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Cost-effectiveness of expanded latent TB infection testing and treatment: Lynn City, Massachusetts, USA

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Abstract

BACKGROUND: Between October 2016 and March 2019, Lynn Community Health Center in Massachusetts implemented a targeted latent TB infection testing and treatment (TTT) program, increasing testing from a baseline of 1,200 patients tested to an average of 3,531 patients tested, or 9% of the population per year.

METHODS: We compared pre-implementation TTT, represented by the first two quarters of implementation data, to TTT, represented by 12 quarters of data. Time, diagnostic, and laboratory resources were estimated using micro-costing. Other cost and testing data were obtained from the electronic health record, pharmaceutical claims, and published reimbursement rates. A Markov cohort model estimated future health outcomes and cost-effectiveness from a societal perspective in 2020 US dollars. Monte Carlo simulation generated 95% uncertainty intervals.

RESULTS: The TTT program exhibited extended dominance over baseline pre-intervention testing and had an incremental cost-effectiveness ratio (ICER) of US$52,603 (US$22,008–US$95,360). When compared to baseline pre-TTT testing, the TTT program averted an estimated additional 7.12 TB cases, 3.49 hospitalizations, and 0.16 deaths per lifetime cohort each year.

CONCLUSIONS: TTT was more cost-effective than baseline pre-implementation testing. Lynn Community Health Center's experience can help inform other clinics considering expanding latent TB infection testing.

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RÉSUMÉ

Entre octobre 2016 et mars 2019, le Lynn Community Health Center au Massachusetts, États Unis, a mis en œuvre un programme ciblé de dépistage et de traitement de l'infection tuberculeuse latente (TTT, pour l'anglais « *latent TB infection testing and treatment* »), augmentant les tests d'une base de référence de 1 200 patients testés à une moyenne de 3 531 patients testés, soit 9% de la population par an.

Nous avons comparé le TTT avant la mise en œuvre, représenté par les deux premiers trimestres de données de mise en œuvre, au TTT, représenté par 12 trimestres de données. Les ressources en temps, en diagnostic et en laboratoire ont été estimées à l'aide du micro-costing. D'autres données sur les coûts et les tests ont été obtenues à partir du dossier médical électronique, des demandes de remboursement de produits pharmaceutiques et des taux de remboursement publiés. Un modèle de cohorte de Markov a permis d'estimer les futurs résultats sanitaires et le rapport coût-efficacité d'un point de vue sociétal en dollars américains de 2020. La simulation de Monte Carlo a généré des intervalles d'incertitude à 95%.

Le programme TTT a montré une dominance étendue par rapport au test de base avant l'intervention et a eu un rapport coût-efficacité différentiel (ICER) de 52 603 $US (22 008 $US–95 360 $US). Par rapport au test de référence effectué avant l'intervention, le programme TTT a permis d'éviter chaque année environ 7,12 cas supplémentaires de TB, 3,49 hospitalisations et 0,16 décès par cohorte à vie.

Le TTT s'est avéré plus rentable que les tests de référence effectués avant la mise en œuvre du programme. L'expérience du Lynn Community Health Center peut aider à informer d'autres cliniques qui envisagent d'étendre le dépistage de l'infection tuberculeuse latente.

Keywords

cost-effectiveness; tuberculosis; economic evaluation; LTBI testing

Non-US-born persons are at higher risk for latent TB infection (LTBI) and TB reactivation. In 2019, 71% of US TB cases were among persons who were born in a country other than the United States;[1] recent transmission was ruled out as the cause of 92% of TB disease cases among non-US-born persons, suggesting these persons were previously infected in their country of origin.[1,2] In addition, the percentage of TB cases in non-US-born persons has increased, primarily attributable to reactivation.[3] The non-US-born population at risk for TB is large; recent studies estimate that there could be up to 7 million non-US-born persons living with LTBI in the United States.[4–6]

Increased testing and treatment of non-US born persons could help reduce TB incidence. To this end, both the Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force recommend screening populations at risk for LTBI or TB disease.[7,8] This recommendation includes non-US-born persons, particularly from countries with high TB prevalence. Only 12% of persons with LTBI have been previously treated.[9]

Lynn, Massachusetts is a diverse city of approximately 90,000 persons located north of Boston.[10] In 2017, 64% of residents were from racial or ethnic minorities, 37% were born

outside the United States, and 53% spoke a language other than English at home.[10] Lynn Community Health Center (CHC) is a federally qualified health center (FQHC) certified as a primary care and patient-centered medical home that serves more than 40,000 patients annually. In October 2016, Lynn CHC became the clinical site for a 3-year demonstration project led by the Massachusetts Department of Public Health (MDPH) to LTBI targeted testing and treatment ('the TTT program'), among the non-US-born population.

