Priorities for Screening and Treatment of Latent Tuberculosis Infection in the United States

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Rationale: To improve the effectiveness of tuberculosis (TB) control programs in the United States by identifying cost-effective priorities for screening for latent tuberculosis infection (LTBI).

Objectives: To estimate the cost-effectiveness of LTBI screening using the tuberculin skin test (TST) and interferon- γ release assays (IGRAs).

Methods: A Markov model of screening for LTBI with TST and IGRA in risk-groups considered in current LTBI screening guidelines.

Measurements and Main Results: In all risk-groups, TST and IGRA screening resulted in increased mean life expectancy, ranging from 0.03–0.24 life-months per person screened. IGRA screening resulted in greater life expectancy gains than TST. Screening always cost more than not screening, but IGRA was cost-saving compared with TST in some groups. Four patterns of cost-effectiveness emerged, related to four risk categories. (1) Individuals at highest risk of TB reactivation (close contacts and those infected with HIV): the incremental cost-effectiveness ratio (ICER) of IGRA compared with TST was less than \$100,000 per quality-adjusted life year (QALY) gained. (2) The foreign-born: IGRA was cost-saving compared with TST and cost-effective compared with no screening (ICER <\$100,000 per QALY gained). (3) Vulnerable populations (e.g., homeless, drug user, or former prisoner): the ICER of TST screening was approximately \$100,000–\$150,000 per QALY gained, but IGRA was not cost-effective. (4) Medical comorbidities (e.g., diabetes): the ICER of screening with TST or IGRA was greater than \$100,000 per QALY. **Conclusions:** LTBI screening guidelines could make progress toward TB elimination by prioritizing screening for close contacts, those infected with HIV, and the foreign-born regardless of time living in the United States. For these groups, IGRA screening was more cost-effective than TST screening.

Keywords: latent tuberculosis; cost-effectiveness; tuberculin skin test; interferon- γ release assay

Reactivation of latent tuberculosis infection (LTBI) accounts for approximately 70% of cases of active tuberculosis (TB) in the United States (1, 2). Screening and treatment for LTBI is therefore a cornerstone of the strategy for the elimination of TB disease in the United States (3, 4). Previous studies have examined priorities for LTBI screening and treatment, and several have found that isoniazid (INH) therapy for low-risk tuberculin

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Previous studies have examined priorities for latent tuberculosis infection (LTBI) screening and treatment, and several have found that isoniazid therapy for low-risk tuberculin reactors is cost-effective, and even cost-saving in some populations. These studies, however, used estimates of the prevalence of LTBI and rates of reactivation tuberculosis (TB) observed in the 1950s and 1960s, and may not reflect current epidemiologic trends. Further, prior studies investigating the cost-effectiveness of interferon- γ release assays (IGRAs) have focused on select risk-groups and did not prioritize screening among the many risk-groups potentially eligible for screening.

What This Study Adds to the Field

This study uses cost-effectiveness methodologies to directly compare tuberculin skin test and IGRA screening in each of the risk-groups considered by current United States LTBI screening guidelines. The results identify optimal risk-groups for LTBI screening and define priorities for the use of IGRAs. TB control programs and guideline panels can use these data to make additional progress toward the ultimate goal of TB elimination.

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reactors is cost-effective, and even cost-saving in some populations (5–8). These studies, however, used estimates of the prevalence of LTBI and rates of reactivation TB observed in the 1950s and 1960s, and may not reflect current epidemiologic trends (9–11). Furthermore, given the development of interferon- γ release assays (IGRA) as a screening test for LTBI, it is important to expand the investigation to compare the effectiveness and cost-effectiveness of both tuberculin skin test (TST) and IGRA screening (4). Although prior studies have investigated the cost-effectiveness of IGRA, they focused on select risk-groups, and did not prioritize screening among the many risk-groups currently recommended for screening (12–14).

Recent reports indicate a lower prevalence of LTBI, lower rate of progression to active TB, and higher proportion of discontinuation of therapy for LTBI than previously assumed (15–20). Further, the Centers for Disease Control and Prevention (CDC) recently released updated guidelines for using IGRA to screen for *Mycobacterium tuberculosis* infection, recommending both TST and IGRA in groups at higher risk for developing active TB (4). Given this evolution of understanding and recommendations, an examination of the cost-effectiveness of TST and IGRA screening for LTBI could provide important insights into the efficient design of programs to reduce the burden of TB in the United States.

Some of the results of these studies have been previously reported in the form of an abstract (21).

METHODS

We constructed a Markov model using TreeAge Pro 2009 (Williamstown, MA) computer software to estimate the effectiveness and cost-effectiveness of using either TST or IGRA to screen for LTBI in each of the CDC-defined risk-groups referenced in current United States LTBI screening guidelines (3, 4). Risk-groups included recent immigrant adults and children; foreign-born residents living in the United States for more than 5 years (stratified by age); close-contact adults and children; individuals infected with HIV; the homeless; injection drug users; former prisoners; gastrectomy patients; underweight patients; and persons with silicosis, diabetes, and end-stage renal disease (Table 1). For each risk-group, we compared the number needed to screen to prevent one case of active TB, life expectancy, quality-adjusted life-expectancy, lifetime medical costs, and the incremental cost-effectiveness ratio (ICER) of three strategies for screening for LTBI: (1) no screening, (2) using TST to screen, or (3) using IGRA to screen. Mortality attributable to causes other than TB was a function of age and sex, and was adjusted to reflect differing competing risks of death between risk-groups. The model included direct healthcare costs expressed in 2011 US dollars (22). We applied a 3% discount rate to future costs and benefits (23). In addition to the description below, further details of the model structure and parameter calculations are available in the online supplement.

