost will be ₹1537 million. If screened 11.35 million by TST it will cost ₹4132 million to detect 3.1 million of true positive LTBI cases and to treat by the preventive therapy the cost will be ₹1581 million. It is estimated that more active TB cases can be prevented by implementing C-Tb as compared to TST (9296 additional TB cases prevented). For this we need to spend ₹1634 million addition budget for India. **If C-Tb kit cost reduced from ₹304 to ₹124, it is estimated that to detect and treat 3 million of true positive LTBI cases will be cost saving of ₹253 million in 2023 for India (**Table-10.1).

Table 10.1. Budget Impact Analysis for India

BIA with the cost of ₹124 for C-Tb (Number of household contacts = 11.35 million)						
Year/ Test	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**
C-Tb	14,13,12,21,839	13,05,86,62,102	12,06,75,09,648	11,15,15,85,666	10,30,51,80,314	9,52,30,17,128
TST	14,40,57,08,658	13,31,23,15,371	12,30,19,10,634	11,36,81,95,617	10,50,53,49,569	9,70,79,93,537
Budget Impact (C-Tb VS TST)	-27,44,86,818	-25,36,53,269	-23,44,00,986	-21,66,09,951	-20,01,69,256	-18,49,76,409

Table 11. Budget Impact Analysis for Tamil Nadu

Year / Test	BIA with the cost of ₹ 304 for C-Tb (N= 173109)					
	2022	**2023**	**2024**	**2025**	**2026**	**2027**
C-Tb	299,572,616	276,835,054	255,823,274	236,406,287	218,463,050	201,881,704
TST	274,102,272	253,297,909	234,072,598	216,306,488	199,888,825	184,717,263
Budget Impact (C-Tb VS TST)	25,470,344	23,537,145	21,750,676	20,099,799	18,574,225	17,164,441

Table-11 shows the budget impact of implementation C-Tb as compared to TST in Tamil Nadu. For the year 2023, it is estimated that ₹91 million has to be spent to detect 62,655 true positive cases by screening 173109 household contacts by C-Tb at the unit cost of ₹ 304 and ₹ 31 million for treating the LTBI. **If C-Tb kit cost reduced from ₹304 to ₹124, it is estimated that to detect and treat around 62,655 of true positive LTBI cases will save ₹5,257,453 in 2023** (Table 11.1).

Table 11.1. Budget Impact Analysis for Tamil Nadu

Year / Test	BIA with the cost of ₹ 124 for C-Tb (N= 173109)					
	2022	**2023**	**2024**	**2025**	**2026**	**2027**
C-Tb	268,413,003	248,040,456	229,214,185	211,816,829	195,739,931	180,883,271
TST	274,102,272	253,297,909	234,072,598	216,306,488	199,888,825	184,717,263
Budget Impact (C-Tb VS TST	-5,689,269	-5,257,453	-4,858,412	-4,489,659	-4,148,894	-3,833,993

Table 12. Expected number of no AE, minor AE, major AE and No LTBI treatment cases among false positive cases per 100000 household contacts

Test	False Positive Cases	LTBI treatment			No LTBI treatment
		No AE	Minor AE	Major AE	
C-Tb	427	125	4	2	296
TST	14030	4118	129	60	9723
Incremental	13603	3993	125	58	9427
Cost					
C-Tb	489166	279591	20418	19303	169853
TST	13547190	8445388	647632	623391	3830779
Incremental cost	-13058024	-8165797	-627214	-604088	-3660926

The sensitivity of both tests is almost similar, but there is a significant difference in specificity. Therefore, the ability of C-Tb to avert false positive detection is high. The number of adverse events are more by TST test screening compared to C-Tb test, since the number of false positive (14030) detected by TST screening are more which results in over treatment of household contacts which are LTBI negative however tested positive. As a result, saving of INR 1,30,58,024 is incurred by screening by screening with C-Tb and the strategy will prove to be cost saving.

VI. DISCUSSION

The salient finding from our study was that TST test sensitivity is higher than the C-Tb test but when we compare the specificity, C-Tb test is more accurate in identifying people without the disease. When comparing to other screening test to diagnose LTBI using a single, universal cut-off unaffected by BCG vaccination C-Tb test is a simple and convenient skin test. C-Tb test may become a valuable tool for the detection of infection by point-of-care staff with combination of high specificity of the costly and technically complex, IFNγ release assays with the low tech procedure of tuberculin and a single cut-off. It also reports less serious adverse events in tuberculosis patients. This could be a replacement for TST to diagnose LTBI.

IGRA was recommended in high income and upper middle-income countries however, it is expensive to implement on a large scale in settings with limited resources. The C-Tb test was designed to provide high specificity in a field friendly approach. It improves on the specificity of the TST in settings where BCG coverage is high, which suggests that if C-Tb test were available worldwide, it could have a substantial effect on morbidity and health expenditure. C-Tb test also gains the advantage because of its modern and simple manufacturing process when comparing with that for PPD, because the periodic shortages of kits have been seen for the TST and other diagnosing kits, but it occurs very rarely with C-Tb test. C-Tb test provide more accurate treatment guidance in settings being unaffected by BCG vaccination status.

Due to the low sensitivity as compared to TST it was estimated that case detection in terms of true positive, C-Tb test was more costly and less effective. However TST is detecting more false positive reactions that occur in people infected with non-tuberculous mycobacteria and in people with previous BCG vaccination. False positive TST reaction can overcome to some extent by use of interpretation algorithms that adjust the cut-off value for a positive results.

Since its introduction of TST in 1908, the TST has been the standard method to test for LTBI. Subsequently IGRA test was introduced to overcome the issues of the interaction with BCG vaccine and infection non-tuberculous mycobacteria seen with TST. IGRA was the alternative test to the TST for LTBI diagnosis. IGRA was more complex and labour intensive than the TST, and it required laboratory infrastructure and skilled manpower, but interpretation of the results are simple and more objective. It was reported that both TST and IGRA have low positive predictive value for the development of active TB. It was also reported that safety and efficacy of the C-Tb test to diagnose mycobacterium tuberculosis infection compared with established test in the contact tracing was more field friendly and it provide more accurate treatment guideline in setting where TST is commonly used. C-Tb test detects similar number of infection and high concordance with IGRA. In the high TB burden countries and where the BCG coverage also high C-Tb test could be a safe, field friendly tool to identification of LTBI which play very important role in TB control.

With respect to adverse events, it was for similar to that for TST. It was designed to provide high specificity in a field friendly format. It improves on the specificity of the TST in setting where BCG coverage was high. It would be very useful to country like India, where the burden of TB is high and the BCG coverage also was very high.

Overall positivity rate is more in TST, however 76% cases (true positive + true negative) of LTBI are diagnosed accurately. Whereas screening by C-Tb 86% cases are getting detected accurately. Based on the 39%[12] prevalence of LTBI in India, there is an urgent need to detect and treat the LTBI patients as this will lead to increase in breakdown of tuberculosis and increase in transmission if not detected on time. With current scenario of BCG vaccination in India, there are more possibilities to detect false positive cases if screening is done by TST. Alternatively screening by C-Tb test will detect correctly individuals with no infection which will result in avoiding of over treatment cost.

