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

Technical Appendix for "Cost-effectiveness of Scaling-up Latent Tuberculosis Infection Testing and Treatment: Lynn City, Massachusetts"

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Time-Motion Analysis

The Institute for Community Health held a half-day pilot session and then designated 5 half-day sessions to record staff time spent on LTBI patient activities during December 2018-May 2019. Dates and times for data collection were selected to reflect times when LTBI patients were seen in the TB clinic as well as patient visit types; visit types included LTBI evaluations, tests, and treatment directly observed therapy (DOT). Specific time spent on patients was tracked per patient per visit, by visit type. Visit type was classified as initial or follow-up, and as DOT for patients with the 3HP regimen prescribed.

For TB team medical providers, additional data fields included LTBI treatment-week number, language of patient, and if side-effects were reported. Start and finish times were recorded across 6 activities: pre-chart review, time in room with patient, updating the electronic health record (EHR), patient care and coordination, paperwork, and other TB- related activities. Other TB-related activities could include patient education, escorting patients to a room, and language interpretation. When providers entered information into the EHR while in the room with a patient, this time was allocated to "updating EHR."

For CHWs and PNs, time-motion tracking included variables on new and returning patients and start and finish times for 5 activities: scheduling patient appointments, patient care, support and navigation, EHR notes, and other TB-related activities.

TB team medical provider time was allocated per patient, by patient type (new, returning, or returning with side-effects) based on the time-motion study. CHW and PN time was allocated per patient activity or multi-session patient activity. Time for multi-session patient activities was averaged over the number of observed sessions (e.g., average time over 5 sessions), weighted by

number of sessions in a week (6 sessions per week), and then multiplied by the number of working weeks in a year (50 weeks).

Cost Indexing

We followed guidance from the Agency for Health Care Research and Quality's guide to determine appropriate indexes for expenditure and income comparisons. [1] 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. [2]

Estimation of Lynn CHC TTT Labor Costs

Cost data summary statistics are reported in Appendix Table 2. To account for total compensation for employees, we inflated wages by a 30% fringe benefit rate. [3] Gamma distributions were empirically fit to cost data collected during the time-motion study using the MASS package in R 4.2.1.[4,5] Resulting gamma distributional parameters were inputted into TreeAge for cost-effectiveness analyses (Appendix Table 2).

Quality Adjusted Life Years

We adjusted health state utilities (also known as quality adjusted life years [QALYs]) by duration of health state. [6] LTBI treatment was assumed to last for 3 months for directly observed once weekly isoniazid and rifapentine (3HP), 4 months of daily rifampin (4R), and 9 months of daily isoniazid (9H). Drug hepatotoxicity was assumed to last 2 weeks.

For active TB we used the Bauer et al. 2015 “Standard Gamble” QALY decrements by time period (baseline: “0.25”, 1 month: “0.1”, 2 months “0.08”, 4 months “0.1”, 6 months: “0.08”, 9 months: “0.03”, 12 months: “0.0”).[7] We further included a decrement for TB symptoms 3 months prior to TB diagnosis. Second, to measure the QALY for hospitalization, we used the HUI3 value estimated for “not well controlled TB” of 0.52 (QALY decrement of 0.48). [8]

Hospitalization was assumed to last 24 days. Among patients with previous TB, we used a decrement of 0.041 for the first three years after the TB episode and then a decrement of 0.025 for all remaining life years; we varied the decrement in sensitivity analyses (Appendix Table 4).[6,9,10]

We also included costs of TB disease (outpatient, hospitalization, and productivity losses); LTBI costs were included as described in the cost data collection process (Table 2). All QALYs and costs were discounted at 3%.

Markov Model

We simulated a Markov cohort using TreeAge version 2022 (TreeAge Software LLC) in a population of 3 531 non-US-born individuals, reflecting the size of the population at LCHC with an annual time step.[11] We created a base-case, no testing and treatment, Markov model with 7 states representing "LTBI", "TB disease", "TB hospitalization", "no TB hospitalization", "no infection", "previous TB disease", and "death" (Appendix Figure 1). Transition probabilities were based on prior literature, systematic reviews, and clinical trials data. Our intervention models included additional states beyond the base model representing true and false positive tests, true and false negative tests, and hepatotoxicity. Probabilities of hepatotoxicity by treatment regimen were 0.018 (range 0.014-0.023), 0.003 (range 0.001-0.005), and 0.004 (range 0.002-0.006) for 9H, 4R, and 3HP respectively.[12-14] We assigned 19.7% to the latent TB infection state based on estimated prevalence during the Lynn CHC demonstration project. The remaining individuals started in the "no infection" state. A proportion of the population (LTBI and no infection individuals) was assigned to "testing" based on the proportion of the population to be tested. Tests were conducted using TST or QFT based on testing data from the TTT project. All non-TB disease states had an age specific background mortality rate. [15]