Key components of the TTT program included adding non-clinical staff to the TB team for patient engagement, education, and retention, health center-wide staff orientation and training, modification of the electronic health record (EHR) to collect country of birth and LTBI care cascade data, and quarterly meetings with the evaluation and project teams to review indicators and identify strategies for improvement. The TTT program also promoted the use of the QuantiFERON®-TB Gold (QFT) blood assay (Qiagen, Germantown, MD, USA), a type of interferon-gamma release assay (IGRA) for non-US-born persons, as opposed to the tuberculin skin test (TST) performed using Tubersol (Sanofi Pasteur Limited, Paris, France) Furthermore, 3 months of rifapentine and isoniazid (3HP) with directly observed therapy (DOT) was introduced as new treatment option for patients. This was in addition to the 4 months of self-administered daily rifampin (4R) and 9 months of daily isoniazid (9H) offered prior to the TTT program.[11,12]

Previous analyses have focused on cost-effectiveness of specific treatment regimens and differences in the cost-effectiveness of populations with comorbidities.[13–15] The objective of this analysis was to estimate the cost-effectiveness of the TTT program from a societal perspective compared to a baseline pre-existing testing program, and a no testing scenario. Funding for the TTT program was provided by the Centers for Disease Control (cooperative agreement NU52PS910159–01-00), Atlanta, GA, USA.

METHODS

Cost data collection

From December 2018 to May 2019, we employed micro-costing to collect: 1) start-up and ongoing resources and costs, 2) resources needed to modify the EHR, and 3) LTBI testing and medication costs. First, evaluators conducted structured interviews to assess TTT program activities. Further, the TTT program hired two community health workers (CHWs) and one patient navigator (PN). They facilitated coordination of care between Lynn CHC primary care and the TB team, assisted with analysis of adherence, and provided patient services such as interpretation. Labor costs was estimated with time-motion analysis of TTT program activities. Total costs associated with other LTBI services were obtained from national reimbursement rates and already included labor costs for these services (Supplementary Data).[16,17]

Treatment cascade data and electronic health record updates

The EHR used by the clinic was OCHIN Epic EHR Services (https://ochin.org/hosted-epic-ehr), a customizable instance of EPIC (EPIC Systems Corporation, Verona, WI, USA). Overall use of TB tests (QFT and TST) and pharmacy prescriptions were obtained through

an analysis of EHR data. Updates to the EHR included a new electronic 'flow sheet' to track patients from start to treatment completion.

Estimation of TTT clinic time and medical costs

TTT clinic flow began with a patient TB risk assessment and referral to TB testing by the primary care physician (PCP) (Figure 1). PCPs then used the EHR to refer patients with a positive test for chest radiograph and TB evaluation. PNs and CHWs followed-up with patients to ensure the chest radiograph was complete, scheduled the initial TB evaluation visit, and maintained patient electronic tracking sheets. Patients with a positive test for whom TB disease was ruled out and treatment was recommended were prescribed medication and scheduled for a follow-up visit. The medical provider prescribed medications for LTBI treatment regimens, and the TB nurse provided DOT for 3HP. Because primary care, radiology, and the TB team were located within Lynn CHC and used the same EHR, testing for diabetes, HIV, hypertension, and other comorbidities were completed in primary care. Prior to starting LTBI treatment, patients received a liver function test and a complete blood count. Costs of tests and medications were obtained from published sources.[16–18]

We estimated wages, including fringe benefits, for all staff using published average salaries for corresponding staff occupations in the Boston-Cambridge-Nashua metropolitan statistical area.[19] We accounted for adverse events during drug therapy using previously published randomized clinical trials.[11,12,20] Staff time associated with adverse events was collected from the time–motion study. We used the *MASS* package in R v4.2.1 (R Computing, Vienna, Austria) to empirically fit gamma distributions to time–motion cost data.[21] The resulting gamma parameter estimates were imported into TreeAge (TreeAge Software, Williamstown, MA, USA) for the cost-effectiveness analyses.