In terms of budget, it is suggested that if C-Tb test were available in large extend for more population coverage, it could have a substantial effect on morbidity and health expenditure. In this study aimed to estimate cost per case LTBI case detection, if we go further can be extrapolated TB prevention, morbidity and mortality due to TB and expenditure to treat TB it would be cost saving strategy for TB control.

Our study has few limitations. This modelling analysis is based on the secondary data available in the literature. Since it is a new tool developed to guide treatment for LTBI in people at risk of developing active TB, there is a paucity of information available on C-Tb test. Sensitivity and specificity was derived for this study using a targeted literature review. A systematic literature review may be performed to estimate more accurate estimates. Expected positive and negative cases were estimated by using the standard formula. This can be validated if the test are compared with the gold standard test. For budget impact analysis household contacts of Tamil Nadu and India were estimated based on the family size reported in the literature.

VI. CONCLUSION

Our hypothetical cohort model (n=100000) shows that, with a background prevalence of 0.39[12] LTBI and considering only true positive cases in account, C-Tb test will yield 2882 tuberculosis active cases at a cost of ₹16,69,87,121 , whereas screening by TST screening will yield 2964 cases at a cost of ₹1,57,23,0,554. The incremental cost effectiveness ratio per case detected (ICER) of TST vs C-Tb is 119128.

Two alternate scenarios of ICER for C-Tb were calculated, first scenario, while TST may be cost saving in terms of identifying true positive cases, still its PPV is affected by prevalent BCG reaction in the population. This could be a limitation in interpreting the cost saving ICER of TST Screening. The number of false positive cases (n = 427) yielded by C-TB is less, whereas the number of false positive cases yielded by TST is 14030. Hence in this scenario, screening by C-Tb would be cost saving, due to less detection of false positive cases as compared to TST which may lead to over detection and/or treatment for false positive cases. The second scenario, if C-Tb unit price is negotiated from ₹304 to a range between ₹204 - ₹124 then it turns cost saving in detecting LTBI in this cohort when compared to TST. Calculating the downstream costs due to over diagnosis and subsequent treatment due to TST vs C-Tb screening must be considered in further analysis.

VII. RECOMMENDATIONS

1. C-Tb test could be prioritised for household LTBI contact tracing in India provided the unit price is negotiated for a 32.89% reduction (INR 204). If procured between INR 204 – INR 124, C-TB is a cost-saving strategy.
2. Bulk purchasing of C-Tb test at this threshold could be a prioritised by the programme in India.

3. TST is not ideal test for screening LTBI in HH contacts of TB patients, as it attributes to a high number of false positive cases due to interference of prior BCG vaccination.
4. The number of false positive cases (n = 427) yielded by C-TB is less, whereas the number of false positive cases yielded by TST is 14030. Hence in this scenario, screening by C-Tb would be cost saving, due to less detection of false positive cases as compared to TST which may lead to over detection and/or treatment for false positive cases.

Annexure-I

Literature review

1. Literature review of IGRA and TST studies in India

S.N	Author	Year	Design	Sample	Population	Methodology	Cost	Specificity	sensitivity	Result	Recommendations
1.	Padmapriyadarsini Chandrasekaran et al[13].,	2018	A prospective cohort study	1048	household contacts	HHCs recruited in 2 cities of India, Pune and Chennai, underwent QFT-GIT (QIAGEN) and TST (PPD SPAN 2TU/5TU). A positive QFT-GIT was defined as a value 0.35 IU/ml and a positive TST as an induration of 5 mm. A secondary outcome of TST induration 10mm was explored.	IGRA- $30	IGRA- 0.52	IGRA- 0.84	Of 1048 HHCs enrolled, 869 had both TST and QFTGIT results available and prevalence of LTBI by QFT-GIT was 54%, by TST was 55%, by either test was 74% and by both tests was 35%.	With the lack of a gold standard and due to varying sensitivity and specificity of the currently available tests, the value of using both tests in combination needs further study particularly in TB endemic countries like India, that are scaling-up TB preventive therapy under programme setting.
2	Kabeer et al[14].,	2010	Case control study		177 adult TB patients and 100 healthy controls	A total of 177 adult TB patients and 100 healthy controls were included for this study. QuantiFERON-TB Gold In-tube (QFT-IT)		QFT- 55 TST- 75.5	QFT- 90.6 TST- 68.9	QFT-IT and IP-10 were highly sensitive in detecting active TB cases. The combination with TST improved the sensitivity of QFT-IT	QFT-IT and IP-10 were highly sensitive in detecting active TB cases. The combination with TST improved the

S.N	Author	Year	Design	Sample	Population	Methodology	Cost	Specificity	sensitivity	Result	Recommendations
						method was used to analyze the sensitivity and specificity of IGRA				and IP-10 significantly. Although the higher sensitivity of combination of QFT-IT/IP-10 and TST may be useful in active TB diagnosis, they are limited by their poor specificity due to the high prevalence of latent TB in our settings.	sensitivity of QFT-IT and IP-10 significantly. Although the higher sensitivity of combination of QFT-IT/IP-10 and TST may be useful in active TB diagnosis, they are limited by their poor specificity due to the high prevalence of latent TB in our settings
3	M. Pai et al[15].,	2007	cohort study	60	Tuberculosis patients	The study measured T-cell responses to TB specific antigens in 60 Indian patients with microbiologically confirmed active pulmonary tuberculosis, before, during, and after TB treatment		QFT-73–81%		At baseline, 44 of 60 (73%) patients were positive by QFT-G. At the second timepoint, 38 of 47 (81%) patients were positive. At treatment completion, 31 of 39 (79%) patients were positive. Changes in IFN-γ responses over time were highly inconsistent - some individuals showed increases, while others	Our data suggest that the QFT-G assay has modest sensitivity in patients with moderate to advanced pulmonary disease, but our results do not show a clear correlation between antigen burden and T-cell responses

S.N	Author	Year	Design	Sample	Population	Methodology	Cost	Specificity	sensitivity	Result	Recommendations
										showed decreases or no changes	
4	Kristen M. Little et al[16].,	2015	Decision analytic model	one million	Hypothetical cohort	A decision analytic model to estimate the incremental cost and effectiveness of IGRAs for the diagnosis of active TB in India. We compared a reference scenario of clinical examination and non-microbiological tests against scenarios in which clinical diagnosis was augmented by the addition of either sputum smear microscopy, IGRA, or Xpert MTB/RIF.	IGRA- $30	IGRA – 0.52	IGRA - 0.84	Relative to sputum smear microscopy, use of IGRA for active TB resulted in 23,700 (95% uncertainty range, UR: 3,800 – 38,300) additional true-positive diagnoses, but at the expense of 315,700 (95% UR: 118,300 – 388,400) additional false-positive diagnoses and an incremental cost of US$49.3 million (95% UR: $34.9 – $58.0 million) (2.9 billion Indian Rupees).	Using IGRAs for diagnosis of active TB in a setting like India results in tremendous overtreatment of people without TB, and substantial incremental cost with little gain in health.
5	S. Sudharshan et al[17].,	2012		50	tubercular uveitis patients	All cases of suspected tubercular uveitis seen at a tertiary care uveitis clinic between October 2006 and June 2008 in whom the QFT-G test was performed were included.		QFT-G- 67–98 %	QFT-G- 80 to 95 %	QFT-G test is very useful in the diagnosis and management of suspected ocular TB. It was found to be very sensitive in identifying latent TB patients who, upon treatment, had a	

