Supplementary Online Content

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eAppendix. Meta-analysis

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Meta-analysis

Introduction

The goal of this analysis is to investigate the relative costs and health benefits associated with testing and treatment for latent tuberculosis infection (LTBI) in foreign-born U.S. residents. We sought to determine which strategy or strategies are cost-effective in the U.S. healthcare system.

Our analysis is conducted through a computer model that we designed to simulate the lifetime progression of a cohort of people with and without latent tuberculosis infection (LTBI). The model is constructed using TreeAge software version 2016 (TreeAge Corporation, Williamstown, MA). Through this model we simulate both the cascade of testing, diagnosis and treatment for LTBI and the remaining lifetime health outcomes of TB morbidity, mortality, and quality adjusted life years gained (QALYs). We use population-level averages of costs and health outcomes to calculate incremental cost-effectiveness measures and draw conclusions about which strategies being studied are most cost effective for clinical practice.

Research Question

For each population studied we developed a model with similar structure but different input values to identify which, if any, of the selected testing strategies would be most cost effective to achieve the greatest QALYs at a commonly used willingness to pay (WTP) cost threshold of $100,000 per QALY gained.

Populations of Interest

We defined four populations of interest: foreign-born with no comorbidities (FB-NC), foreign-born with diabetes mellitus (FB-D), foreign-born with HIV (FB-HIV), and foreign-born with end v-stage renal disease (FB-ESRD). These populations have different life expectancies, associated healthcare costs and rates of TB reactivation.

Costs

We applied economic costs from the healthcare sector perspective. All costs in our analysis are reported in 2015 dollars; any costs from literature reported in other years were adjusted using an online calculator reflecting the Consumer Price Index (CPI) found at www.usinflationcalculator.com. We assumed that average costs from various data sources for the U.S. population overall would be equivalent to those specifically for FB populations. We used U.S. age- and sex-specific averages of background healthcare costs for the FB-NC population; we estimated costs using payments for care as reported by the Agency for Healthcare Research and Quality (AHRQ) Medical Expenditure Panel Survey (MEPS).[1] We obtained U.S. average payments for diabetes from the Diabetes Care Survey supplement to MEPS and applied them to FB-D. For FB-ESRD costs, we used a publish report of insurance claims among individuals with end-stage renal disease.[2,3] The FB-HIV population has healthcare costs associated with U.S. residents with HIV as reported by Cost-Effectiveness of Preventing AIDS Complications (CEPAC) group.[4] All other healthcare costs are estimated as follows. Physician and lab costs are estimated using Centers for Medicare and Medicaid Services (CMS) Medicare allowable fee schedules for physician and lab services. Pharmaceutical wholesale prices are used to

estimate medication costs and are obtained from Redbook© Online. While these data sources overestimate to some extent actual economic costs, they are the best estimates of costs that we were able to obtain.

Life Expectancy

The FB-NC population has a life expectancy without LTBI of 80 years, consistent with that of the general U.S. population.[5] The FB-HIV population has a life expectancy without LTBI of 69 years.[4,6] The FB-D population has a life expectancy without LTBI of 75 years.[7] The FB-ESRD population has a life expectancy without LTBI of 69 years.[8] On general, life expectancy is decreased in those with LTBI due to the risk of TB reactivation and subsequent possibility of death.

Testing Strategies

No testing In this strategy, no testing is performed. Thus, no TB cases are prevented, no individuals initiate LTBI treatment and the risk of TB reactivation throughout the lifetime is unmitigated.

TST In this strategy, a tuberculin skin test (TST) is placed and patients are required to return within 48 to 72 hours to have the results read. In the base case, 82% of patients returned to have their TST read, while the remainder are lost to follow up.[9] The results of this single test are considered to be final—those with a positive result are diagnosed with LTBI while those with a negative result receive no further clinical intervention.

IGRA In this strategy, a blood sample is taken for analysis using interferon gamma release assay (IGRA). The results of this single test are considered to be final—those

with a positive result are diagnosed with LTBI while those with a negative result receive no further clinical intervention.

Confirm positive In this strategy, a TST is placed and patients are required to return to have the test results read, with the same loss to follow-up as in the "TST" strategy. If the result is negative, no further action is taken. If, however, the result is positive, a blood sample is taken for IGRA. Only those individuals with positive results on both TST and IGRA are diagnosed with LTBI; those who have a negative result for either test do not receive any further clinical intervention. This strategy is used to "confirm" the positive findings of TST.