To assess costs from the healthcare and societal perspectives, TB disease costs, including outpatient and hospitalization medical and patient costs, were based on previously published studies updated to US$ 2020 (Table 1).[13,22,23] Among future LTBI patients who progressed to TB, in addition to the outpatient, hospitalization, and patient costs associated with active TB, we also include health department contact investigation costs, as these would be averted costs with fewer future TB cases.[24,25] TB disease medical and patient costs, as well as patient costs of LTBI treatment were adjusted to Massachusetts 2019 local prices and inflated to US$ 2020 (Supplementary Data). Patient costs included transportation out-of-pocket costs and the value of patient time, while at, and when traveling to and from the clinic.

Health impacts—To track health outcomes, costs, and cost-effectiveness from the health system and societal perspectives, we created a Markov cohort simulation model in TreeAge 2022. In particular, the model estimated benefits in terms of averted TB cases as well as any harm associated with toxicity from LTBI treatment.

The model included three scenarios: 1) the TTT program fully implemented, 2) the 'baseline' pre-TTT testing program as represented by the first two quarters of TTT data, and 3) a no-testing scenario. The first two quarters of TTT data of the baseline scenario (Table

2) were characterized by a lower proportion of QFT tests (relative to TST), fewer total annual tests, and two treatment regimens: 4R and 9H. Implementation of TTT introduced 3HP as a new regimen and increased labor costs via addition of CHWs and PNs and EHR modification costs.

For each scenario, the Markov model simulated lifetime progression to TB among a cohort of individuals aged 35 years (the median age of a patient tested during the TTT program), and followed patients until a life expectancy of 78.7 years (US life expectancy in 2019).[26] Parameter estimates for transition probabilities, sensitivity and specificity of QFT and TST, LTBI treatment initiation, efficacy, and completion rates were based on data from Lynn CHC and published clinical trials (Table 2).[11,27,28] The health state quality-adjusted life-year (QALY) utility weights were obtained from the literature.[29–32] LTBI prevalence in the population was estimated from the test positivity rate, sensitivity, and specificity of QFT.[33] Patients with LTBI had a 0.088 per 100 person-year rate of progressing to TB each year, which was converted to a probability (Supplementary Data).[5] We used a Monte Carlo simulation to account for the variability in health outcomes, costs, and time associated with LTBI patient testing and treatment. The simulation included probability distributions for all variables in the model (Supplementary Data). This evaluation was determined to be non-research by the Institutional Review Board of the Centers for Disease Control and Prevention, Atlanta, GA, USA.

RESULTS

Over the 30-month program period (October 1, 2016–March 31, 2019), 8,827 patients were tested for LTBI. This amounts to an average of 3,531 tests per year (Table 2). Although QFT was the preferred test, the demonstration project was also, in part, to educate providers on the preferred use of QFT, and some TST tests were still performed. Of the total tests during the 3year program, 8,010 tests (91%) were QFT, compared with 817 (9%) TSTs. However, TST use during the program declined steadily from 22.9% in the first quarter to 4.5% in the 10th quarter. The QFT test positivity among patients was 16.4%, implying an 19.7% LTBI prevalence in the population.[33] The highest percentage of patients started a regimen of 4R (63.7%), followed by 3HP (18.3%) and 9H (18.0%) (Table 2). Population demographics are provided in the Supplementary Data. The initial visit was associated with the greatest labor cost from the physician (US$44.04, range: US$6.37– US$160.4; Supplementary Data). Nurse labor cost was primarily associated with follow-up and DOT visits (US$40.28 and US$20.75 per visit, respectively). Similarly, the average cost associated with an initial visit for PNs and CHWs was greater than for follow-up visits, though not statistically different (US$8.92 vs. US$8.24 per visit, respectively).