S.N	Author	Year	Design	Sample	Population	Methodology	Cost	Specificity	sensitivity	Result	Recommendations
										significantly reduced frequency of recurrences. It was more sensitive than the Mantoux test and is not significantly affected by previous treatment with systemic steroids or immunosuppressive.	
6	Kalpana Babu et al[18].,	2013	Cross-sectional Survey	37	Healthcare workers	A survey was distributed among 46 uveitis specialists, rheumatologists, and pulmonologists with a minimum of 2 years of experience in the management of tuberculosis, in order to restrict the respondents to specialists who have used this test in their practice in the diagnosis of tuberculosis	IGRA- ₹ 2000				
7	SenbagavalliPrakash Babu et al[19].,	2022	A prospective cohort study	139	Female household contacts	Participants are injected with TST, purified protein derivative (PPD)] and				The prevalence of LTBI was found to be 69% (either TST or IGRA positive). Positivity rate	The study was found that IGRA is more consistent to diagnosis of latent

S.N	Author	Year	Design	Sample	Population	Methodology	Cost	Specificity	sensitivity	Result	Recommendations
						IGRA [QuantiFERON-TB Gold Plus kit (QFT-Plus)]. All the household contacts were followed-up for one year for incident TB cases.				of IGRA was higher when compared to that of TST. Out of 139 participants, 68 (49%) tested positive for TST, 80 (57.6%) tested positive for IGRA and 52 (37.4%) tested positive for both.	tuberculosis infection than the TST. Such studies can also be performed in varied settings among different populations which would help us to improve the diagnosis of LTBI and consequently help in TB control.
8	Alok Kumar Mantri et al[20].	2021	A prospective observational analysis	257	Inflammatory Bowel Disease Patients and healthy individuals	Both TST and IGRA were performed in consecutive patients diagnosed with IBD (131 patients) and in 126 healthy individuals. Both tests were performed on the same day. LTBI diagnosis was considered if any one of TST or IGRA was found to be positive				Out of a total of 257 participants, 66 (25.7%) were detected to have LTBI. 38 (29%) of the IBD patients and 28 (22%) of the control subjects had LTBI. The mean TST in IBD patients was 5.9 (± 1.6); in IBD patients with positive TST, mean TST was -5.9 (±1.8), whereas it was 5.8 mm (±1.6) in control subjects (p value = NS)	TST positivity was slightly higher than IGRA (23.3% vs. 19%).
9	Madhukar Pai et al[21].,	2005	A cross-sectional	726	health care workers	Health care workers with no history of				A large proportion of the health care workers were	Our study showed high latent

S.N	Author	Year	Design	Sample	Population	Methodology	Cost	Specificity	sensitivity	Result	Recommendations
			comparison study			active tuberculosis were conducted from January to May 2004, at a rural medical school in India. A total of 493 (68%) of the health care workers had direct contact with patients with tuberculosis and 514 (71%) had BCG vaccine scars.				latently infected; 360 (50%) were positive by either TST or IFN- assay, and 226 (31%) were positive by both tests. The prevalence estimates of TST and IFN- assay positivity were comparable (41%; 95% confidence interval [CI], 38%-45% and 40%; 95% CI, 37%-43%, respectively). Agreement between the tests was high (81.4%; =0.61; 95% CI, 0.56-0.67)	tuberculosis infection prevalence in Indian health care workers, high agreement between TST and IFN- assay, and similar association between positive test results and risk factors. Although TST and IFN- assay appear comparable in this population, they have different performance and operational characteristics.
10	Mohammad Javad Nasiri et al[22].,	2019	Systematic review					TST-86% QFT-G-89%	TST-46% QFT-G-58%		IGRAs were more sensitive and specific than the TST with regard to the diagnosis of LTBI in the transplant candidates. They have added value and can be complementary to TST.

S.N	Author	Year	Design	Sample	Population	Methodology	Cost	Specificity	sensitivity	Result	Recommendations
11	Shekhar Neema et al[23].,	2022	Cross sectional study	75	chronic plaque psoriasis patients	It was a diagnostic study conducted in a tertiary care centre during the study period from January 20 to December 20. Patients more than 18 years of age with chronic plaque psoriasis planned for systemic therapy were included.		TST-77.3% QFT-95-100%	TST-68.8% QFT-76%-95%	ROC curve was plotted for the absolute value of TST in mm considering IGRA as the gold standard. The area under the curve was 0.805. For the TST positivity cut-off of 10 and 15 mm, specificity was 77.3% and 95.5%, respectively; the sensitivity was 68.8% irrespective of the cut-off value.	Use of both TST and IGRA rather than two-step testing (TST followed by IGRA) or IGRA alone for the diagnosis of LTBI, especially in patients with a high risk of reactivation.

2. Literature review of cost-effectiveness studies of IGRA and TST for other countries

S.N	Author	Year	Design	Country	Sample	Population	Strategies	Per test cost	Result	Recommendations
1.	Sofia Sousa et al[24].,	2021	CEA	Portugal	499	Household contacts	Two strategies 1.IGRA 2.TST+IGRA	IGRA-€12.83 TST+IGRA-€49.74	The calculated ICER was €106 per LTBI diagnosis, representing increased effectiveness with a slightly increased cost of IGRA screening strategy.	LTBI screening with IGRA alone is more cost-effective
2.	A.Kowda et al[25].,	2015	CEA	Japan	1264	Healthcare workers	Six strategies: 1. TST 2. QuantiFERON-TB Gold In-Tube (QFT) 3. T-SPOT.TB (T-SPOT) 4. TST followed by QFT 5. TST followed by T-SPOT 6. CXR	1.TST- $15.4 2.QFT-$60.6 3.T-SPOT- $ 60.6	QFT was the most cost-effective strategy at the 'willingness to pay' level of US$ 50,000/QALYs gained	Systematic TB screening using QFT is cost-effective for screening HCWs.
3.	S. Deuffic Burban et al[26].,	2009	CEA	France	15000	Simulated adults in close contatct with tuberculosis	Four strategies 1. No testing 2. TST 3. QFT 4. TST+QFT	TST test – €2.16 QFT test- €40.50	TST had higher costs and lower efficacy than QFT; TST+QFT was associated with an ICER of €560 per year of life gained (YLG) compared to no testing, and QFT was associated with an ICER of €730/ YLG compared to TST+QFT.	QFT is more effective and cost-effective than TST+ QFT under a wide range of realistic test performance scenarios.
4.	F. Marra et al[27].,	2008	CEA	Canada		Household contacts	Three screening strategies 1. TST alone 2. QFT-G alone	TST test – $25.41 QFT test- $45.32	The most economically attractive strategy was to administer QFT-G in BCG-vaccinated contacts, and to reserve TST for all others	Selected use of QFT-G appears to be cost-effective.