Model Summary

The model began with a decision between not screening for LTBI, screening with TST, or screening with IGRA. To model less than optimal follow-up with TST, only 88% of individuals who had the TST planted returned for reading (13, 24). Individuals who did not return for TST reading were not eligible for INH therapy. For both TST and IGRA screening, 90% of patients with a positive test started INH therapy (Table 2) (19).

Prevalence of LTBI. The model distinguished between an individual's true LTBI status and clinical knowledge of LTBI status attained through screening test results. Thus, the input parameters required estimates of the prevalence of true LTBI (as opposed to prevalence of positive skin tests) in each risk-group (Table 1). We used published estimates of TST test characteristics and reports of risk-group-specific prevalence of a positive TST to estimate the prevalence of true LTBI in each risk-group (4, 17, 25–29):

$$\text{Positive TST prevalence} = (\text{TST_sensitivity} * \text{Prev_LTBI}) + [(1 - \text{TST_specificity}) * (1 - \text{Prev_LTBI})]$$

where:

$$\text{TST_sensitivity} = \text{sensitivity of TST}$$

$$\text{TST_specificity} = \text{specificity of TST}$$

$$\text{Prev_LTBI} = \text{prevalence of true LTBI}$$

Test characteristics for TST and IGRA. The base case scenario assumed that TST was 92% specific in foreign-born individuals, and 98% specific in individuals in the United States (Table 2) (4, 25–29). IGRA was 99% specific in all risk-groups (4, 25–29). TST was more sensitive than IGRA for all risk-groups (89% vs. 83% sensitivity) (4, 26, 28, 30–33). Patients with a positive screening test were eligible to start INH prophylaxis regardless of their LTBI status. A proportion of patients with a positive screening test started INH therapy for a planned 9-month course. In sensitivity analyses, we varied assumptions about test characteristics.

INH prophylaxis. While taking INH, patients faced an age-stratified, monthly risk of developing nonfatal or fatal INH-related hepatitis (34). Patients taking INH also had a monthly probability of stopping therapy for reasons other than toxicity (nonadherence) (35). We modeled the efficacy of INH therapy as a relative decrease in the rate of reactivation TB. The protective effect of INH was as a function of the length of treatment completed (Table 2) (36).

Risk of reactivation TB. Only those with underlying LTBI (and not those with a false-positive screening test) were at risk for developing reactivation TB. To estimate the rate of reactivation in patients with LTBI, we used a four-step approach. First, we estimated the rate of reactivation TB in individuals with a positive TST, using the following, previously published formula (18, 19):

$$\begin{aligned} \text{Rate per 100 person-years} &= 100 * \\ &\frac{[(\text{Total TB cases} - \text{HIV TB cases}) * (\% \text{ non-cluster TB cases})]}{(\text{Total population} - \text{HIV population}) * (\text{Positive TST prevalence})} \end{aligned}$$

TABLE 1. CHARACTERISTICS OF EACH COHORT EVALUATED IN A COST-EFFECTIVENESS ANALYSIS OF SCREENING FOR LATENT TUBERCULOSIS INFECTION IN THE UNITED STATES

Risk-group	Mean Age (range evaluated)	LTBI Prevalence, % (range evaluated)*	Baseline Rate Reactivation TB Per 100 Person-years	INH Completion Rate (%)†	Sources
Foreign-born living in the United States >5 yr					
6–14 yr	11 (6–14)	11.4 (3–26)	0.079	58	(15)
15–24 yr	20 (15–24)	12.4 (3–30)	0.079	44	(17)
25–44 yr	35 (25–44)	21.4 (14–30)	0.079	44	(17)
45–64 yr	55 (45–64)	26.8 (17–38)	0.079	49	(17)
65+ yr	65 (65–85)	11.4 (3–26)	0.079	48	(17)
Recent immigrant adult	27 (17–37)	41.4 (40–43)	0.079	51	(17,54,70,71)
Recent immigrant child	2.5 (0–5)	7.0 (1–18)	0.079	51	(17,54,70,71)
Close-contact adult	35 (17–65)	43.7 (42–46)	1.020	48	(18,37)
Close-contact child	2.5 (0–5)	19.5 (16–23)	1.640	48	(18,37)
Infected with HIV	35 (25–55)	5.3 (2–9)	2.070	52	(17,72)
Immunosuppressive drugs	55 (45–65)	5.3 (2–9)	0.158	50	(17,73)
Homeless	34 (24–44)	28.7 (27–30)	0.079	25	(74–78)
Injection drug user	34 (24–44)	23.0 (21–24)	0.079	24	(78–80)
Former prisoner	40 (30–50)	19.0 (18–19)	0.079	33	(81,82)
Gastrectomy	39 (29–49)	2.8 (1–5)	0.100	50	(17,83)
Underweight	42 (32–52)	2.8 (1–5)	0.123	50	(17,84)
Silicosis	50 (40–60)	2.8 (1–5)	0.100	50	(17,85)
Diabetic	57 (47–67)	2.8 (1–5)	0.131	41	(17,86)
End-stage renal disease	58 (48–68)	2.8 (1–5)	0.185	43	(17,49)

*Prevalence of LTBI was calculated from reports of the prevalence of positive TST and TST sensitivity and specificity; details are included in the METHODS section. In sensitivity analyses, the prevalence of positive TST ranged from 5–40%.

†Completion rates observed in the Glades Health Survey (35). In sensitivity analyses, the INH completion rate ranged from 25–100%.

