Cost-effectiveness of Latent Tuberculosis Infection Screening before Immigration to Low-Incidence Countries

Jonathon R. Campbell, James C. Johnston, Victoria J. Cook, Mohsen Sadatsafavi, R. Kevin Elwood, Fawziah Marra

Prospective migrants to countries where the incidence of tuberculosis (TB) is low (low-incidence countries) receive TB screening; however, screening for latent TB infection (LTBI) before immigration is rare. We evaluated the cost-effectiveness of mandated and sponsored preimmigration LTBI screening for migrants to low-incidence countries. We used discrete event simulation to model preimmigration LTBI screening coupled with postarrival follow-up and treatment for those who test positive. Preimmigration interferon-gamma release assay screening and postarrival rifampin treatment was preferred in deterministic analysis. We calculated cost per quality-adjusted life-year gained for migrants from countries with different TB incidences. Our analysis provides evidence of the cost-effectiveness of preimmigration LTBI screening for migrants to low-incidence countries. Coupled with research on sustainability, acceptability, and program implementation, these results can inform policy decisions.

The World Health Organization (WHO) has continued working toward tuberculosis (TB) elimination, aiming to reduce the overall TB burden by ≈90% to <1 case/1 million persons in countries where TB incidence is low (low-incidence countries) (*1*). Meeting this target will require new and innovative strategies. Typically, the TB burden in low-incidence countries is highest among populations born abroad; ≈70% of TB cases occur in these populations in Canada, the United States, and much of Europe (*2*). For the most part, TB prevention in these populations has focused on identifying persons with active TB before immigration to reduce transmission after arrival. Stagnant rates of TB suggest additional methods are required to accelerate declines in TB incidence (*3*).

Author affiliations: University of British Columbia, Vancouver, British Columbia, Canada (J.R. Campbell, J.C. Johnston, V.J. Cook, M. Sadatsafavi, R.K. Elwood, F. Marra); British Columbia Centre for Disease Control, Vancouver (J.C. Johnston, V.J. Cook, R.K. Elwood)

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Universal or targeted postarrival screening for latent TB infection (LTBI) has been suggested as a method to accelerate the decline of TB (*4*); however, domestic LTBI programs exhibit suboptimal performance (*5*), are resource intensive (*6*), and may not be cost-effective (*7*). One major reason for the reduced effectiveness of postarrival LTBI screening programs is the substantial attrition in the LTBI cascade of care. More than half of patients do not reach the point of initiating treatment, which results in fewer than one fifth completing treatment (*5*).

Currently, most immigrant-receiving, low-incidence countries employ mandatory preimmigration medical exams (*8*). As part of these medical exams, a chest radiograph and medical evaluation are performed to detect TB disease before arrival or identify those who may be at increased risk for TB disease in the future; these costs are borne by the patient within their country of origin. Only a select few countries employ some form of mandated LTBI screening (*8*), and data are scarce on the yield of such programs.

A report sponsored by the US Centers for Disease Control and Prevention (Atlanta, GA, USA) suggested mandatory LTBI screening and treatment as part of routine preimmigration medical exams (*9*); however, this strategy was viewed as inequitable and unjustly coercive (*10*) and has never been employed. Alternatively, mandating and fully sponsoring only LTBI screening as a formal part of the immigration process would avoid such ethics quandaries and could substantially reduce postarrival TB incidence. Preimmigration screening coupled with postarrival follow-up could improve the yield of LTBI screening programs >2-fold (*5*), because all case-patients reporting postarrival would already have completed LTBI screening.

We evaluated the cost-effectiveness of mandating and fully sponsoring LTBI screening in prospective migrants as part of routine preimmigration medical exams, coupled with passive postarrival follow-up and treatment. We evaluated 6 strategies among migrants from 4 different TB incidence groups to determine the optimal strategy in each group for this intervention.

Methods

Model Overview

We chose discrete event simulation for this model because of its flexibility in varying transition times between health states in a single simulation, ability to simulate simultaneous events, and capability to model several different patient covariates. These advantages make it preferable to traditional Markov models and enable the creation of a highly representative cohort in a single simulation (*11*). We modeled new migrants, which in this evaluation refers specifically to persons who have been granted permanent resident status but have not yet become citizens of the countries they reside in. Of interest were migrants from countries belonging to 4 distinct TB incidence categories: low, <30 cases/100,000 persons/year; moderate, ≥30 and <100 cases/100,000 persons/year; high, ≥100 and <200 cases/100,000 persons/year; and very high, ≥200 cases/100,000 persons/year.