S.N	Author	Year	Design	Country	Sample	Population	Strategies	Per test cost	Result	Recommendations
							3. Sequential screening of TST then QFT-G were evaluated.		(INMB CA$3.70/ contact). The least cost-effective strategy was QFT-G for all contacts, which resulted in an INMB of CA$–11.50 per contact.	
5.	Seif Al Abri et al[28].,	2020	CEA	Oman		Migrants arriving in Oman	Seven strategies assessed: 1. QFT-Plus with 6H 2. QFT-Plus with 3HP 3. QFT-Plus with 4R 4. TST with 6H 5. TST with 3HP and directly observed therapy (DOT) 6. TST with 4R 7. CXR	1.QFT-Plus with 6H – $1430 2. QFT-Plus with 3HP-$ 1480 3. QFT-Plus with 4R- $1420 4. TST with 6H- $1872 5. TST with 3HP (DOT)-$ 1951 6 .TST with 4R- 41872 7. CXR - $3277	In the base-case analysis, QFT-Plus with 3HP (cost, USD 1480; 28.28 QALYs; ICER, USD 2915 per QALY gained) was more cost-effective than the other TB strategies. The CXR strategy was the least cost-effective (cost, USD 3278; 26.84 QALYs).	IGRA testing followed by 3 months of preventive treatment with rifapentine/ isoniazid (3HP) was the most cost-effective intervention.
6.	Rafaela Borge Loureiro et al[29].,	2019	CEA	Brazil	10,000	Healthcare workers	five strategies: 1. tuberculin skin testing using ≥5 mm cut-off	1. QFT-GIT test kit - $33.88 2. TST kit- PPD RT23	The most cost-effective strategy was the tuberculin skin test considering ≥10mm cut-off. The isolated use of the	TST constitutes the LTBI screening strategy as cost effective in the Brazilian scene, even after a significant reduction in QFT-GIT costs

S.N	Author	Year	Design	Country	Sample	Population	Strategies	Per test cost	Result	Recommendations
							2. tuberculin skin testing≥10 mm cut-off 3. QuantiFERON-TB Gold in-Tube 4. tuberculin skin testing using ≥5 mm cut-off confirmed by QuantiFERON-TB Gold In-Tube if TST positive 5. tuberculin skin testing using ≥10 mm cut-off confirmed by QuantiFERON-TB Gold In-Tube if TST positive.	2 UT/1.5 ml - $4.14	QuantiFERON-TB Gold In-Tube revealed the strategy of lower efficiency with incremental cost-effectiveness ratio (ICER) of US$ 146.05 for each HCW correctly classified by the test.	and despite the high number of patients undergoing treatment for LTBI.
7.	Marie A. de Perio et al[30].,	2009	CEA	Cincinnati		Healthcare workers	Three Strategies: 1. QFT-G 2. QFT-GIT 3. TST.	1.TST- $ 12.48 2. QFT-G- $ 34.78 3. QFT-GIT $ 31.18	Both IGRAs were more effective and less costly than the TST, whether or not the HCW had been vaccinated with BCG previously. The incremental cost-effectiveness ratio of the QFT-G compared with the QFT-GIT was $14 092/QALY for non–BCG-vaccinated HCWs and $103 047/QALY for BCG-vaccinated HCWs	QFT-G and QFT-GIT are clinically and economically worthwhile alternatives to the TST in testing HCWs for LTBI, as both IGRA strategies are more effective and less costly than the TST strategy.

S.N	Author	Year	Design	Country	Sample	Population	Strategies	Per test cost	Result	Recommendations
8.	A B Hardy et al[31].,	2009	CEA	UK	280	immigrants	Strategies included the 1. QFT 2. TST. 3. CXR	1. QFT- £25.67 2. TST- £13.69 3. CXR - £23.24	Using the NICE approach, the cost of screening these 280 immigrants would be £13 346.75 (£47.67 per immigrant) and would identify 83 cases of latent TB infection (LTBI). Using first-line QFT followed by CXR the cost was £9781.82 (£34.94 per immigrant) and identified 105 cases of LTBI. The cost to identify one case of LTBI following NICE guidelines would be £160.81 and using the present protocol was £93.16.	QFT blood testing followed by CXR is feasible for TB screening, cheaper than screening using the NICE guideline and identifies more cases of LTBI.
9.	Ricardo E. Stefen et al[32].,	2020	CEA	Brazil	1000	Close contacts	four strategies 1. Diaskintest 2. EC skin test 3. QFT-Plus 4. TST PPD RT 23	1. Diaskintest- $1.43 2. EC skin test-$ 6 3. QFT-Plus- $15.90 4. TST PPD RT 23- $7.26	The Diaskintest was cost saving at US $41 with an incremental gain of 0.03 QALYs, or US $1360 per QALY (95% UC $978–1948). Te EC and QFT-Plus strategies were also cost saving at US $1283 (95% UC 904–2746) and US$771 (95% UC US $339–1336) per QALY, respectively.	The Diaskintest was dominant over all other examined strategies. The cost saving estimate per QALY was US $1375. In sensitivity analyses, the Diaskintest and other newer tests remained cost-saving compared to TST
10	Ricardo Ewbank Steffen et al[33].,	2013	CEA	Brazil	1,000	close contacts	Three strategies ne, T, the only IGRA T-GIT,	1. QFT-GIT test kit - $42.95	TST was the most cost-effective strategy (US$ 16,021/averted case, followed by TST/QFT-GIT (US$ 18,259) and QFT-GIT	QFT-Plus is cost saving when compared to TST. Having additional options for the diagnosis of latent tuberculosis infection should contribute to

S.N	Author	Year	Design	Country	Sample	Population	Strategies	Per test cost	Result	Recommendations
								2. TST Kit (PPD RT23 2UT/01 ml)- $ 4.90	alone (US$ 22,211). ICER was US$227,977/averted case for the QFT-GIT strategy. The TST/QFT-GIT strategy was dominated.	eliminating the PPD RT 23 shortages.
11	Abriana Tasillo et al[34].,	2017	CEA	United States		Non-US born populations: with no comorbidities, with diabetes, with HIV, and with ESRD	We modeled 5 testing strategies: 1. no testing 2. TST 3. IGRA, 4. Confirm positive (patients with a positive TST given IGRA, with both positive resulting in LTBI diagnosis) 5. Confirm negative (patients with a negative IGRA given TST, with either positive resulting in LTBI diagnosis).	1. IGRA-$ 84.350 2. TST- $ 7.870	IGRA was likely cost-effective at $83 000/QALY; patients with diabetes, both confirm positive ($53 000/QALY) and IGRA ($120 000/QALY) were likely cost-effective; patients with HIV, confirm negative was clearly preferred ($63 000/QALY); and patients with ESRD, no testing was cost-effective. Increased LTBI prevalence and reduced return for TST reading improved IGRA's relative performance. In 10 000 probabilistic simulations among non-US born patients with no comorbidities, with diabetes, and with HIV, some form of testing was virtually always cost-effective	A single test with improved characteristics and a lower cost than that of IGRA could reduce investment needed in terms of patient and provider time and cost and make universal testing for non–US born patients even more attractive.
12	Anil Pooran et al.[35].,	2010	CEA	UK		close contacts	Strategies TST alone,	T-SPOT.TB kit- £55.00	Examining costs alone, the TST/IGRA dual screening strategies (TST/T-	In both versions of the IGRA, dual screening was more cost effective than single screening;