Confirm negative In this strategy, a blood sample is taken for IGRA analysis. If the result is positive, the patient is diagnosed with LTBI. If the result is negative, a TST is placed and patients are required to return for results, with the same loss to follow-up as in the "TST" strategy. If the results of both tests are negative, no further intervention is received. If the result of the TST is positive, the patient is diagnosed with LTBI. This strategy "confirms" any negative IGRA with a follow-up TST.

Test Characteristics

There is no gold standard against which to quantify the performance of commercially-available tests for LTBI. Estimates from the literature are varied and depend heavily on population of interest, especially by age, health status and country of origin. We conducted a thorough review of available literature followed by a comprehensive meta-analysis to estimate the performance of both TST and IGRA.

Our literature search identified 41 studies reporting the cross-classification of results of TST and IGRA for LTBI in various populations.[10-50] From these, we extracted cross-classification of results of TST and IGRA by age and by whether subjects: were immigrants; originated from countries with an annual TB case rate greater than 50 per 100,000 population; had history of BCG vaccination; had recent contact with active TB cases; or had a comorbidity of interest, and on the. We developed a Bayesian hierarchical random effects model that treated the unobserved disease status as a latent variable. For each of three comorbid categories (no comorbidities, HIV, diabetes mellitus/ESRD) the model generated probability distributions of the sensitivity and specificity for TST and IGRA. In our primary analysis, we used average test performance from these distributions and assumed test independence (Table S1).

Table S1 Test characteristics developed through hierarchical Bayesian meta-analysis and regression

	FB-NC	**FB-HIV**	**FB-D**	**FB-ESRD**
TST Sensitivity (%)	71	67	67	67
IGRA Sensitivity (%)	79	77	78	78
TST Specificity (%)	89	87	87	87
IGRA Specificity (%)	99	99	98	98

Treatment

We estimate that 90% of individuals diagnosed with LTBI will initiate treatment.[51] We model a regimen of twelve weeks of self-administered high dose isoniazid and rifapentine (3HP).[52] We estimated the cost of this regimen to include the cost of the medicines as well as a monthly physician visit. Of those who initiate treatment, 78.3% are estimated to complete the three-month course.[53] Patients who initiate treatment have an equal

probability of dropping out of treatment each month, and thus partial cost is accrued for those who do not finish the regimen. Of those who do drop out, a small proportion (<2%) do so due to hepatotoxicity.[52,53] Of those who develop hepatotoxicity, 0.1% die.[54] Both non-fatal and fatal drug-induced hepatotoxicity are associated with additional cost; for non-fatal cases this includes the cost of two specialty physician visits as well as two liver panels (a total of $323), estimated using Medicare allowable physician fees for a one new and one established physician visit (CPT codes 99203 and 99204) and Medicare allowable lab fees for a liver panel (CPT code 80076). For fatal cases, we estimated the cost of hospitalization with other liver disease at $13,780, obtained from the AHRQ National Inpatient Sample.[55] After the completion of treatment, patients experience a 90% reduction in the monthly risk of tuberculosis. Patients who initiate, but fail to complete, treatment are assumed not to receive any partial benefit.

Reactivation of LTBI

Persons with latent tuberculosis infection are exposed to a probability of TB reactivation every month throughout the simulation. The reactivation rate for foreign-born U.S. residents based on TST results was adjusted using the Rogan-Gladen calculation to account for the possibility that false-positive and false-negative results might have distorted the true reactivation rate.[56] The rate of reactivation in foreign-born persons reported by Shea, *et. al* was 98 cases per 100,000 person-years at risk; after correction, the rate used in the model was 104 cases per 100,000 person-years at risk. This probability of reactivation was increased by a factor of 1.8 in persons with either diabetes mellitus or end-stage renal disease.[57] For individuals with HIV, the probability of TB