Primary activities for CHWs and PNs included creating patient status reports from the EHR, providing TB education for patients, scheduling, and providing language interpretation when needed. PCPs stated there was no increase in time spent with patients when a patient

Cost-effectiveness

Overall, the TTT program ICER of US$52,603 (range US$22,008–US$95,360) exhibited extended dominance of the baseline pre-intervention program in that TTT obtained greater

health outcomes at a lower ICER per QALY gained (Table 3). Compared to the baseline, the TTT program averted an estimated additional 7.12 TB cases, 3.49 hospitalizations, and 0.16 deaths per lifetime cohort.

Sensitivity analyses

The ICER mean estimate of the TTT program had a large range, as represented by the 2.5 and 97.5 quartiles of the distribution of simulation outcomes (Figure 2). The most influential factor affecting the results was the prevalence of LTBI in the population tested. In particular, a population with an LTBI prevalence of 10% increased the estimated ICER to over US$100,000 per QALY gained, while a population with 30% prevalence reduced the program's ICER to 36,441. Other factors that could increase cost-effectiveness included higher proportion of patients starting treatment, greater sensitivity of QFT, lower cost of QFT, greater proportion of tests QFT, and lower patient DOT out-of-pocket cost (Supplementary Data). Finally, increasing cohort age at testing (40 and 50 years) decreased cost-effectiveness.

DISCUSSION

We found that expanding LTBI testing and treatment among the non-US-born population in Lynn, Massachusetts, USA, would prevent TB, avert TB hospitalizations and deaths, and increase QALYs. In particular, the TTT program was estimated to be more cost-effective than the baseline program. This is likely due to several factors that increased the efficiency of the TTT program – preference of QFT testing for non-US-born persons, better patient tracking with an updated EHR, introduction of the 3HP regimen (thus, more patients switched from 9H to shorter treatment regimens), and the inclusion of CHWs and PNs to help facilitate clinic interdepartmental communication and perform patient education and follow-up.

These results are generalizable to the state of Massachusetts; however, application to other localities may be limited by several factors. For example, prior to starting treatment, 14% of patients at Lynn CHC were uninsured. Because Massachusetts is a Medicaid expansion state, most patients were able to become insured through the Massachusetts Medicaid Program. Furthermore, MDPH and Lynn CHC ensured that patients did not incur out-of-pocket prescription costs. Similarly, at the national level, given the US Preventive Services Task Force Grade B recommendation for LTBI testing and treatment for at-risk individuals, patients should have no out-of-pocket costs LTBI testing and treatment.[8]

Lynn CHC had many 'in-house' services such as radiology and primary care. This reduced patient costs associated with treatment. In addition, the EHR was modified at little cost to Lynn CHC. The modified EHR enabled TB clinicians to identify pre-existing conditions, infectious disease co-infections, or other factors that could affect LTBI treatment, which reduced testing cost.

Other differences between localities include healthcare staff wages. Higher labor costs in Massachusetts increase costs of the TTT program, lowering cost-effectiveness. However,

sensitivity analyses on labor costs did not substantially change the cost-effectiveness results (Supplementary Data).

This analysis is subject to at least three limitations. First, due to data collection limitations at the start of the TTT program, we used the first two quarters of TTT program data for the baseline pre-TTT intervention. This likely underestimated the change due to the TTT program as many changes were already implemented in the first two quarters. In addition, we did not have data on the proportion of patients who started treatment on 9H and 4R pre-TTT program. Second, this evaluation only collected cost data from a single clinic in Massachusetts and may not be generalizable beyond the setting modeled. Third, while the TTT program cost per QALY gained was similar to other published studies on testing and treatment in the non-US-born population (ranging from US$53,000 to US$174,000),[14,15] it is possible that we underestimated cost-effectiveness, as our static model did not include associated future transmission between contacts of TB cases. In particular, our static model under-estimated the benefits of greater expansions of the TTT program as higher levels of testing and treatment would reduce future TB cases more quickly than predicted in the current model.

One of the greatest barriers to the start-up of a TTT program is convincing primary care providers that the process is feasible and does not take a disproportionate amount of time away from other patients. Our analysis highlighted the role of the CHWs and PNs who provided critical functions through communication with patients and providers, and regular review of EHR reports. These results suggest that success of an expanded LTBI testing and treatment program must account for non-medical costs, as they are key to ensuring medical staff are not overwhelmed, and patients are tested, return for follow-up visits, and complete treatment.