S.N	Author	Year	Design	Country	Sample	Population	Strategies	Per test cost	Result	Recommendations
							the T-SPOT.TB assay alone TST followed by T-SPOT.TB assay when TST was positive (TST/T-SPOT.TB) Quantiferon-TB-Gold-In-Tube (QFT-GIT) alone TST followed by QFT-GIT when TST was positive (TST/QFT-GIT).	TST- £16.14 QFT-GIT- £45.00	SPOT.TB and TST/QFT-GIT; £162,387 and £157,048 per 1000 contacts, respectively) cost less than their single strategy counterparts (T-SPOT.TB and QFT-GIT; £203,983 and £202,921 per 1000 contacts) which have higher IGRA test costs and greater numbers of persons undergoing LTBI treatment.	TST/ T-SPOT.TB was £2,506 better than the T-SPOT.TB single strategy and TST/QFT-GIT was £4,351 better than screening with QFT-GIT only.
13	Ank E. Nijhawan et al[36].	2016	Prospective pilot study	Dallas, Texas, USA	529	Inmates in jail	(1) estimate the LTBI prevalence based on TST and an IGRA test (QFT-GIT) results in individuals entering a large county jail in Dallas, Texas and (2) measure the discordance of TST and QFT-GIT results in this setting in order to achieve our overarching aim (3) to use prospective utilization data to compare costs between the TST and QFT-GIT test for LTBI screening.	TST - $8 QFT-GIT-$ $37	It costs $23.27 more per inmate per year to screen with QFT-GIT than TST in this population, though the cost per LTBI case detected was nearly three times higher for TST than QFT-GIT.	Further research is needed to determine the long-term performance of IGRA testing in the correctional setting and the public health implications of pairing QFT-GIT screening with other tests for communicable diseases.

S.N	Author	Year	Design	Country	Sample	Population	Strategies	Per test cost	Result	Recommendations
14	Albert Nienhaus et al[37].	2011	Systematic review				Structured review and critical appraisal of the methods used for the model-based cost-effectiveness analysis of TB screening programmes		All 13 studies observed a decrease in costs when the IGRAs were used. Six studies compared the use of an IGRA as a test to confirm a positive TST (TST/IGRA strategy) to the use of an IGRA only strategy.	The available studies on cost-effectiveness provide strong evidence in support of the use of IGRAs in screening risk groups such as HCWs, immigrants from high-incidence countries and close contacts. So far, only two studies provide evidence that the IGRA-only screening strategy is more cost-effective.
15	J.R.Campbell et al[38].	2015	Systematic review	Multi-centric			A literature search of MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Web of Knowledge, and PubMed was performed from database start to November 2014. Of 415 studies identified, ultimately eight studies were included in the review.		Screening of adult immigrants was found to be cost effective with a TST in one study, but moderately cost effective with an IGRA in another study; screening immigrants arriving more than 5 years prior with an IGRA was moderately cost effective until 44 years of age (n = 1). Screening HIV-positive patients was highly cost effective with a TST (n = 1) and moderately cost effective with an IGRA (n = 1). Screening in those with renal diseases (n = 2) and diabetes (n = 1) was not cost effective.	Despite this, some cautionary recommendations emerged: screening HIV patients with a TST is highly cost effective, while screening adult immigrants with an IGRA is moderately cost effective

3. **Literature review of C-Tb skin test**

S.N	Author	Year	Study design	Study area	Sample size	Methodology	Result	Recommendations
1.	Soren T. Hoff et al[39]	2015	Case-control study	Cape Town, South Africa	253 patients	C-Tb and TST were randomly administered in a double-blinded fashion to one or the other forearm in 253 patients with active TB with or without HIV co-infection. QFT-GIT testing was performed prior to skin testing.	C-Tb has similar sensitivity compared with QFT-GIT for the diagnosis of M. tuberculosis infection.	Further studies in different settings are required to validate the proposed 5 mm cut-point.
2.	Morten Ruhwald et al[5]	2017	Randomised controlled trial	Spain	979 participants	Negative controls, close contacts, occasional contacts, and patients with active pulmonary tuberculosis were enrolled at 13 centres in Spain.	A strong positive trend towards C-Tb test positivity with increasing risk of infection, from 3% in negative controls to 16% in occasional contacts, to 43% in close contacts. C-Tb and QFT results were concordant in 785 (94%) of 834 participants aged 5 years and older, and results did not diff er signifi cantly between	C-Tb delivered IGRA-like results in a field-friendly format. Being unaffected by BCG vaccination status, the C-Tb skin test might provide more accurate treatment guidance in settings where the TST is commonly used.

S.N	Author	Year	Study design	Study area	Sample size	Methodology	Result	Recommendations
							exposure groups. The safety profile of C-Tb was similar to that for the TST.	
3	Henrik Aggerbeck et al[40]	2013	Randomised Clinical Trial		147 participant for skin test. 38 TB patients for Dose finding trial included.	In a dose finding phase I trial 0.01 or 0.1 mg preserved and unpreserved C-Tb was injected by Mantoux technique in 38 patients with active tuberculosis and induration responses measured. In a phase II specificity trial in 151 uninfected, BCG vaccinated participants 0.1 mg C-Tb was compared to 2 TU PPD.	The specificity of C-Tb was 99.3% (95% CI 96–100%) regarding indurations $5 mm as a positive outcome. This was higher than the specificity of PPD (63% using a cut-off of 5 mm or 92% using a cut-off of 15 mm to adjust for non-specific BCG responses).	C-Tb offers a simple and convenient skin test to diagnose M. tuberculosis infection using a single, universal cut off unaffected by BCG vaccination.
4	H. Aggerbeck et al[4]	2018	Randomised Clinical Trial	South Africa	456 patients with active TB	Adult patients with active TB were randomised to receive only C-Tb, only PPD, or concomitant injection of both C-Tb and PPD using the Mantoux technique.	In patients with active TB, C-Tb sensitivity (78%) was similar to PPD (81%) and QFT (84%; excluding 82/429 [19%] indeterminate results).	In patients with active TB, there was no interaction between C-Tb and PPD during the concomitant injection of both agents.

S.N	Author	Year	Study design	Study area	Sample size	Methodology	Result	Recommendations
						Indurations were read after 48–72 hours.		