We further defined the 4 populations of interest by 4 covariates: patient age, bacillus Calmette-Guérin (BCG) vaccination status, chest radiograph results, and LTBI prevalence. Patient age was defined based on an age distribution of a reference cohort of permanent residents to Canada in 2014 (*12*). BCG vaccination was determined through presence of a universal BCG vaccination policy in each country of origin and adjusted by 36-year average BCG vaccine uptake (*13–15*). For chest radiograph, a reference cohort of permanent residents who came to Ontario during 2002–2011 was used to identify prevalence of abnormal chest radiograph results (*15*). LTBI prevalence was calibrated in each population using 2-year TB incidence in permanent resident cohorts to Ontario during 2002–2011 (*15*) and age-adjusted using the results of a meta-analysis of test-positive rates (*16*).

We estimated LTBI prevalence using several assumptions. First, we assumed that 85% of incident TB resulted from reactivation of LTBI (*17*); second, that TB reactivation did not change over time post arrival (*18*); and last, that LTBI prevalence approximately matched reported rates of interferon-gamma release assay (IGRA) positivity in persons from each of the 4 TB incidence categories (*16*). In sum, an LTBI reactivation rate of 1.1 cases/1,000 person-years approximated literature values and yielded reasonable estimates of LTBI prevalence (*17*).

The model evaluates implementation of the intervention: preimmigration LTBI screening coupled with postarrival follow-up and treatment. The base case in this model was considered to be preimmigration TB screening without any evaluation for LTBI before or after arrival but with routine postarrival follow-up for those flagged through TB screening. We calibrated baseline TB incidence estimates and rates of postarrival follow-up to TB incidence data in permanent resident cohorts to Ontario during 2002–2011 (*15*). We considered 3 preimmigration LTBI screening options and 2 postarrival LTBI treatment options, for a total of 6 unique strategies to compare with the base case (Table 1).

We screened migrants with a tuberculin skin test (TST), IGRA, or sequential screening, in which persons testing positive by TST were given a confirmatory IGRA. We defined a positive TST result as an induration measuring ≥10 mm and a positive IGRA result using manufacturer's recommendations, with IGRA performance being a composite measure of results from commercially available products (*19–21*). Although preimmigration testing was mandated, postarrival follow-up and treatment was not mandated and instead assumed to be passive, following published rates of postarrival follow-up in several countries (*22*). That is, in migrants who tested positive for LTBI, it was recommended that they attend a clinic for treatment postarrival, but no system was in place to enforce this. Those who reported for care postarrival would be treated with 9 months of isoniazid or 4 months of rifampin.

The model took a healthcare system perspective for the fully sponsored and mandated preimmigration LTBI screening: all LTBI screening costs preimmigration, along with typical postarrival costs, were the responsibility of the receiving country's healthcare system. We used a 3% annual discount rate for costs and outcomes (*23*) and a 25-year time horizon from arrival. The main outcomes of the model were quality-adjusted life-years (QALYs), number of TB cases, and costs per 1,000 permanent residents from each of the 4 populations analyzed. These data were used to calculate the cost-effectiveness ratio, a measure that indicates the cost per additional QALY gained by an intervention strategy compared with the base case (Appendix, https://wwwnc.cdc.gov/EID/article/25/4/17-1630-App1.pdf).

A simplified model structure is displayed in Figure 1. In the intervention, migrants were given an LTBI diagnostic test along with the rest of their medical exam; those who tested positive were referred for postarrival follow-up. Those who complied with postarrival follow-up were recommended for LTBI therapy. After initiating treatment, they either completed treatment in full, partially completed treatment, or ceased due to an adverse event that may result in death. After treatment, results for all patients were simulated to the 25-year time horizon, with annual risks of TB reactivation and death.