Estimation of TB Fatality Rate

We estimated TB deaths as a proportion of TB cases by age group from 1999-2016 using National Vital Statistics Mortality Rates and the Online Tuberculosis Information System (OTIS). [16,17] We then fit a spline model to the age group data, estimating fatality rates for each year of age with the smoothing spline function using R 4.2.1.[18]

Sensitivity Analyses

Input parameter ranges were used to perform sensitivity analyses in TreeAge. LCHC labor cost data distributions were estimated in R 4.2.1 and then inputted into TreeAge. All other variables were fit in TreeAge (Appendix Table 3). We performed a Monte Carlo probabilistic sensitivity analysis with seed set to 168 and drew 1000 random draws for each simulation. One way sensitivity analyses are presented for key variables (Appendix Table 5).

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Supplementary Tables and Figures

Supplementary Table S1: Demographic Characteristics of Lynn City and Lynn Community Health Center, MA 2019[a]

	City of Lynn	(%)	LCHC	(%)
	(n = 94,299)		(n = 41,115)	
Racial and/or ethnic minorities[b]	60,446	(64.1)	38,780	(94.3)
Non-US-born	34,608	(36.7)	Unavailable	
Language other than English[c]	50,444	(53.4)	24,126	(58.6)
Population at or below federal poverty level[d]	15,653	(16.5)	30,505	(74.7)
Uninsured	5,186	(5.49)	5,726	(13.9)

LCHC, Lynn Community Health Center; MA, Massachusetts.

[a]US Census Bureau, Quick Facts, Estimates for July 2019. Accessed 5/12/21.

[b]Black or African American, American Indian and Alaska Native, Asian, Hispanic/Latino, Native Hawaiian and Other Pacific Islander, or Other race.

[c]City of Lynn denominator is persons > 5 years of age: 85,764. LCHC denominator is among patients with known language preference and best served in language other than English.

[d]2019 family of 4 annual income at or below $25,750. Denominator for LCHC patients with known income N= 40,802.

Supplementary Table S2: Lynn Community Health Center Estimated Labor Costs per Visit (US$ 2020)

	N	Mean Cost ($)	95% Uncertainty Range[a]
Evaluation			
TB risk assessment[b]	-	13.07	(6.53, 19.61)
Initial visit			
Labor			
CHW and PN	43	8.92	(1.09, 49.73)
Physician	15	44.04	(6.37, 160.4)
Follow-up visits (no side-effects)			
Labor			
CHW and PN	85	8.24	(0.54, 46.04)
Physician	6	16.51	(9.73, 20.94)
RN	6	38.16	(25.37, 51.12)
Other PN administrative time[c]	4	40.28	(27.00, 53.56)
DOT visit (3HP)			
RN	12	20.75	(13, 35.52)
Visit w/ side effects			
Physician	1	54.27	N/A
RN	4	48.25	(26.07, 70)
EHR modification	N/A	0.15	N/A

CHW, community health worker; DOT, directly observed therapy; EHR, electronic health record; RN, resident nurse; PN, patient navigator; 3HP, 3 months once weekly isoniazid and rifapentine.

[a]Unless otherwise stated, all means estimated from gamma distribution empirically fit to time-motion study cost data. Range is 2.5 and 97.5 percentiles of the fit gamma distribution.

[b]Range set to 50% above and below mean value.

[c]Other PN time was distributed over multiple patients. PNs reported four activities covering multiple patients during 3 of the 5 observed sessions.

Supplementary Table S3a: Monte Carlo Sensitivity Analysis Distributional Assumptions