In order to obtain TB elimination, the impact of one single clinic scaling LTBI testing and treatment will need to be scaled in many other clinics. This analysis offers a glimpse of a TTT that can be successfully scaled-up for the non-US-born population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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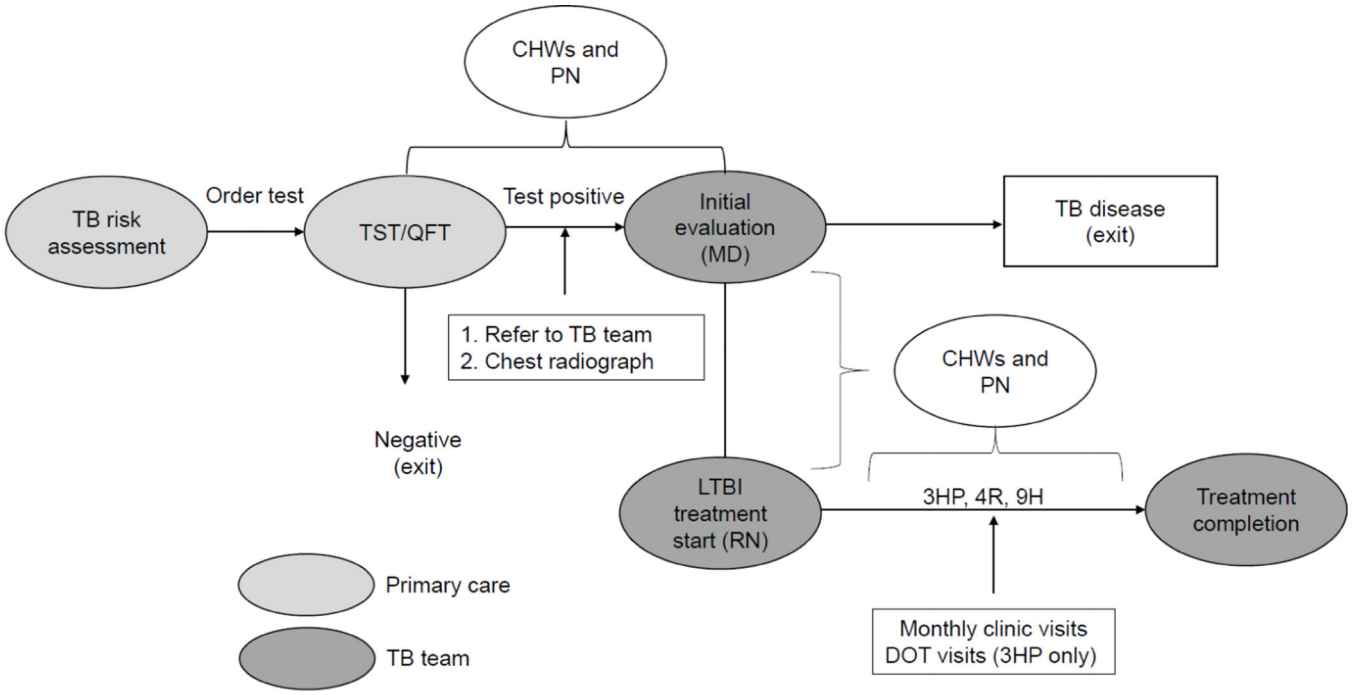

Figure 1.

Lynn Health Center Clinic flow and staff roles. CHW = community health worker; PN = patient navigator; QFT = QuantiFERON-TB Gold; MD = medical doctor; 3HP = 3 months once weekly isoniazid and rifapentine; 4R = 4 months daily rifampin; 9H = 9 months daily isoniazid; LTBI = latent TB infection; RN = registered nurse.