We made the following assumptions in the model. Those with previous TB or an abnormal chest radiograph result identified during the preimmigration medical exam were also referred for postarrival follow-up. With the intervention, all those who began screening completed it,

Table 1. Intervention strategies for screening and treatment of latent TB infection in immigrants*

Intervention strategy	Preimmigration	Postarrival if test is positive
Base case	TB screening as part of routine preimmigration medical exams, consisting of a chest radiograph, medical history, and symptom screen. If diagnosed with TB, treatment must be completed before immigrating.	Routine follow-up of those with abnormal chest radiograph results or previous TB.
TST/INH	In addition to the base case, a TST is performed at the time of the medical exam. If the result is positive (induration ≥10 mm) referral is made for follow-up postarrival. If the TST result is negative, no further action is taken.	Recommendation for follow-up; if patient reports for follow-up, 9-month course of INH.
TST/RIF	Same as above.	Recommendation for follow-up; at follow-up, 4-month course of RIF.
IGRA/INH	In addition to the base case, an IGRA is placed at the time of the medical exam. If the result is positive (as defined by the manufacturer) referral is made for follow-up postarrival. If the IGRA result is negative, no further action is taken. If the IGRA result is indeterminate, a second is performed; a second consecutive indeterminate is treated as a negative.	Recommendation for follow-up; if patient reports for follow-up, 9-month course of INH.
IGRA/RIF	Same as above.	Recommendation for follow-up; if patient reports for follow-up, 4-month course of RIF.
SEQ/INH	In addition to the base case, a TST is placed at the time of the medical exam. If the result is positive (as defined by an induration ≥10 mm) a second test is performed with an IGRA. If the subsequent IGRA result is positive (as defined by the manufacturer) referral is made for follow-up postarrival. If the initial TST is negative or if the subsequent IGRA is negative, no further action is taken. If the IGRA result is indeterminate, a second is performed; a second consecutive indeterminate is treated as a negative.	Recommendation for follow-up; at follow-up, 9-month course of INH.
SEQ/RIF	Same as above.	Recommendation for follow-up; at follow-up, 4-month course of RIF.

*No intervention required for migrants with negative results of base case screening. IGRA, interferon-gamma release assay; INH, isoniazid; RIF, rifampin; SEQ, sequential screening; TB, tuberculosis TST, tuberculin skin test.

eliminating dropout during this stage of the LTBI cascade of care. Drug-resistant TB and self-cure of LTBI were not modeled. It was assumed that all those who tested positive were offered LTBI treatment to limit extrapolation of care provider decisions. All reactivation TB cases had a 17.6% chance of causing a secondary case; further transmission was not modeled (Appendix). Modeling was completed in Simio version 8.146.14121 (Simio LLC, https://www.simio.com).

Model Parameters

We derived model estimates from the literature or expert opinion (Table 2). A meta-analysis provided evidence for domestic LTBI program performance (*5*), therapy efficacy was derived from the literature (*24*,*27*,*28*), and adverse events were imputed from several randomized controlled trials reported in previous analysis (*24*,*25*). Diagnostic performance of LTBI screening tests was derived from systematic reviews and modeled to be the same in each country (*19*–*21*). Adherence with postarrival follow-up was estimated by reanalysis of reported data (*22*) (Appendix Figure 1). Death from tuberculosis (*3*), probability of TB therapy extension (*30*), and relapse rate (*31*) were derived from Canada sources. Life tables for Canada estimated background mortality (*32*).

We derived all costs from Canada sources and assumed that the costs of screening abroad were equal to screening costs in Canada. We derived costs for LTBI treatment and screening, including drugs, screening tests, routine monitoring, and clinician time, from the British Columbia Centre for Disease Control. Adverse event costs, including hospitalization rates and time, and the cost of TB disease were as reported in the literature (*30*,*33*,*34*). We inflated all costs to 2016 Canadian dollars using consumer price indices (*35*) (Table 3).

We derived health utility data from a study (*38*) in Canada of migrants who reported for postarrival follow-up. We based adjustments due to adverse events or hospitalization on previous studies (*30*,*33*).