Epidemiological parameters	Distribution
Progression per 100,000 population	Gamma(64.00, 72,727.27)
Estimated LTBI prevalence	Gamma(21.62, 116.25)
QFT sensitivity non-US-born	Beta(51.63, 13.73)
Prop. initiating treatment (of test positive)	PERT(0.5, 0.61, 0.90)
QFT specificity non-US-born	PERT(0.96, 0.99, 1.00, 6)
Efficacy treatment	Uniform(0.93, 1.00, 2)
3HP complete prob.	PERT(0.76, 0.86, 0.96, 4)
4R complete prob.	PERT(0.67, 0.77, 0.87, 4)
9H complete prob.	PERT(0.63, 0.73, 0.83, 4)
3HP hepatotoxicity prob.	PERT(0.002, 0.004, 0.006, 4)
4R hepatotoxicity prob.	PERT(0.001, 0.003, 0.005, 4)
9H hepatotoxicity prob.	PERT(0.014, 0.018, 0.023, 4)
LTBI testing and diagnostic costs	
TST	LogNormal(2.33, 0.12)
QFT	LogNormal(4.09, 0.25)
CXR	LogNormal(3.3, 0.31)
LFT	LogNormal(1.7, 0.37)
CBC	LogNormal(2.12, 0.28)
LTBI treatment costs	
9H	LogNormal(3.91, 0.28)
4R	LogNormal(4.3, 0.32)
3HP	LogNormal(4.94, 0.39)
Initial visit physician	Gamma(1.34, 0.03)
Initial visit CHW or PN	Gamma(2.21, 0.25)
Follow-up visit physician	Gamma(12.45, 0.75)
Follow-up visit RN	Gamma(15.61, 0.36)
DOT visit RN	Gamma(9.26, 0.39)
Side effects visit RN	Gamma(6.2, 0.12)
Follow-up visit CHW or PN	Gamma(0.66, 0.08)
Medical cost hepatotoxicity	Gamma(12.96, 0.07)

CBC, complete blood count; CHW, community health worker; CXR, chest radiograph; DOT, directly observed therapy; LFT, liver function test; LTBI, Latent Tuberculosis Infection; PN, patient navigator; QFT, QuantiFERON ® -TB Gold blood assay; RN, registered nurse; 3HP, 3 months treatment with isoniazid and rifapentine; 4R, 4 months treatment with rifampin; 9H, 9 months treatment with isoniazid.

Supplementary Table S3b: Monte Carlo Sensitivity Analysis Distributional Assumptions

Patient costs LTBI treatment	
Initial visit	Gamma(24.01, 0.49)
Follow-up visit	Gamma(33.64, 1.16)
DOT visit	Gamma(2.82, 0.1)
DOT visit (travel, other)	Gamma(17.47, 0.52)
TB disease costs	
Risk assessment (medical cost)	LogNormal(2.48, 0.41)
Diagnostic (medical cost)	LogNormal(5.6, 0.33)
Diagnostic (patient cost)	LogNormal(3.9, 0.33)
Outpatient (medical cost)	LogNormal(7.96, 0.32)
Outpatient (patient cost)	LogNormal(5.69, 0.33)
Hospitalization (medical cost)	LogNormal(10.33, 0.35)
Hospitalization (patient cost)	LogNormal(8.3, 0.45)
Death (productivity loss)	LogNormal(13.3, 0.39)
Contacts elicited per TB case (number of persons)	PERT(5, 13.5, 25, 5)
Contact tracing cost per contact elicited (public health cost)	Gamma(10.49, 0.07)
QALYs	
TB disease	PERT(0.7, 0.85, 0.90, 0.50)

AE, adverse event; CBC, complete blood count; RN, registered nurse; CHW, community health worker; CXR, chest radiograph; LFT, liver function test; LTBI, Latent Tuberculosis Infection; PN, patient navigator; QFT, QuantiFERON ® -TB Gold blood assay; 3HP, 3 months treatment with isoniazid and rifapentine; 4R, 4 months treatment with rifampin; 9H, 9 months treatment with isoniazid.

Supplementary Table S4: Cost Data Inventory Base Values (US$ 2020) and Source

	Mean Cost per Unit ($)	Source
LTBI testing and diagnostic costs		
QFT	61.98	[19]
CXR	28.39	[20]
LFT	5.89	[19]
CBC	8.63	[19]
LTBI medical costs		
9H	52.00	[21]
4R	78.00	[21]
3HP	151.00	[21]
Risk assessment	13.08	LCHC
Initial visit physician	43	LCHC
Initial visit CHW or PN	15	LCHC
Follow-up visit physician	6	LCHC
Follow-up visit RN	6	LCHC
Follow-up visit CHW and PN	8.5	LCHC
DOT visit RN	12	LCHC
Side effects visit RN	4	LCHC
Medical cost hepatotoxicity	219	[6]
Patient costs LTBI treatment		
Initial visit	58	[6]
Follow-up visit	34	[6]
DOT visit	3	[22]
DOT visit (travel, other)	33	[22]
TB disease costs		
Medical costs		
Diagnostic (medical cost)	286	[6]
Outpatient (medical cost)	3,009	[6]
Hospitalization (medical cost)	34,523	[23]
Public health costs		
Contact tracing	146	[24]
Patient costs		
Diagnostic (patient cost)	52	[6]
Outpatient (patient cost)	311	[6]
Hospitalization (patient cost)	4,456	[6]