TABLE 2. SELECT INPUT PARAMETERS FOR A COST-EFFECTIVENESS MODEL OF SCREENING FOR LATENT TUBERCULOSIS IN THE UNITED STATES

Variable	Base Case Estimate	Range Evaluated	Source
Test characteristics			
TST sensitivity	0.89	0.5–1	(4,26,28,30–33)
TST specificity			
Foreign born	0.92	0.5–1	(4,14,25–29)
United States born	0.98	0.5–1	
IGRA sensitivity	0.83	0.5–1	(4,26,28,30–33)
IGRA specificity	0.99	0.5–1	(4,25–29)
Probability of return to have TST read	0.88	0.5–1	(13,24)
Proportion of patients with positive screening TST who start INH	0.90	0.25–1	(19)
TB risk reduction from INH, %			(36)
3–5 mo INH completed	30	0–69	
6–8 mo INH completed	60	50–75	
9 mo INH completed	90	75–100	
Probability of INH-related hepatitis			(34,87)
Age 0–34 yr	0.001	0.0005–0.0015	
Age ≥ 35 yr	0.01	0.005–0.015	
INH-related hepatitis mortality rate per case	0.01	0.005–0.015	(6,36,87)
Probability of death with active TB			(13,20)
No medical comorbidities	0.05	0.03–0.07	
All groups with chronic conditions	0.06	0.03–0.12	
Probability of extended TB therapy			
HIV or immunosuppressive drugs	1.0	0.124–1	(88)
All others	0.124	0.006–0.25	(87,89)
Secondary TB cases per primary case	0.31	0.25–1.1	(37,40,90)
Quality adjustments			(41–43)
INH therapy without toxicity	1.0	0.9–1	
Nonfatal INH hepatitis	0.85	0.6–1	
Active TB	0.8	0.6–1	
Month of TB or INH-related death	0.3	0.2–0.5	
After having active TB	1.0	0.9–1	
Cost of TST placement and reading			
TST reagents	\$2.37		(22,44,91)
One nursing visit	\$19.71		(22,44,92)
Total	\$22.09	\$11–\$33	
Cost of TST read			
One nursing visit	\$19.71	\$9–\$30	
Cost of IGRA screening [‡]	\$51.77	\$26–\$104	(13,14,22,24,44)
Cost resulting from a positive screening test			
New patient visit	\$73.35		(22,44,92)
Chest radiograph	\$33.12		(22,44,93)
Total	\$106.47	\$52–\$163	
Cost of INH therapy per month on treatment			
30 d INH, 300 mg daily	\$2.83		(22,44,91)
Physician clinic visit	\$48.51		(22,44,92)
Total	\$51.34	\$26–\$78	
Cost of nonfatal INH-induced hepatitis			
Two physician visits	\$150.66		(22,44,92)
Two sets of liver enzymes	\$31.95		(22,44,93)
Total	\$182.61	\$91–\$274	
Cost of hospitalization with fatal INH hepatitis	\$7,906.66	\$3,900–\$11,900	(6,22,44,94)
Costs of active TB			
First month of diagnosis			
TB hospitalization and drugs [§]	\$10,071.78		(22,44,95,96)
Diagnostic costs	\$463.88		(22,44,87)
Contact tracing	\$486.66		(22,44,87)
Total	\$11,021.28	\$5,500–\$16,600	
Month 2			
Drug (INH, RIF, PZA, ETH)	\$299.06		(22,44,91)
DOT daily	\$693.33		(22,44,87)
Physician clinic visit	\$75.33		(22,44,92)
Chest radiograph	\$33.12		(22,44,93)
Liver enzymes	\$15.98		(22,44,93)
Total	\$1,116.21	\$500–\$1,600	
Months 3+			
Drug (INH, RIF)	\$14.82		(22,44,91)
DOT twice per week	\$184.89		(22,44,87)
Physician clinic visit	\$75.33		(22,44,92)
Liver enzymes	\$15.98		(22,44,93)
Mycobacterial identification	\$21.12		(22,44,93)
Mycobacterial culture	\$21.39		(22,44,93)
Chest radiograph	\$33.12		(22,44,93)

(Continued)

TABLE 2. (CONTINUED)

Variable	Base Case Estimate	Range Evaluated	Source
Total per month, months 3+	\$309.92	\$200–\$500	
Total per case (6-mo treatment)	\$13,377.95	\$6,700–\$20,100	
Total per case (9-mo treatment)	\$14,307.78	\$7,100–\$21,500	
Costs of TB-related mortality			
TB hospitalization (15 d)	\$22,464.11	\$10,400–\$31,100	(22,44,95)

Definition of abbreviations: DOT = directly observed therapy; ETH = ethambutol; IGRA = interferon- γ release assays; INH = isoniazid; LTBI = latent tuberculosis infection; PZA = pyrazinamide; RIF = rifampin; TB = tuberculosis; TST = tuberculin skin test.

[†] Cost of IGRA varies by site and laboratory resources available. The value selected for the base case scenario reflects an IGRA cost relative to TST cost similar to that reported in other cost-effectiveness analyses. We varied the cost of IGRA widely in sensitivity analyses.

[§] Costs of active TB hospitalization were based on estimates that 45% of HIV-negative patients with active TB are hospitalized because of their disease. For patients infected with HIV and those taking immune suppressive drugs, 63% were assumed to need hospitalization and hospital costs were \$13,100 (96).

^{||} Costs of outpatient TB care in months 3 and beyond included one sputum smear for mycobacterial identification and culture and one chest radiograph posterior-anterior and lateral obtained at some point during months 3–6.