Annexure-II

Figure 1. Per test cost for TST

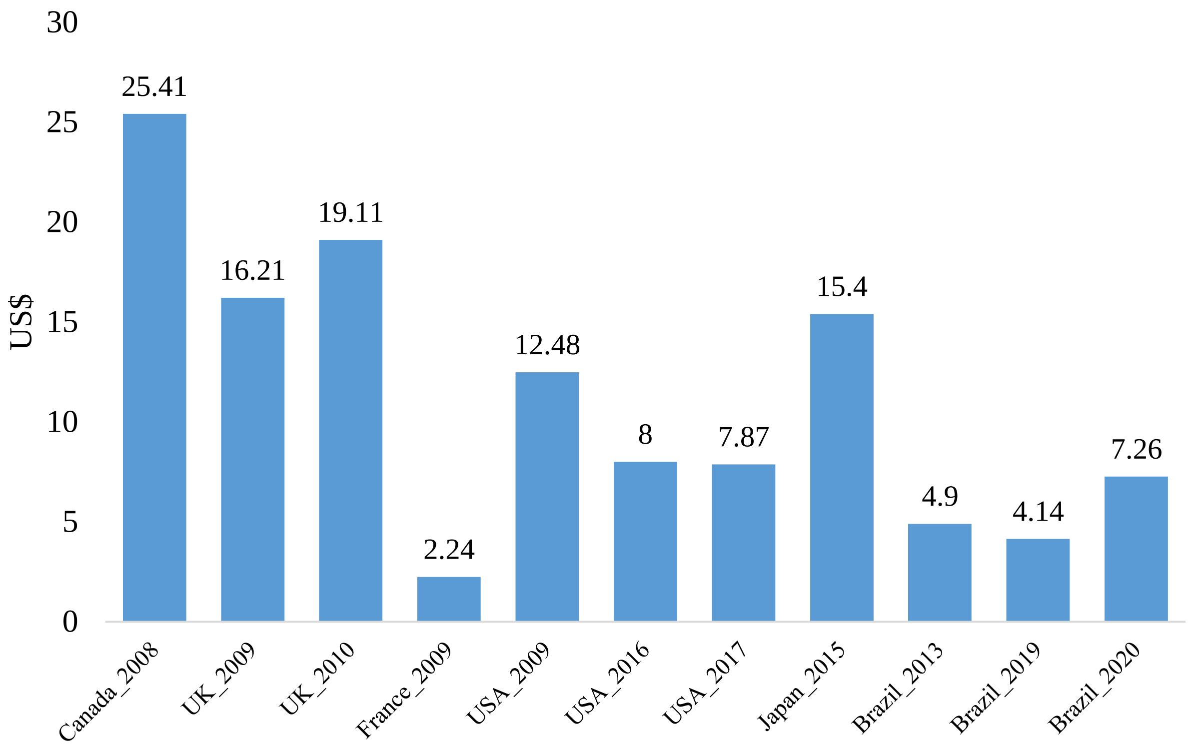


Figure 2. Per test cost for TST (2021)