Sensitivity Analysis

We performed a probabilistic sensitivity analysis (PSA) to capture uncertainty of model estimates using an outer sample size of 1,000 and inner sample size of 50,000 (Tables 2, 3). To guide policymakers, we created cost-effectiveness acceptability curves (CEAC) to determine the probability that the most cost-effective intervention strategy in deterministic analysis would fall below various willingness-to-pay (WTP) thresholds. Exploratory sensitivity analysis and additional probabilistic sensitivity analyses are included in the Appendix.

Results

Primary Results

Among migrants from moderate- to very high–incidence countries, IGRA screening coupled with postarrival rifampin treatment was the optimal intervention strategy in deterministic analysis. Sequential screening coupled with postarrival rifampin treatment was the optimal intervention strategy among migrants from low-incidence countries. Intervention strategies involving TST identified the most migrants for postarrival follow-up, whereas strategies involving sequential screening identified the fewest. Intervention strategies involving rifampin resulted in the fewest TB cases (46% reduction compared with the base case) (Table 4).

Low-Incidence Countries

For migrants from low-incidence countries, screening with TST alone resulted in a net loss in population QALYs because of poor specificity of the TST. Sequential screening, the most specific screening method, coupled with postarrival rifampin treatment yielded the lowest cost per QALY gained at $191,889. IGRA screening, the most sensitive screening method, coupled with rifampin treatment resulted in the fewest TB cases (46.2% reduction) but had a higher cost per QALY gained ($373,773) because of its lower specificity compared with that of sequential screening.

Moderate-Incidence Countries

For migrants from moderate-incidence countries, the optimal intervention strategy was IGRA screening coupled with postarrival rifampin treatment for those from moderate-incidence countries with a cost per QALY gained of $43,343. Sequential screening coupled with postarrival rifampin treatment was cheaper overall but had a cost per QALY gained of $47,561.

High-Incidence Countries

Among migrants from high-incidence countries, IGRA screening coupled with postarrival rifampin treatment was the optimal intervention strategy, at a cost per QALY