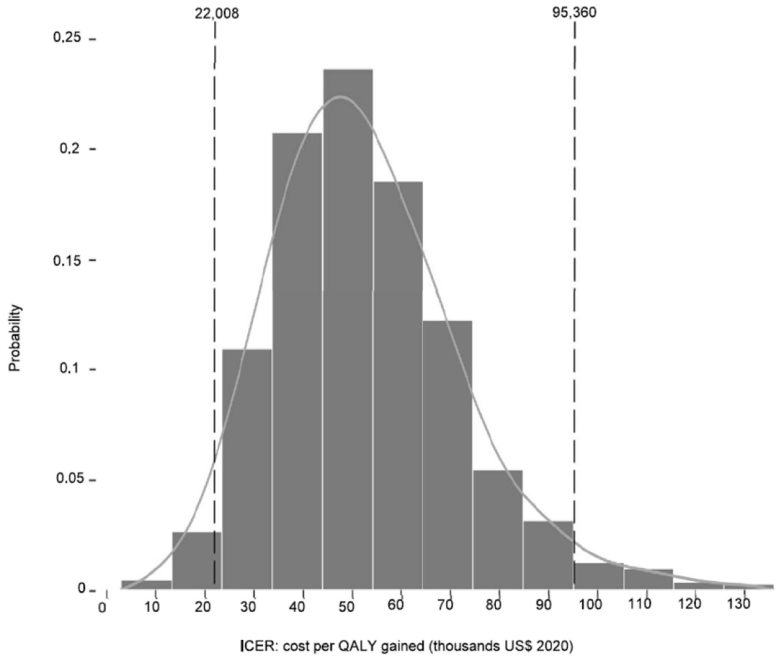

Figure 2.

Targeted testing and treatment ICER simulation results. ICER histogram of Monte Carlo simulation generated cost-effectiveness ratios with 1,000 draws. Mean value of US$52,603 per QALY gained; 95% uncertainty range depicted by vertical dashed lines (2020 US dollars). ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Table 1.

LTBI treatment and TB disease costs (US$ 2020).

	Mean	Range	Distribution	Source
Tests and laboratory costs				
TST	10.25	5.13–15.38	Log normal	17
QFT	61.98	30.99–92.97	Log normal	18
Chest radiograph	28.39	16.64–49.92	Log normal	17
Liver function test	5.89	3.45–10.35	Log normal	18
Complete blood count	8.63	5.05–15.17	Log normal	18
LTBI medication costs *				
9H	52	26–78	Log normal	16
4R	78	39–117	Log normal	16
3HP	151	76–227	Log normal	16
Drug-related toxicity	219	128–385	Gamma	13
Patient costs LTBI treatment				
Initial visit	58	34–102	Gamma	13
Follow-up visit	34	20–60	Gamma	13
3HP DOT visit (clinic time)	3	2–5	Gamma	23
3HP DOT visit (travel, other) †	33	20–59	Gamma	23
TB disease				
Diagnostic				
Medical costs	236	168–503	Log normal	13
Patient costs	52	31–92	Log normal	13
Outpatient				
Medical costs	3,009	1,764–5,291	Log normal	13
Patient costs	311	182–547	Log normal	13
Hospitalization				
Medical costs	34,523	20,239–60,716	Log normal	22
Patient costs	4,456	2,612–7,836	Log normal	13
Contact tracing	146	52–247	Gamma	24
Discount rate	0.03	Fixed	N/A	Assumed

[*] 3HP = INH (11 doses 900 mg) and RPT/Priftin (Sanofi-Aventis US, Bridgewater, NJ, USA) (10,800 mg); 4R = RIF 72,000 mg; and 9H = INH 81,000 mg. Individuals with unknown treatment start and complete status were assigned treatment regimes in the same proportion those with as known status.

[†] Patient DOT costs include value of time spent traveling, travel out-of-pocket costs, and dependent care costs.

LTBI = latent TB infection; TST = tuberculin skin test; QFT = QuantiFERON-TB Gold; DOT = directly observed therapy; INH = isoniazid; RPT = rifapentine; RIF = rifampin; N/A = not applicable.

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Table 2.

Markov Model simulation parameters.