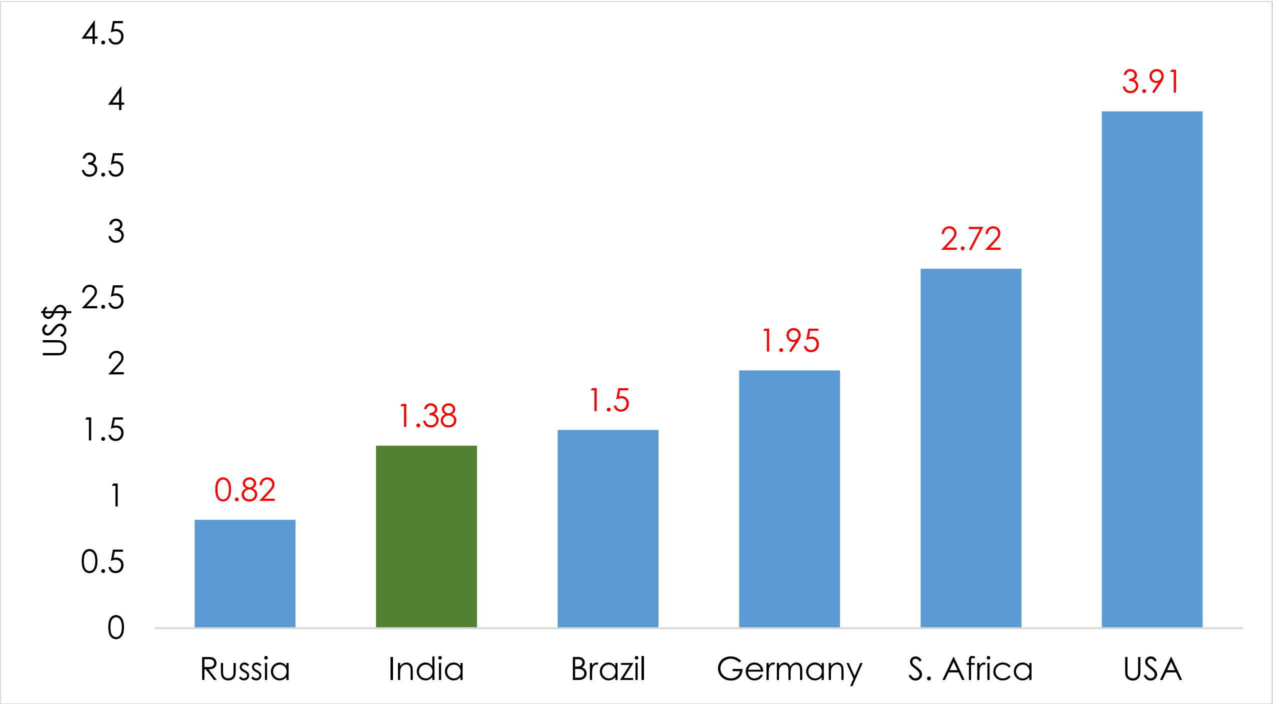


Figure 3. Per test cost for IGRA

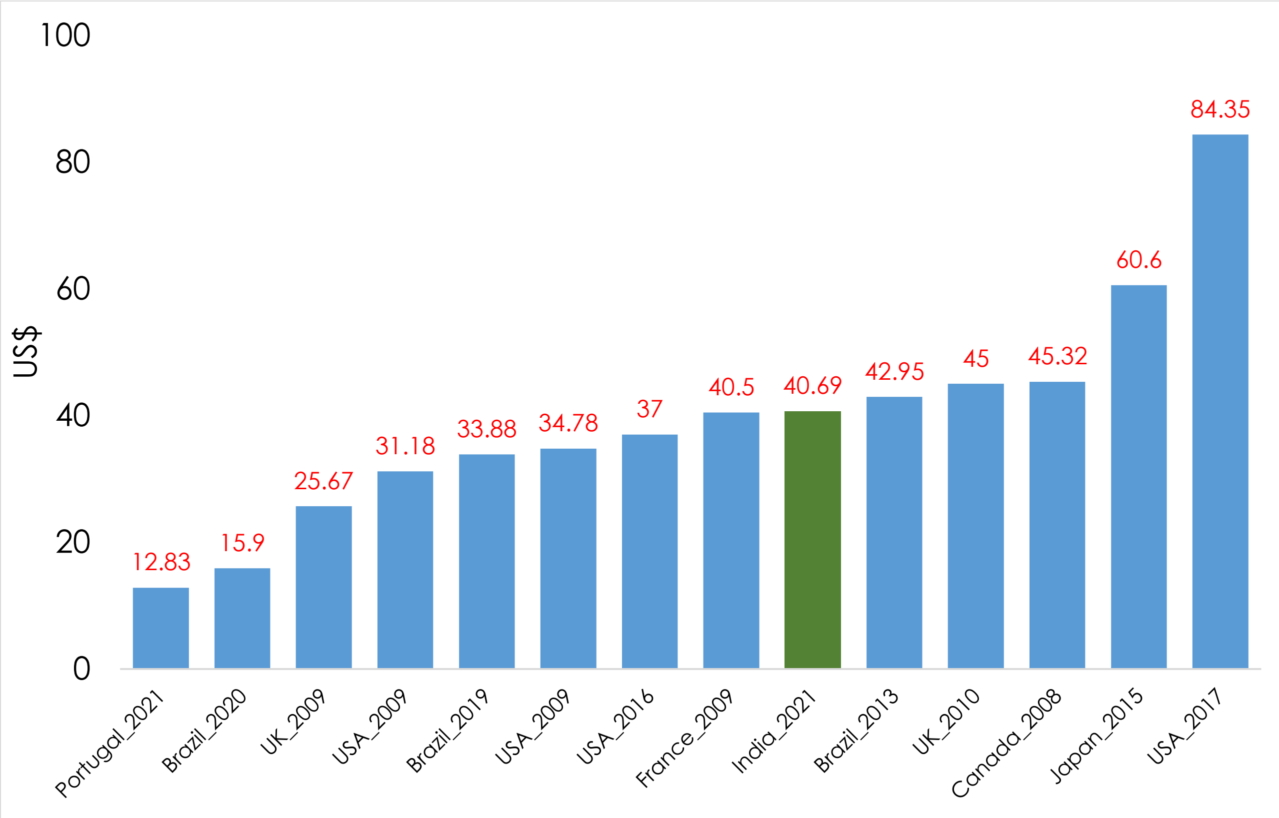


Table 1. Expected number of true positive, false positive, false negative and true negative cases per 100000 household contacts

Test	Total Number of Case Tested	True Positive	False Positive	False Negative	True Negative
C-Tb	100000	28821	427	10179	60573
TST	100000	29640	14030	9360	46970

Table-7 shows the expected number of true positive, false positive, true negative and false negative cases after screening the cohort of 100000 household contacts with each test. It was calculated based on the formula which was derived from the sensitivity and specificity of each test and the prevalence of LTBI. The number of true positive cases are more when the cohort is tested by TST compared to C-Tb test (29640 vs 28821). Whereas the number of true negative cases (60573) are more by C-Tb test than TST (46970) which denotes that C-Tb test is correctly detecting the negative cases than TST.

Table 2. Proportion of the true positive and false positive cases from the total positive cases

Test	Number of positive cases	True Positive	False Positive	Proportion (TN)	Proportion (FP)
C-Tb	29248	28821	427	0.99	0.01
TST	43670	29640	14030	0.68	0.32

Table-1 shows that when cohort is screened, true positive cases are more in TST than C-Tb test which signifies that TST is better than C-Tb test. When we consider the proportion of true positive cases from total positive cases by C-Tb test the proportion is 0.99 whereas by TST it is 0.68, which implies that the C-Tb test has ability to correctly identify household with LTBI (Table-2).

Table 3. Proportion of the true negative and false negative cases from the total negative cases

Test	Number of cases	False Negative	True Negative	Proportion (FN)	Proportion (TN)
C-Tb	70752	10179	60573	0.14	0.86
TST	56330	9360	46970	0.17	0.83

Table-1 illustrates that when the cohort is screened, true negative cases are more by C-Tb test than TST, however in Table-3 the proportion (0.86 vs 0.83) of true negative cases from negative cases differs, which signifies that C-Tb test has the ability to correctly identify household contacts without the LTBI

Table 4. Analysis of costs of each screening strategy for 100000 household contacts (at ₹304)

Test	True Positive	False Positive	True Negative	False Negative	Total
C-Tb	28821	427	10179	60573	100000
TST	29640	14030	9360	46970	100000
Total	85371	33367	31629	149633	300000
Screening Cost					
C-Tb	16543254	245098	34768902	5842746	57400000
TST	11678160	5527820	18506180	3687840	39400000
Treatment Cost of LTBI					
C-Tb	14661214	217214	0	0	14878428
TST	15077838	7137047	0	0	22214885
Adverse Effect Cost					
C-Tb	1812505	26853	0	0	1839358
TST	1864010	882323	0	0	2746334
Diagnosis Cost of TB					
C-Tb	45940674	0	0	16225326	62166000
TST	47246160	0	0	14919840	62166000
Treatment Cost for active TB					
C-Tb	22689765	0	0	8013570	30703335
TST	23334535	0	0	7368800	30703335
Total Cost					
C-Tb	101647411	489166	34768902	30081642	166987121
TST	99200703	13547190	18506180	25976480	157230554

Table 5. Budget Impact Analysis for India

Year / Test	BIA with the cost of ₹ 304 for C-Tb (Number of household contacts = 11.35 million)					
	Number of True Positive Cases					
	2022	**2023**	**2024**	**2025**	**2026**	**2027**
C-Tb	3,271,184	3,022,901	2,793,463	2,581,439	2,385,508	2,204,447
TST	3,364,140	3,108,802	2,872,844	2,654,795	2,453,296	2,267,091
Screening Cost (₹)						
C-Tb	651,49,00,000	602,04,19,090	556,34,69,281	5,141,201,963	4,750,984,734	4,390,384,992
TST	4,471,900,000	4,132,482,790	3,818,827,346	3,528,978,351	3,261,128,894	3,013,609,211
Treatment Cost of LTBI (₹)						
C-Tb	1,664,047,775	1,537,746,549	1,421,031,586	1,313,175,289	1,213,505,284	1,121,400,233
TST	1,711,334,654	1,581,444,354	1,461,412,727	1,350,491,501	1,247,989,196	1,153,266,816
Adverse Effect Cost (₹)						

C-Tb	205,719,287	190,105,193	175,676,209	162,342,385	150,020,598	138,634,034
TST	211,565,167	195,507,371	180,668,361	166,955,632	154,283,700	142,573,567
Diagnosis Cost of TB (₹)						
C-Tb	5,214,266,499	4,818,503,672	4,452,779,243	4,114,813,298	3,802,498,969	3,513,889,297
TST	5,362,439,160	4,955,430,028	4,579,312,889	4,231,743,040	3,910,553,744	3,613,742,714
Treatment Cost for active TB (₹)						
C-Tb	2,575,288,278	2,379,823,898	2,199,195,264	2,032,276,343	1,878,026,569	1,735,484,352
TST	2,648,469,677	2,447,450,829	2,261,689,311	2,090,027,092	1,931,394,036	1,784,801,228
Total Cost (₹)						
C-Tb	16,174,221,839	14,946,598,402	13,812,151,583	12,763,809,278	11,795,036,154	10,899,792,910
TST	14,405,708,658	13,312,315,371	12,301,910,634	11,368,195,617	10,505,349,569	9,707,993,537
Budget Impact (C-Tb vs TST	1,768,513,182	1,634,283,031	1,510,240,949	1,395,613,661	1,289,686,584	1,191,799,373

Table-5 shows the budget impact of C-Tb and TST tests for total predicted household contacts in India for the five years. For the year 2023, it is expected that 3 million of true positive LTBI cases will be yielded by screening 11.35 million household contacts and it will cost ₹6020 million, by C-Tb at the unit cost of ₹304. It was also estimated that to treat by the preventive therapy the cost will be ₹1537 million. If screened 11.35 million by TST it will cost ₹4132 million to detect 3.1 million of true positive LTBI cases and to treat by the preventive therapy the cost will be ₹1581 million. It is estimated that more active TB cases can be prevented by implementing C-Tb as compared to TST (9296 additional TB cases prevented). For this we need to spend ₹1634 million addition budget for India. **If C-Tb kit cost reduced from ₹304 to ₹124, it is estimated that to detect and treat 3 million of true positive LTBI cases will be cost saving of ₹253 million in 2023 for India (**Table-5.1).