We used CDC surveillance data of the number of cases of active TB in the United States and percent of TB cases that are nonclustered, National Health and Nutrition Examination Survey estimates of the prevalence of positive TST, and United States census population estimates to inform each variable in the equation (15, 17, 20).

Second, we applied risk-group-specific relative risks of reactivation to this general population rate to calculate risk-group-specific reactivation given a positive TST (18, 19, 37). Third, to calculate the rate of reactivation TB in individuals with LTBI (as opposed to in those with a positive TST) we used the following formula:

$$\text{Reactivation} \mid \text{POS_TST} = (\text{Reactivation} \mid \text{LTBI} * \%_{\text{True_POS}}) + (\text{Reactivation} \mid \overline{\text{LTBI}} * 1 - \%_{\text{True_POS}})$$

where:

$\text{Reactivation} \mid \text{POS_TST}$ = rate of reactivation TB in all individuals with a positive TST

$\text{Reactivation} \mid \text{LTBI}$ = rate of reactivation TB in individuals with true LTBI infection

$\text{Reactivation} \mid \overline{\text{LTBI}}$
= rate of reactivation TB in individuals without LTBI infection
= 0 cases/100 person-years

$\%_{\text{True_POS}}$ = the percent of all positive TST results that are true positive tests

$\%_{\text{True_POS}}$
= the percent of all positive TST results that are true positive tests
$$= \frac{\text{TST_sensitivity}}{\text{TST_sensitivity} + (1 - \text{TST_specificity})}$$

Fourth, we accounted for self-cure of LTBI and resultant reductions in risk of reactivation with time. Approximately 10% of TST-positive persons lose their skin test reactivity over a decade of follow-up. Such persons are believed to have self-cured, and they have no individual-risk of reactivation. Among those who remain skin test positive, however, the risk of reactivation remains constant (38). The effect is that over time, the group-risk among all those who had a positive skin test at the beginning of the observation declines by 10% each year. We modeled this phenomenon by assuming a 10% reduction in the rate of reactivation each decade (18, 39).

For close contacts, we modeled early latent and late latent phases of infection. The high rate of reactivation disease in the early latent phase decreased exponentially over the course of the first 10 years down to the risk of a patient with a nonconversion skin test, and subsequently further decreased 10% every 10 years (18, 37).

Secondary cases of active TB. Each case of reactivation TB resulted in 0.31 cases of secondary TB distributed throughout the expected lifetime of contact cases (40). We included the present value of lost life expectancy and increased costs attributable to all secondary cases of TB in cost-effectiveness calculations.

Quality of life. Quality of life parameters were based on published estimates collected using the Medical Outcomes Study SF-36 and the EQ-5D (41–43). In the base case analysis, we assumed that quality of life with cured TB was the same as that for healthy individuals. In sensitivity analyses, we varied this assumption to allow for long-term quality of life decrements for patients with cured TB.

Costs. Costs were expressed in 2011 U.S. dollars (22, 44, 92–94). Costs included such components as nursing and physician visits, diagnostic tests, medications, hospitalizations, contact tracing, and directly observed therapy (Table 2). In the base case analysis, we assumed that potential targets for screening were already identified and managed by existing resources, such as primary care providers and community health centers, and therefore did not include programmatic costs associated with expanded screening interventions. In sensitivity analyses, we relaxed this assumption by varying the cost of screening. Risk-group-specific healthcare costs not related to LTBI were informed by the Medical Expenditure Panel Survey and published reports of the relative increase in healthcare costs for specific risk-groups (45–52).

Base Case Analyses

For each risk-group, we simulated the lifetime progression of a cohort of patients from the time of screening to death. We compared three screening strategies: (1) no screening, (2) screening with TST, and (3) screening with IGRA. We used both \$50,000 per quality-adjusted life-year (QALY) gained and \$100,000 per QALY gained thresholds to define screening as cost-effective (53). To provide an estimate of the absolute public health benefit of screening, we used published estimates of the number of individuals from each risk-group living in the United States (N) and model-based estimates of the number needed to screen to prevent one case of active TB (NNS) to estimate the total number of cases of active TB that could be prevented by screening every individual in a given risk-group (total cases preventable = N/NNS) (54–65).

Sensitivity Analyses

We performed a series of one-way and two-way sensitivity analyses in which we altered the value of all model parameters through their plausible ranges to explore the role of uncertainty in key model parameters and better understand the factors that drive the cost-effectiveness of LTBI screening (66). Sensitivity analyses paid particular focus on uncertainty in rates of reactivation TB, TST, and IGRA test characteristics, and IGRA cost. We repeated the base case analysis using two different estimates of TB reactivation: the higher rate of reactivation that informs current guidelines, 0.11 cases per 100 person-years (prior estimate); and the rate of reactivation observed in the most recent Glades Health Survey, 0.040 cases per 100 person-years (low estimate) (18, 19). We also performed a series of two-way sensitivity analyses in which we varied the test characteristics of each screening test to observe how assumptions about sensitivity and specificity affected the