reactivation was adjusted to hit a lifetime target of reactivation for infected and untreated individuals of 10%.[58] This baseline probability of reactivation is decreased by 10% each decade; this reduction in probability accounts for the potential for self-cure of LTBI over time as demonstrated by reductions in TST positivity when individuals are re-tested after ten years.[59] Although epidemiological data may demonstrate increased reactivation in older persons, this is confounded with higher prevalence of disease in earlier birth cohorts.[60] Of those who progress to reactivation TB, 50.3% develop a case severe enough to warrant hospitalization and increased medical attention; we model this through the proportion of individuals developing cavitary tuberculosis.[61] This estimate aligns with the 49% of patients found by Taylor *et al* to require hospitalization during the course of their TB illness.[62] Non-severe tuberculosis results in excess mortality and cost and decreased quality of life for six months; severe tuberculosis extends for a total of nine months. Costs associated with tuberculosis include the multi-drug pharmaceutical regimen, clinical visits, chest x-rays, contact tracing and bacterial cultures and total $2,900 in TB treated in an outpatient setting. We assumed that severe disease includes the cost of a hospitalization episode with tuberculosis, obtained from the AHRQ National Inpatient Sample ($25,200).[55] Of those who develop reactivation TB, 5% die, with the majority of deaths concentrated in severe cases.[63] Once a person has survived active TB, they are no longer exposed to the risk of reactivation. For every active case of tuberculosis, we model 0.25 additional cases.[64] The effect of additional cases is the difference in both quality-adjusted life expectancy and lifetime healthcare costs between an otherwise healthy 35 year old and one with tuberculosis.

Sensitivity Analyses

The results of key sensitivity analyses referenced in manuscript text are presented below.

FB-NC, age 30	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB+	0.65%	0.46%	0.41%	0.33%	0.28%
NNT	–	527	415	307	272
Incremental Cost per Person($)	–	47	30	50	42
Incremental QALY	–	0.0015	0.0004	0.0007	0.0003
ICER ($/QALY)	–	32,000	79,000	76,000	135,000

FB-NC, age 44	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB+	0.51%	0.36%	0.32%	0.26%	0.22%
NNT	–	671	528	391	346
Incremental Cost per Person($)	–	48	30	50	42
Incremental QALY	–	0.0011	0.0003	0.0005	0.0002
ICER ($/QALY)	–	43,000	105,000	101,000	179,000

FB-NC, age 60	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB+	0.86%	0.61%	0.54%	0.43%	0.38%
NNT	–	398	313	232	205
Incremental Cost per Person($)	–	44	29	49	42
Incremental QALY	–	0.0019	0.0005	0.0009	0.0004
ICER ($/QALY)	–	23,000	58,000	56,000	100,000

FB-NC, age 70	No testing	Confirm positive	TST	IGRA	Confirm negative

Lifetime Probability of Reactivation TB^{+}	0.24%	0.17%	0.15 %	0.12 %	0.10%
NNT	–	1440	1135	839	744
Incremental Cost per Person($)	–	51	31	52	43
Incremental QALY	–	0.0004	0.000 1	0.000 2	0.0001
ICER ($/QALY)	–	115,000	286,0 00	262,0 00	483,000

FB-NC, age 35 prevalence = 23%	**No testing**	**Confirm positive**	**TST**	**IGR A**	**Confirm negative**
Lifetime Probability of Reactivation TB^{+}	0.87%	0.62%	0.55 %	0.44 %	0.38%
NNT	–	393	310	229	203
Incremental Cost per Person($)	–	61	27	58	42
Incremental QALY	–	0.002	0.00 05	0.00 09	0.0004
ICER ($/QALY)	–	31,000	53,0 00	65,0 00	99,000

FB-NC, age 35, prevalence = 12.5%	**No testing**	**Confirm positive**	**TST**	**IGR A**	**Confirm negative**
Lifetime Probability of Reactivation TB^{+}	0.47%	0.34%	0.30 %	0.24 %	0.21%
NNT	–	723	570	422	374
Incremental Cost per Person($)	–	40	32	46	42
Incremental QALY	–	0.0011	0.000 3	0.000 5	0.0002
ICER ($/QALY)	–	38,000	117,0 00	102,0 00	191,000

FB-NC, age 35, prevalence = 2.5%	**No testing**	**Confirm positive**	**TST**	**IGR A**	**Confirm negative**
Lifetime Probability of Reactivation TB^{+}	0.09%	0.07%	0.06 %	0.05 %	0.04%
NNT	–	3616	2850	2108	1868
Incremental Cost per Person($)	–	21	36	35	43
Incremental QALY	–	0.0002	0	0.000 1	0
ICER ($/QALY)	–	97,000	886,0 00	466,0 00	1,293,000

FB-NC, age 35, TST specificity = 92.5%	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB+	0.60%	0.43%	0.38%	0.30%	0.26%
NNT	–	569	448	332	294
Incremental Cost per Person($)	–	45	19	63	32
Incremental QALY	–	0.0014	0.0004	0.0006	0.0003
ICER ($/QALY)	–	33,000	55,000	103,000	109,000