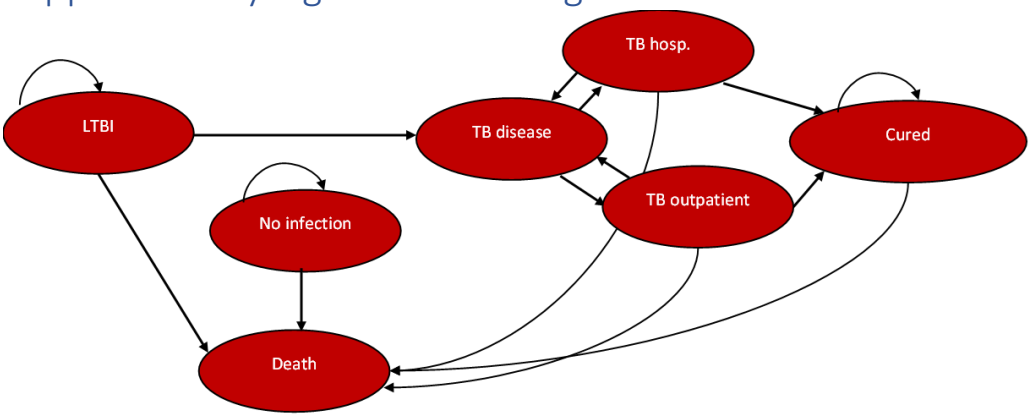
AE, adverse event; CBC, complete blood count; CHW, community health worker; CXR, chest radiograph; DOT, directly observed therapy; LFT, liver function test; LCHC, Lynn Community Health Center; LTBI, Latent Tuberculosis Infection; PN, patient navigator; QFT, QuantiFERON ® -TB Gold blood assay; RN, registered nurse; 3HP, 3 months treatment with isoniazid and rifapentine; 4R, 4 months treatment with rifampin; 9H, 9 months treatment with isoniazid.

Supplementary Table S5: MA LTBI TTT Monte Carlo Simulation Results for Changes in Specified Variables

No screening comparator	ICER	95% Uncertainty Interval
LTBI prevalence (Base: 19.7%)		
10%	110,173	42,272–261,766
30%	36,441	13,870–64,152
TTT proportion starting treatment (Base: 61%)		
65%	50,575	20,886–91,388
75%	47,103	20,314–86,125
CHW/ PN labor cost		
10% above	52,817	22,294–95,562
25% above	53,140	22,615–95,866
Cost QFT (Base $61.98)		
50% below	37,634	14,270–69,863
50% above	67,242	31,398–118,464
Proportion QFT tests (Base: 96%)		
90%	58,061	26,146–103,487
100%	48,959	20,092–88,642
Sensitivity QFT (Base 79%)		
70%	57,862	24,774–104,243
90%	47,596	19,523–86,128
Cohort start age (Base: 35 years)		
40 years	61,506	27,228–109,903
50 years	95,433	47,774–164,603
Patient in-person DOT per-visit time and travel out-of-pocket costs (Base: $35.67)		
$0.00	48,030	19,005–88,775
50% above	54,861	24,274–97,301
Utility weight: Active TB disease (Base: 0.85)		
0.75	49,829	21,318–89,471
0.80	51,100	21,289–91,386
Utility weight: Previous TB disease (Base: 0.96 first 3 years, 0.975 remaining years)		
0.95	47,454	19,879–85,789
1.00	92,678	39,097–165,618