TABLE 3. BASE CASE RESULTS OF AN ANALYSIS OF SCREENING FOR LTBI IN THE UNITED STATES

Risk-group	Number Needed to Screen	Discounted per Person Lifetime Cost (\$)	Undiscounted per Person Life Expectancy	Discounted per Person Quality-adjusted Life Expectancy (QALM)	Incremental Cost-Effectiveness Ratio (\$/QALY)
Close-contact child					
No screen	—	129,920	890.79	350.29	—
Screen TST	110	129,970	891.03	350.39	6,200
Screen IGRA	104	129,980	891.04	350.40	21,100
Close-contact adult					
No screen	—	125,510	522.39	281.14	—
Screen TST	73	125,610	522.60	281.27	8,900
Screen IGRA	69	125,620	522.61	281.28	21,500
HIV-infected					
No screen	—	503,300	516.72	279.55	—
Screen TST	71	503,420	516.93	279.67	12,800
Screen IGRA	67	503,440	516.95	279.68	23,800
Recent immigrant adult					
No screen	—	122,560	630.50	308.26	—
Screen TST	136	122,700	630.60	308.31	Dominated
Screen IGRA	128	122,700	630.61	308.31	35,200
Foreign-born living in the US >5 yr age 6–14 yr					
No screen	—	96,130	823.68	341.99	—
Screen IGRA	358	96,210	823.73	342.01	52,900
Screen TST	380	96,210	823.73	342.01	Dominated
Foreign-born living in the US >5 yr age 25–44 yr					
No screen	—	130,210	545.90	287.97	—
Screen IGRA	301	130,310	545.94	287.99	57,400
Screen TST	319	130,310	545.93	287.99	Dominated
Foreign-born living in the US >5 yr age 15–24 yr					
No screen	—	110,140	716.87	325.02	—
Screen IGRA	424	110,220	716.91	325.03	63,200
Screen TST	450	110,230	716.90	325.03	Dominated
Recent immigrant child					
No screen	—	131,940	917.12	360.16	—
Screen IGRA	582	132,010	917.15	360.34	74,800
Screen TST	617	132,020	917.15	360.36	Dominated
Homeless					
No screen	—	645,470	386.09	231.93	—
Screen TST	436	645,600	386.11	231.94	95,000
Screen IGRA	411	645,610	386.11	231.94	194,300
Foreign-born living in the US >5 yr age 45–64 yr					
No screen	—	140,330	330.51	214.50	—
Screen TST	363	140,450	330.52	214.51	Dominated
Screen IGRA	343	140,450	330.52	214.51	103,000
Injection drug user					
No screen	—	645,490	386.11	231.93	—
Screen TST	557	645,600	386.13	231.95	104,600
Screen IGRA	525	645,610	386.13	231.95	227,900
Immunosuppressive medications					
No screen	—	230,700	260.67	181.66	—
Screen TST	1,128	230,750	260.68	181.67	129,000
Screen IGRA	1,064	230,760	260.68	181.67	286,100
Prisoner					
No screen	—	673,650	326.35	208.02	—
Screen TST	655	673,740	326.36	208.02	147,600
Screen IGRA	618	673,760	326.36	208.02	281,300
Underweight					
No screen	—	124,690	356.87	223.54	—
Screen TST	2,062	124,740	356.87	223.54	227,300
Screen IGRA	1,946	124,750	356.87	223.54	370,800
Gastrectomy					
No screen	—	134,570	427.66	249.70	—
Screen TST	2,176	134,620	427.66	249.70	242,900
Screen IGRA	2,054	134,630	427.66	249.70	361,900
Foreign-born living in the US >5 yr age 65+ yrs					
No screen	—	137,110	223.73	162.65	—
Screen IGRA	1,147	137,200	223.73	162.65	283,300
Screen TST	1,216	137,200	223.73	162.65	Dominated
Silicosis					
No screen	—	253,070	295.27	198.18	—
Screen TST	2,962	253,140	295.27	198.18	385,700
Screen IGRA	2,795	253,150	295.27	198.18	502,700

(Continued)

TABLE 3. (CONTINUED)

Risk-group	Number Needed to Screen	Discounted per Person Lifetime Cost (\$)	Undiscounted per Person Life Expectancy	Discounted per Person Quality-adjusted Life Expectancy (QALM)	Incremental Cost-Effectiveness Ratio (\$/QALY)
Diabetes					
No screen	—	233,460	197.55	147.52	—
Screen TST	3,631	233,510	197.56	147.52	511,300
Screen IGRA	3,426	223,520	197.56	147.52	684,400
End-stage renal disease					
No screen	—	581,280	95.85	80.19	—
Screen TST	4,904	581,330	95.85	80.19	824,500
Screen IGRA	4,628	581,340	95.85	80.19	1,168,300

Definition of abbreviations: Dominated = denotes a strategy that provides decreased life expectancy at a higher cost than an alternative approach, or a strategy that provides increased life expectancy, but at a higher cost per QALY gained than an alternative approach; IGRA = interferon- γ release assay; LTBI = latent tuberculosis infection; NNS = number needed to screen to prevent one infection; QALM = quality-adjusted life month; QALY = quality-adjusted life-year; TST = tuberculin skin test.

cost-effectiveness of each test. In addition, we performed a series of analyses in which we simultaneously varied TST test characteristics and IGRA cost to understand the relationship between the relative performance of IGRA and TST, IGRA cost, and cost-effectiveness.

RESULTS

Compared with no screening, screening with TST resulted in undiscounted life-expectancy gains between 0.00 and 0.24 life months (0.00–0.13 discounted quality-adjusted life months) at an incremental cost from \$50–\$140 depending on the risk-group. Compared with TST screening, IGRA screening resulted in undiscounted life expectancy gains of 0.00–0.01 life months (0.00–0.008 discounted quality-adjusted life months) at incremental costs ranging from a savings of \$10 to a cost of \$20. The cost-effectiveness of screening for LTBI with TST or IGRA varied by risk-group, with four patterns of cost-effectiveness emerging related to four categories of risk: (1) patients at the highest risk of reactivation (close contacts and those living with HIV infection); (2) the foreign-born (both recent immigrants to the United States and those living in the United States for >5 yr); (3) vulnerable persons (the homeless, injection drug users, and former prisoners); and (4) individuals with chronic medical conditions (Table 3).