	Value				
	Baseline	**TTT program***	**Range**	**Distribution†**	**Source**
Epidemiological characteristics					
Patients screened per year	1,200	3,531		N/A	LCHC
Test positivity	0.164		0.100–0.200	Gamma	LCHC
Estimated LTBI prevalence‡	0.197		0.115–0.244	Gamma	Calculated
Progression per 100,000 population	88		69–114	Gamma	[5]
TB					
Successful treatment <1 year	0.898		Fixed	N/A	CDC 2020
Death during TB treatment	Age-dependent		N/A	N/A	[34,35]
TB hospitalization	0.490		Fixed	N/A	[27]
LTBI tests					
Proportion of QFT tests, %	0.770	0.960	Fixed	N/A	LCHC
TST sensitivity	0.807		0.720–0.910	Beta	[28]
TST specificity	0.700		0.680–0.720	Bela-PERT	[28]
QFT sensitivity	0.790		0.700–0.900	Beta	[28]
QFT specificity	0.990		0.960–1.000	Beta-PERT	[28]
LTBI treatment					
Proportion initiating treatment	0.610		0.600–0.900	Beta-PERT	LCHC
Treatment efficacy	0.950		0.930–1.000	Uniform	[13]
Proportion that started treatment regimen§					
9H	0.23	0.18	Fixed	N/A	LCHC
4R	0.76	0.63	Fixed	N/A	LCHC
3HP	0.00	0.18	Fixed	N/A	LCHC
Proportion that started and completed treatment, %§¶					
9H	0.733		0.633–0.833	Beta-PERT	LCHC
4R	0.769		0.669–0.869	Beta-PERT	LCHC
3HP	0.858		0.758–0.958	Beta-PERT	LCHC

	Value				
	Baseline	**TTT program***	**Range**	**Distribution†**	**Source**
Utility weights					
TB disease	0.85		0.70–0.90	Beta-PERT	31
Hepatotoxicity	0.75		Fixed	N/A	29
Previous TB disease (3 years)#	0.96		0.95–1.00	N/A	13,15,32
TB hospitalization	0.52		Fixed	N/A	29
Life expectancy, ** years	78.7		Fixed	N/A	26

*Unless listed, TTT program parameters are identical to baseline.

†Distributional assumptions for probabilistic sensitivity analysis (see Supplementary Table S3 for distribution parameters).

‡Estimated LTBI prevalence calculated using the positivity adjustment formula.[33]

§Individuals with unknown start and complete status were assigned treatment regimens in the same proportion as those with known status.

¶Probabilities of hepatotoxicity by treatment regimen were as follows: 9H: 0.018 (range 0.014–0.023),[20] 4R: 0.003 (range 0.001–0.005),[12] and 3HP: 0.004 (range: 0.002–0.006).[20]

#After 3 years, the utility weight among persons with previous TB increases to 0.975.

**During each cycle of the model, individuals face an age-dependent, all-cause mortality probability.

TTT = (LTBI) targeted testing and treatment; LCHC = Lynn Community Health Center; N/A = not applicable; LTBI = latent TB infection; CDC = Centers for Disease Control and Prevention; QFT = QuantiFERON-TB Gold; PERT = program evaluation and review technique; 3HP = 3 months once weekly isoniazid and rifapentine; 4R = 4 months daily rifampin; 9H = 9 months daily isoniazid.

Table 3.

Lynn Community Health Center LTBI TTT incremental cost-effectiveness results.

	TB cases averted	TB hospitalizations averted	TB deaths averted	ICER	95% uncertainty interval
No screening comparator					
Baseline pre-TTT	3.45	1.69	0.08	60,993	26,681–112,377
TTT Program *†	10.57	5.18	0.24	52,603	22,008–95,360
TTT expansion vs. baseline pre-TTT % (number of TTT patients per year)					
5% (*n* = 1,760)	2.42	1.19	0.05	40,643	14,779–75,633
9% (*n* = 3,531)	7.12	3.49	0.16	48,536	20,065–87,171
12% (*n* = 4,934)	10.64	5.21	0.24	49,883	20,729–88,945
15% (*n* = 5,300)	14.16	6.94	0.32	50,560	20,926–90,040

*TTT program exhibits extended dominance of the baseline pre-TTT program with lower ICER value.

†Cost-effectiveness of TTT program compared to no screening after removal of extended dominated strategy.

TTT = (LTBI) targeted testing and treatment; LTBI = latent TB infection; ICER = incremental cost-effectiveness ratio.