FB-NC, age 35, return rate = 92%	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB+	0.60%	0.41%	0.35%	0.30%	0.25%
NNT	–	507	399	332	285
Incremental Cost per Person($)	–	52	34	41	52
Incremental QALY	–	0.0015	0.0004	0.0004	0.0004
ICER ($/QALY)	–	34,000	86,000	101,000	145,000

FB-NC, age 35, utility of LTBI = 0.99	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB+	0.60%	0.43%	0.38%	0.30%	0.26%
NNT	–	569	448	332	294
Incremental Cost per Person($)	–	47	30	50	42
Incremental QALY	–	0.0135	0.0036	0.006	0.003
ICER ($/QALY)	–	3,000	8,000	8,000	14,000

FB-NC, age 35, post-TB utility = 0.95	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB+	0.60%	0.43%	0.38%	0.30%	0.26%
NNT	–	569	448	332	294
Incremental Cost per Person($)	–	47	30	50	42
Incremental QALY	–	0.0022	0.0006	0.001	0.0005
ICER ($/QALY)	–	21,000	52,000	50,000	88,000

FB-NC, age 35, post-TB utility = 0.965	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB+	0.60%	0.43%	0.38%	0.30%	0.26%
NNT	–	569	448	332	294
Incremental Cost per Person($)	–	47	30	50	42
Incremental QALY	–	0.002	0.0005	0.0009	0.0004
ICER ($/QALY)	–	24,000	59,000	57,000	100,000

FB-NC, age 35, post-TB utility = 0.99	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB+	0.60%	0.43%	0.38%	0.30%	0.26%
NNT	–	569	448	332	294
Incremental Cost per Person($)	–	47	30	50	42
Incremental QALY	–	0.0015	0.0004	0.0007	0.0003
ICER ($/QALY)	–	31,000	76,000	73,000	130,000

FB-HIV, age 35, LTBI prevalence = 1%	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB^{+}	0.10%	0.07%	0.07 %	0.05 %	0.04%
NNT	–	3767	2889	2060	1813
Incremental Cost per Person($)	–	20	42	31	48
Incremental QALY	–	0.0002	0	0.0001	0
ICER ($/QALY)	–	99,000	951,000	437,000	1,340,000

FB-D, age 57, LTBI prevalence = 5%	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB^{+}	0.16%	0.11%	0.10 %	0.08 %	0.07%
NNT	–	2383	1846	1299	1150
Incremental Cost per Person($)	–	27	40	41	48
Incremental QALY	–	0.0003	0.0001	0.0002	0.0001
ICER ($/QALY)	–	98,000	594,000	348,000	867,000

FB-D, age 57, LTBI prevalence = 19.5%	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB^{+}	0.61%	0.45%	0.40 %	0.31 %	0.27%
NNT	–	611	473	333	295
Incremental Cost per Person($)	–	54	33	58	46
Incremental QALY	–	0.0011	0.0003	0.0006	0.0003
ICER ($/QALY)	–	49,000	109,000	100,000	184,000

FB-D, age 57, LTBI prevalence = 34%	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB+	1.06%	0.78%	0.69%	0.54%	0.47%
NNT	–	350	272	191	169
Incremental Cost per Person($)	–	80	27	76	44
Incremental QALY	–	0.0019	0.0005	0.001	0.0004
ICER ($/QALY)	–	42,000	49,000	72,000	99,000

FB-D, age 30	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB+	0.98%	0.72%	0.64%	0.50%	0.44%
NNT	–	379	294	207	183
Incremental Cost per Person($)	–	48	36	55	47
Incremental QALY	–	0.002	0.0006	0.0011	0.0005
ICER ($/QALY)	–	24,000	62,000	53,000	100,000

FB-D, age 57, utility with LTBI = 0.99	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB+	0.50%	0.36%	0.32%	0.25%	0.22%
NNT	–	749	581	409	362
Incremental Cost per Person($)	–	47	35	54	47
Incremental QALY	–	0.0071	0.0021	0.0039	0.0017
ICER ($/QALY)	–	7,000	17,000	15,000	28,000

FB-D, age 57, utility post-TB = 0.87	No testing	Confirm positive	TST	IGRA	Confirm negative
Lifetime Probability of Reactivation TB^{+}	0.50%	0.36%	0.32 %	0.25 %	0.22%
NNT	–	749	581	409	362
Incremental Cost per Person($)	–	47	35	54	47
Incremental QALY	–	0.002	0.0006	0.0011	0.0005
ICER ($/QALY)	–	23,000	61,000	53,000	99,000

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