Patients at the Highest Risk of Reactivation

In close-contact children and adults and in individuals infected with HIV, the ICER of screening with TST compared with no screening was less than \$50,000 per QALY, as was the ICER of screening with IGRA compared with TST. Although the sensitivity of IGRA was slightly lower than that of TST, because IGRA screening requires only one visit to obtain and interpret results, IGRA minimized loss to follow-up and increased receipt of test results. Thus, IGRA identified a greater number of patients with LTBI than TST screening identified, and IGRA screening was associated with longer life expectancy.

Recent Immigrants and Foreign-born Residents Living in the United States for More Than 5 Years

In recent immigrants to the United States and foreign-born residents who have lived in the United States for more than 5 years (foreign-born residents), IGRA screening resulted in either cost savings compared with TST, or in extended life expectancy with a lower cost per QALY gained compared with TST. Thus, IGRA dominated TST, meaning that any resources dedicated to using TST to screen would be better used providing IGRA screening.

In these risk-groups, IGRA dominated TST for two reasons. First, because IGRA reduced loss to follow-up, it functioned as

a more sensitive screening test than TST, and led to longer mean life expectancy. Second, IGRA was substantially more specific than TST (99% vs. 92% specific), and therefore provided cost savings by minimizing the number of patients unnecessarily treated for LTBI.

The ICER of IGRA screening compared with no screening was less than \$50,000 per QALY gained for recent immigrant adults and was less than \$100,000 per QALY gained for recent immigrant children and foreign-born residents up to age 45 years. The ICER of IGRA screening compared with no screening for foreign-born residents age 45–64 years was \$103,000 per QALY gained. In addition, as a result of a large population of foreign-born United States residents, and a relatively small number needed to screen to prevent one case of active TB, screening the foreign-born living in the United States for more than 5 years could potentially prevent more than 65,000 cases of active TB over the lifetime of those individuals, one of the largest potential absolute impacts of any risk-group (Figure 1).

Vulnerable Populations

The ICER of screening with TST compared with no screening was \$95,000 per QALY gained in the homeless, \$104,600 per QALY gained in injection drug users, and \$147,600 per QALY gained in former prisoners. The ICER of IGRA was \$194,300 for the homeless and more than \$200,000 per QALY gained in injection drug users and former prisoners. In these risk-groups, IGRA continued to have a better case detection rate than TST, but improved case detection resulted in little life-expectancy gain because the risk of reactivation TB was small, and the rate of INH completion low.

Individuals with Chronic Medical Conditions

In patients taking immunosuppressive medications, the ICER of screening with TST compared with no screening was \$129,000 per QALY gained. In all other risk-groups, including underweight patients, gastrectomy patients, and patients with silicosis, diabetes, and end-stage renal disease, the ICER of using TST to screen for LTBI compared with no screening was greater than \$200,000 per QALY gained and the ICER of using IGRA to screen for LTBI compared with using TST was greater than \$300,000 per QALY gained. In these risk-groups, the prevalence of LTBI was low, and the risk of reactivation TB was reduced by competing risks of mortality, such that no screening test was cost-effective.

Sensitivity Analyses on Rate of Reactivation TB

When we assumed the lower rate of reactivation TB observed in the Glades Health Survey (low estimate), the ICER of IGRA

Figure 1. Number of cases of active tuberculosis (TB) preventable through latent tuberculosis infection (LTBI) screening in each risk-group considered by current United States LTBI screening guidelines. The bar graph depicts the absolute number of cases of active TB that could be prevented through screening all members of a given risk-group currently living in the United States. The Y-axis is denominated in terms of the absolute number of cases of active TB that could be prevented through screening with either interferon- γ release assays (IGRA) (for risk-groups in which the incremental cost-effectiveness ratio [ICER] of IGRA screening is <\$100,000 per quality-adjusted life-year [QALY] gained), or tuberculin skin test (TST) (for risk-groups in which the ICER of TST is <\$100,000 per QALY gained). The number of cases preventable was calculated using estimates of the number of individuals in each risk-group living in the United States at the start of the analysis (N), and model-based estimates of the number needed to screen to prevent one case of active TB (NNS). We defined total pre-

ventable cases as N/NNS . *Black bars* illustrate risk-groups in which the ICER of screening with either IGRA or TST is less than \$100,000 per QALY gained, but for whom screening is not currently recommended. The *shaded bars* illustrate risk-groups in which the ICER of screening with either TST or IGRA is less than \$100,000 per QALY gained and for whom screening currently is recommended. The *white bars* indicate risk-groups in which the ICER of both IGRA and TST screening are greater than \$100,000 per QALY gained, but for whom screening currently is recommended.

screening remained less than \$100,000 per QALY gained in close-contact adults and children, recent immigrant adults, and individuals infected with HIV. The ICER of both TST and IGRA screening was greater than \$100,000 per QALY gained in all other risk-groups (Table 4). However, assuming the higher rate of reactivation that informs current United States screening guidelines (prior estimate), the ICER of TST screening was less than \$100,000 per QALY gained in the homeless, injection drug users, and patients taking immunosuppressive medications. The ICER of IGRA screening was less than \$100,000 per QALY gained in close-contact children and adults, individuals infected with HIV, recent immigrants to the United States, and foreign-born United States residents up to age 65 years (Table 4).