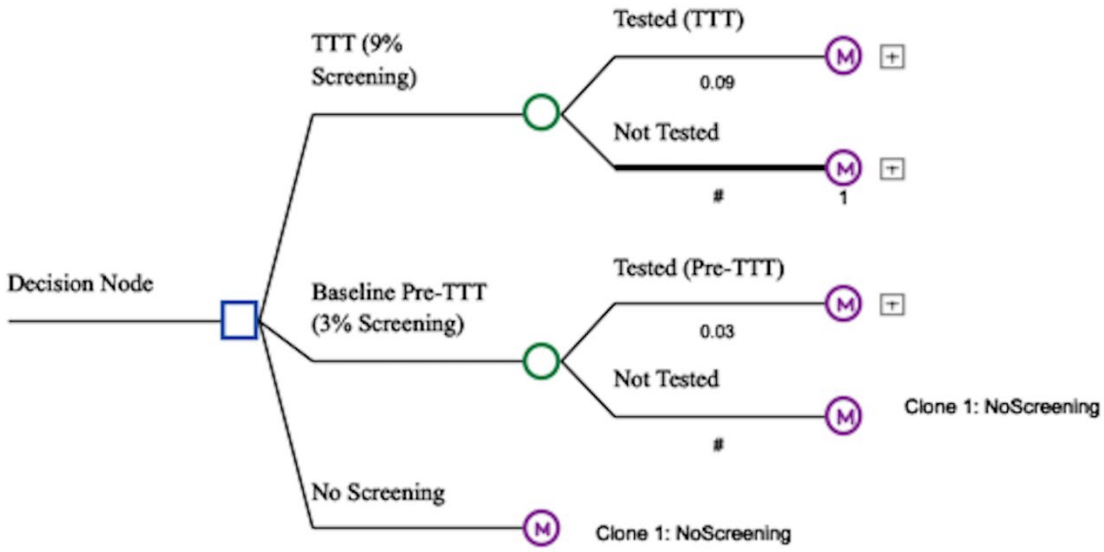
DOT, directly observed therapy; ICER, Incremental Cost-Effectiveness Ratio; TTT, Latent TB infection targeted testing and treatment program; QALY, quality adjusted life year; SAT, self-administered therapy.

Supplementary Figure S1: TB Progression Markov Model



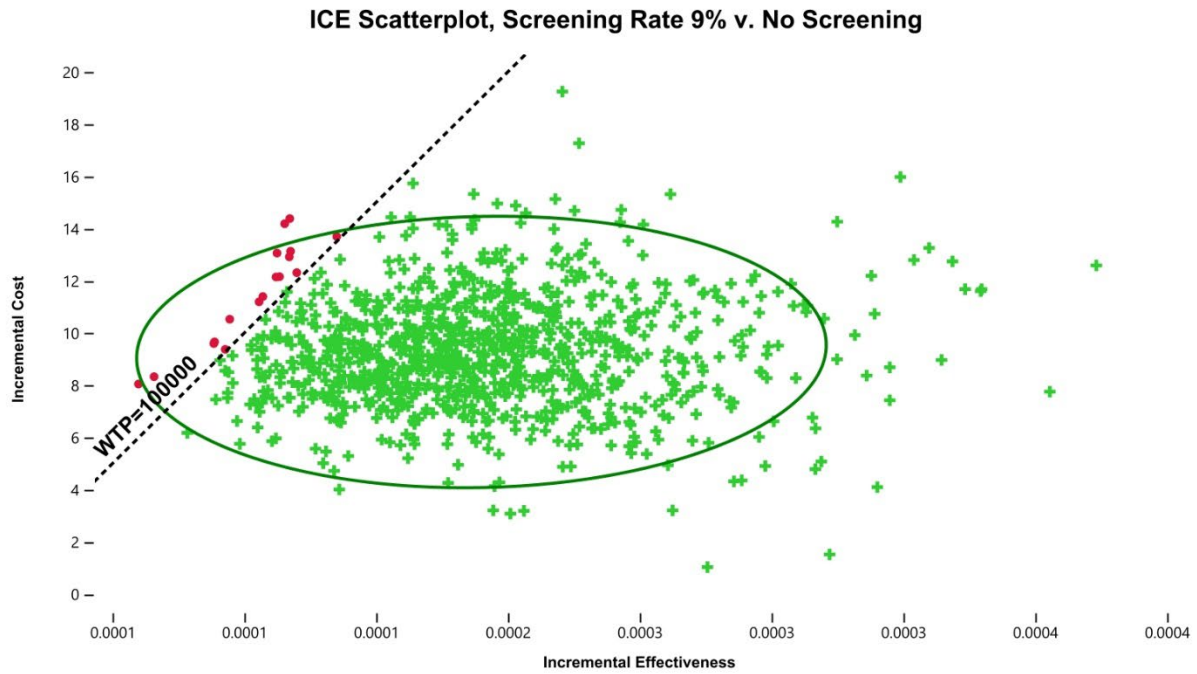
Initial values set to 0.197 for "LTBI" state and 0.803 for "No infection" state. All other states initial values set to zero.

Supplementary Figure S2: TTT Model Decision Tree



TTT: Targeted Testing and Treatment program; (M) Represents Markov node.

Supplementary Figure S3: TTT Project Incremental Cost Effectiveness Scatterplot



TTT, targeted testing and treatment; WTP, willingness to pay threshold; "+" represents ICER values below 100 000 per QALY. Ellipse represents the 95% uncertainty interval.