Table 5.1. Budget Impact Analysis for India

Test	**BIA with the cost of ₹124 for C-Tb (Number of household contacts = 11.35 million)**					
	Number of True Positive Cases					
Year / Test	2022	2023	2024	2025	2026	2027
C-Tb	32,71,184	30,22,901	27,93,463	25,81,439	23,85,508	22,04,447
TST	33,64,140	31,08,802	28,72,844	26,54,795	24,53,296	22,67,091
Screening Cost (₹)						
C-Tb	4,47,19,00,000	4,13,24,82,790	3,81,88,27,346	3,52,89,78,351	3,26,11,28,894	3,01,36,09,211
TST	4,47,19,00,000	4,13,24,82,790	3,81,88,27,346	3,52,89,78,351	3,26,11,28,894	3,01,36,09,211
Treatment Cost of LTBI (₹)						
C-Tb	1,66,40,47,775	1,53,77,46,549	1,42,10,31,586	1,31,31,75,289	1,21,35,05,284	1,12,14,00,233
TST	1,71,13,34,654	1,58,14,44,354	1,46,14,12,727	1,35,04,91,501	1,24,79,89,196	1,15,32,66,816
Adverse Effect Cost (₹)						

C-Tb	20,57,19,287	19,01,05,193	17,56,76,209	16,23,42,385	15,00,20,598	13,86,34,034
TST	21,15,65,167	19,55,07,371	18,06,68,361	16,69,55,632	15,42,83,700	14,25,73,567
Diagnosis Cost of TB (₹)						
C-Tb	5,21,42,66,499	4,81,85,03,672	4,45,27,79,243	4,11,48,13,298	3,80,24,98,969	3,51,38,89,297
TST	5,36,24,39,160	4,95,54,30,028	4,57,93,12,889	4,23,17,43,040	3,91,05,53,744	3,61,37,42,714
Treatment Cost for active TB (₹)						
C-Tb	2,57,52,88,278	2,37,98,23,898	2,19,91,95,264	2,03,22,76,343	1,87,80,26,569	1,73,54,84,352
TST	2,64,84,69,677	2,44,74,50,829	2,26,16,89,311	2,09,00,27,092	1,93,13,94,036	1,78,48,01,228
Total Cost (₹)						
C-Tb	14,13,12,21,839	13,05,86,62,102	12,06,75,09,648	11,15,15,85,666	10,30,51,80,314	9,52,30,17,128
TST	14,40,57,08,658	13,31,23,15,371	12,30,19,10,634	11,36,81,95,617	10,50,53,49,569	9,70,79,93,537
Budget Impact (C-Tb VS TST	-27,44,86,818	-25,36,53,269	-23,44,00,986	-21,66,09,951	-20,01,69,256	-18,49,76,409

Table 6. Budget Impact Analysis for Tamil Nadu

Year / Test	BIA with the cost of ₹ 304 for C-Tb (N= 173109)					
	Number of True Positive Cases					
	2022	2023	2024	2025	2026	2027
C-Tb	67,802	62,655	57,900	53,505	49,444	45,691
TST	69,728	64,436	59,545	55,026	50,849	46,990
Screening Cost (₹)						
C-Tb	99,364,543	91,822,774	84,853,426	78,413,051	72,461,500	66,961,672
TST	68,204,930	63,028,176	58,244,337	53,823,592	49,738,382	45,963,238
Treatment Cost of LTBI (₹)						
C-Tb	34,490,599	31,872,763	29,453,620	27,218,090	25,152,237	23,243,182
TST	35,470,711	32,778,484	30,290,597	27,991,541	25,866,983	23,903,679
Adverse Event Cost (₹)						

C-Tb	4,263,929	3,940,297	3,641,228	3,364,859	3,109,466	2,873,458
TST	4,385,096	4,052,267	3,744,700	3,460,477	3,197,827	2,955,112
Diagnosis Cost of TB (₹)						
C-Tb	108,075,729	99,872,781	92,292,437	85,287,441	78,814,124	72,832,132
TST	111,146,893	102,710,844	94,915,091	87,711,035	81,053,768	74,901,787
Treatment Cost for active TB (₹)						
C-Tb	53,377,816	49,326,440	45,582,563	42,122,846	38,925,722	35,971,260
TST	54,894,642	50,728,138	46,877,873	43,319,842	40,031,866	36,993,447
Total Cost (₹)						
C-Tb	299,572,616	276,835,054	255,823,274	236,406,287	218,463,050	201,881,704
TST	274,102,272	253,297,909	234,072,598	216,306,488	199,888,825	184,717,263
Budget Impact (C-Tb VS TST)	25,470,344	23,537,145	21,750,676	20,099,799	18,574,225	17,164,441

Table-16 shows the budget impact of implementation C-Tb as compared to TST in Tamil Nadu. For the year 2023, it is estimated that ₹91 million has to be spent to detect 62,655 true positive cases by screening 173109 household contacts by C-Tb at the unit cost of ₹ 304 and ₹ 31 million for treating the LTBI. **If C-Tb kit cost reduced from ₹304 to ₹124, it is estimated that to detect and treat around 62,655 of true positive LTBI cases will save ₹5,257,453 in 2023** (Table 6.1).

Table 6.1. Budget Impact Analysis for Tamil Nadu

Year / Test	BIA with the cost of ₹ 124 for C-Tb (N= 173109)					
	Number of True Positive Cases					
	2022	2023	2024	2025	2026	2027
C-Tb	67,802	62,655	57,900	53,505	49,444	45,691
TST	69,728	64,436	59,545	55,026	50,849	46,990
Screening Cost (₹)						
C-Tb	68,204,930	63,028,176	58,244,337	53,823,592	72,461,500	45,963,238
TST	68,204,930	63,028,176	58,244,337	53,823,592	49,738,382	45,963,238
Treatment Cost of LTBI (₹)						
C-Tb	34,490,599	31,872,763	29,453,620	27,218,090	25,152,237	23,243,182
TST	35,470,711	32,778,484	30,290,597	27,991,541	25,866,983	23,903,679
Adverse Effect Cost (₹)						
C-Tb	4,263,929	3,940,297	3,641,228	3,364,859	3,109,466	2,873,458

TST	4,385,096	4,052,267	3,744,700	3,460,477	3,197,827	2,955,112
Diagnosis Cost of TB (₹)						
C-Tb	108,075,729	99,872,781	92,292,437	85,287,441	78,814,124	72,832,132
TST	111,146,893	102,710,844	94,915,091	87,711,035	81,053,768	74,901,787
Treatment Cost for active TB (₹)						
C-Tb	53,377,816	49,326,440	45,582,563	42,122,846	38,925,722	35,971,260
TST	54,894,642	50,728,138	46,877,873	43,319,842	40,031,866	36,993,447
Total Cost (₹)						
C-Tb	268,413,003	248,040,456	229,214,185	211,816,829	195,739,931	180,883,271
TST	274,102,272	253,297,909	234,072,598	216,306,488	199,888,825	184,717,263
Budget Impact (C-Tb VS TST	-5,689,269	-5,257,453	-4,858,412	-4,489,659	-4,148,894	-3,833,993

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