Sensitivity Analyses on TST and IGRA Test Characteristics

In recent immigrants and foreign-born United States residents, screening with either TST or IGRA was cost-effective across all plausible estimates of sensitivity. The ICER of IGRA compared with TST was sensitive to TST specificity, but remained less than \$100,000 per QALY gained across a wide range of assumptions about test characteristics (Figure 2).

In close-contact adults, the impact of false-negative results was larger than that of false-positive results and test sensitivity determined cost-effectiveness. TST sensitivity, however, was mitigated by imperfect follow-up for TST results. Thus, IGRA remained cost-effective as long as the sensitivity of IGRA was greater than 79% (base case 83%) (see Figure E3 in the online supplement). If we assumed that 100% of patients returned for TST reading, however, TST was more sensitive than IGRA and provided greater life expectancy at lower cost (Table E1).

Sensitivity Analyses on Cost of IGRA

In foreign-born residents living in the United States for more than 5 years, age 25–44 years, the ICER of IGRA compared with TST screening was less than \$100,000 per QALY gained across a range

of estimates of IGRA test cost and TST test specificity. In the base case (TST specificity in the foreign-born = 92%), IGRA screening remained cost-effective up to an IGRA test cost of \$64 (base case assumption \$52). If the specificity of TST screening is only 85%, IGRA screening remained cost-effective up to an IGRA test cost of \$83 (see Figure E4).

Additional Sensitivity Analyses

Patient age affected cost-effectiveness results through its impact on the lifetime risk of reactivation. When we increased the mean age to 65 years, screening remained cost-effective only for close-contact adults of a case of active TB and persons infected with HIV (Table E2).

INH toxicity had little impact on the cost-effectiveness of screening. When we both halved or doubled the rate of INH toxicity, the ICER of screening did not shift across the \$100,000 per QALY threshold for any risk-group (Table E3).

Rates of INH treatment initiation and adherence to INH therapy had the greatest impact on cost-effectiveness in the homeless, injection drug users, and former prisoners, where very low rates of INH adherence reduced cost-effectiveness compared with the base case scenario (Tables E4 and E5).

The cost-effectiveness of screening was also sensitive to changes in estimates of the quality of life in patients who recovered from active TB. In the base case, we assumed that patients cured of active TB returned to full health. If a history of cured active TB was associated with a life-long 10% decrement in quality of life, the cost-effectiveness of screening with either IGRA or TST was less than \$100,000 per QALY gained for all cohorts except foreign-born United States residents aged 65 years or older, and patients with silicosis, diabetes, and end-stage renal disease (Table E6).

DISCUSSION

As the incidence of active TB in the United States declines, targeted screening for LTBI plays an increasingly important role in

TABLE 4. COST-EFFECTIVENESS OF SCREENING FOR LATENT TUBERCULOSIS INFECTION USING TST OR IGRA UNDER VARYING ESTIMATES OF THE RATE OF REACTIVATION TB

Risk-group	Rate of Reactivation = 0.040 ICER	Rate of Reactivation = 0.079 ICER	Rate of Reactivation = 0.11 ICER
Close-contact child			
Screen TST	23,700	6,200	5,300
Screen IGRA	60,600	21,100	19,200
Close-contact adult			
Screen TST	15,300	8,900	2,100
Screen IGRA	33,200	19,700	8,800
HIV-infected			
Screen TST	16,800	12,800	11,600
Screen IGRA	35,300	23,800	20,400
Recent immigrant adult			
Screen TST	Dominated	Dominated	Dominated
Screen IGRA	74,100	35,200	22,900
Foreign-born age 6–14 yr*			
Screen TST	Dominated	Dominated	Dominated
Screen IGRA	108,000	52,900	35,400
Foreign-born age 25–44 yr*			
Screen TST	Dominated	Dominated	Dominated
Screen IGRA	117,900	57,400	38,300
Foreign-born age 15–24 yr*			
Screen TST	Dominated	Dominated	Dominated
Screen IGRA	128,400	63,200	42,600
Recent immigrant child			
Screen TST	Dominated	Dominated	Dominated
Screen IGRA	150,600	74,800	50,700
Homeless			
Screen TST	172,100	95,000	70,800
Screen IGRA	363,000	194,200	140,600
Foreign-born age 45–64 yr*			
Screen TST	Dominated	Dominated	Dominated
Screen IGRA	291,700	103,000	63,200
Injection Drug User			
Screen TST	191,200	104,600	77,600
Screen IGRA	428,800	228,800	164,900
Immunosuppressive medications			
Screen TST	305,200	129,000	83,800
Screen IGRA	476,900	286,100	210,600
Prisoner			
Screen TST	393,100	147,600	99,600
Screen IGRA	564,300	281,300	198,400
Underweight			
Screen TST	Dominated	227,300	145,500
Screen IGRA	582,500	370,800	291,700
Gastrectomy			
Screen TST	Dominated	242,900	153,800
Screen IGRA	1,059,500	361,900	287,500
Foreign-born aged 65+ yr*			
Screen TST	Dominated	Dominated	Dominated
Screen IGRA	921,600	283,300	172,100
Silicosis			
Screen TST	Dominated	385,700	240,700
Screen IGRA	582,500	502,700	405,900
Diabetes			
Screen TST	Dominated	511,300	318,500
Screen IGRA	1,428,500	684,400	552,600
End-stage renal disease			
Screen TST	Dominated	824,500	531,800
Screen IGRA	2,148,900	1,168,300	944,100

Definition of abbreviations: Dominated = denotes a strategy that provides decreased life expectancy at a higher cost than an alternative approach, or a strategy that provides increased life expectancy, but at a higher cost per QALY gained than an alternative approach; ICER = incremental cost-effectiveness ratio; IGRA = interferon- γ release assays; TST = tuberculin skin test.

Bold italic formatting illustrates risk-groups in which the cost effectiveness of screening with either TST or IGRA is less than \$100,000 per QALY gained.

* “Foreign-born” indicates foreign-born United States residents who have lived in the United States for more than 5 years, in contrast to “recent immigrants” who have lived in the United States for 5 years or less.

TB elimination (3). This analysis demonstrates that screening strategies can be improved to ensure a more efficient use of limited TB control resources. The results demonstrate that the ICER of IGRA compared with TST screening is less than \$50,000 per QALY gained in close contacts of a case of active

TB and individuals infected with HIV. In the foreign-born, both recent immigrants and those living in the United States for more than 5 years, IGRA screening is cost-saving compared with TST screening and the ICER of IGRA screening compared with no screening is less than \$100,000 per QALY gained.

Figure 2. Two-way sensitivity analysis of the incremental cost-effectiveness ratio of screening for latent tuberculosis infection (LTBI) using tuberculin skin test (TST) or interferon- γ release assays (IGRA) in foreign-born residents living in the United States more than 5 years, age 25–44 years. The figure illustrates the choice of screening strategy assuming a willingness to pay \$100,000 per quality-adjusted life-year gained. The vertical axis depicts IGRA test specificity and the horizontal axis TST test specificity. The *solid lines* define the boundaries between combinations of IGRA and TST test specificity that result in either IGRA, TST, or no screening having an incremental cost-effectiveness ratio less than \$100,000 per quality-adjusted life-year gained. The *asterisk* represents the test characteristics assumed in the base case scenario.

The ICER of TST screening is less than \$100,000 per QALY in the homeless, but IGRA is less economically attractive. Screening for LTBI with TST or IGRA is not cost-effective in any other risk-group currently recommended for screening by United States guidelines (3).

This analysis has two important implications for addressing TB elimination in the United States. First, current guidelines recommend screening and treatment only for foreign-born persons living in the United States for 5 years or less (3). Nearly half of United States TB cases, however, occur in foreign-born persons who have been in the United States for more than 5 years, and most of these cases represent reactivation of LTBI (67). This analysis demonstrates that screening the 21 million current foreign-born United States residents living in the United States for more than 5 years could prevent approximately 65,000 cases of active TB over the lifetime of those individuals, at an incremental life-time cost of \$2 billion compared with no screening. Although the total cost seems high, it corresponds to a cost of approximately \$100 per person. In addition, screening such individuals represents good “value for money” in that the ICER of screening the foreign-born compares favorably with that of other well-accepted screening interventions (updated to 2011 \$US), such as annual digital mammography for women aged 40–50 years compared with annual film mammography (\$29,900 per QALY gained), and colonoscopy every 10 years in individuals over 50 years compared with annual fecal occult blood testing (\$14,900 per QALY gained) (68, 69). At the same time, screening in many risk-groups currently recommended for screening prevents fewer cases of TB at a higher cost per QALY gained. Screening foreign-born persons who have lived in the United States for more than 5 years would likely improve progress toward TB elimination in the United States.

Second, the analysis provides evidence to support movement toward IGRA screening for high-risk groups, including close-contact adults and children, individuals infected with HIV, recent immigrants, and foreign-born United States residents. The improved specificity and test completion rate for IGRA compared with TST make IGRA useful for screening in these high-risk groups. However, IGRA is not cost-effective in other groups, and does not make screening cost-effective in risk-groups for which screening with TST is not cost-effective.

There are several limitations to the analysis. First, there are no prospective observational data in the United States to inform

the rate of reactivation TB. The availability of INH prophylaxis for patients with identified LTBI renders natural history cohorts unethical. We used established methods of estimating TB reactivation from public health data, however, and varied the rate of reactivation TB widely in one-way sensitivity analyses. The rank order of cost-effectiveness of screening in various risk-groups, and the cost-effectiveness of IGRA compared with TST, were robust to this uncertainty.

In addition, there is no gold standard to confirm the diagnosis of LTBI. Estimates of TST and IGRA test characteristics are therefore inherently uncertain (4). We used the best available estimates of IGRA and TST test characteristics, however, and included sensitivity analyses to both explore the impact of test characteristics on cost-effectiveness and assess the stability of base case results to parameter uncertainty. The finding that screening foreign-born United States residents with either IGRA or TST is cost-effective compared with no screening was stable across all plausible assumptions about TST and IGRA test specificity. The cost-effectiveness of IGRA compared with TST was more dependent on the relative characteristics of each test, but was stable across most reasonable estimates of both sensitivity and specificity.

Third, costs in the model included direct medical costs, but not indirect costs, such as lost productivity time and transportation costs. The complexity of accurately assessing such costs for an extremely heterogeneous set of risk-groups made including them infeasible. Perhaps most importantly, however, introducing such costs into the model would generate ethical concerns, in that the time of vulnerable populations and those with comorbidities that restrict their ability to work would be valued less than that of healthy and less disadvantaged populations.

Policy makers and United States guidelines panels can use these results to prioritize groups for targeted LTBI screening. Seeking to maximize the public health impact of TB control resources, programs should prioritize screening foreign-born United States residents up to age 45 years, regardless of their time living in the United States. Further, programs should consider using IGRA screening in close contacts, individuals infected with HIV, and foreign-born persons, but not for other risk-groups. This approach would improve the efficiency of TB control programs, and maximize the impact of public health resources in the effort to eradicate TB infection in the United States.

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