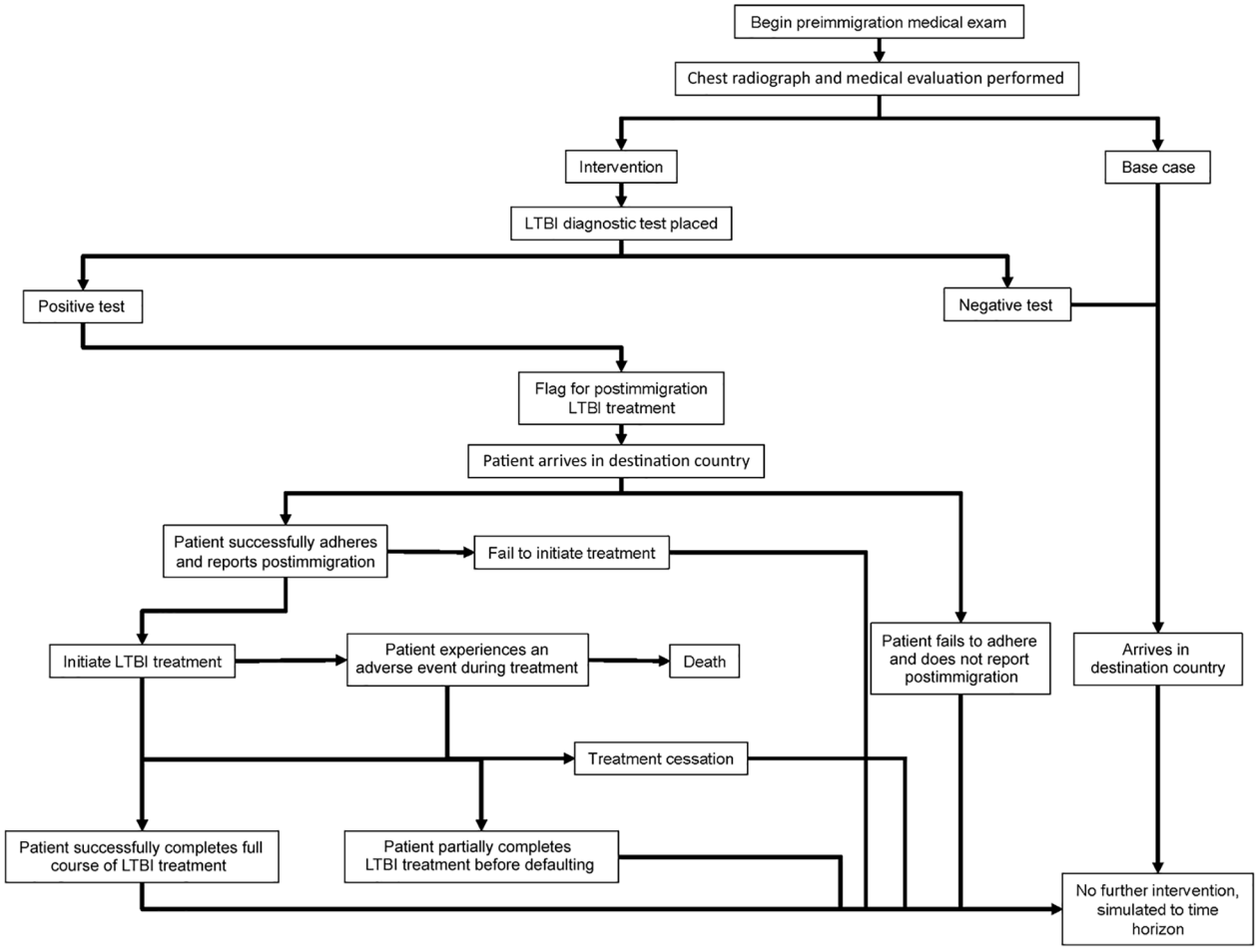

Figure 1. Flow structure of model used for cost-effectiveness analysis of screening and interventions of migrants for TB and LTBI. LTBI, latent tuberculosis infection; TB, tuberculosis.

gained of $26,350. Sequential screening coupled with rifampin treatment was less expensive, but also less efficient, with a cost per QALY gained of $29,997.

Very High–Incidence Countries

Among migrants from very high–incidence countries, IGRA screening coupled with postarrival rifampin treatment had a

Table 2. Model parameter estimates and values used for sensitivity analyses of intervention strategies for screening and treatment of latent TB infection in immigrants*

Parameter	Estimate	Range evaluated in PSA	PSA distribution	References
Screening parameters				
TST sensitivity	0.782	0.69–0.87	Beta (43,12)	(*19*)
TST specificity, no BCG	0.974	0.963–0.982	Beta (770,21)	(*20*,*21*)
TST specificity, BCG	0.602	0.561–0.642	Beta (239,158)	(*20*,*21*)
IGRA sensitivity	0.889	0.688–0.993	Beta (8,1)	(*19*)
IGRA specificity	0.957	0.946–0.968	Beta (900,40)	(*20*,*21*)
IGRA indeterminate†	0.06	0.05–0.07	Beta (83,1286)	(*21*)
Complete TST‡	1	Fixed	Fixed	
Complete medical evaluation§	1	Fixed	Fixed	
Population characteristics¶				
LTBI prevalence				
Very high incidence	0.3162	0.2686–0.3880	Varied with reactivation rate	(*12*,*15*–*17*)
High incidence	0.2016	0.1706–0.2464	Varied with reactivation rate	(*12*,*15*–*17*)
Moderate incidence	0.0902	0.0763–0.1102	Varied with reactivation rate	(*12*,*15*–*17*)
Low incidence	0.0159	0.0135–0.0195	Varied with reactivation rate	(*12*,*15*–*17*)
Abnormal chest radiograph results or previous TB				
Very high incidence	0.039	Fixed	Fixed	(*15*)
High incidence	0.028	Fixed	Fixed	(*15*)
Moderate incidence	0.029	Fixed	Fixed	(*15*)
Low incidence	0.008	Fixed	Fixed	(*15*)
Adherence to postarrival follow-up#	0.684	0.646–0.721	Beta (404.50,186.87)	(*22*)
Treatment parameters				
Initiate**	0.938	0.907–0.964	Beta (180.83,11.95)	(*5*)
Complete, INH	0.616	0.561–0.670	Beta (131.66,82.07)	(*5*)
Complete, RIF	0.814	0.745–0.876	Beta (76.85,17.56)	(*5*)
Adverse event, INH	0.049	0.044–0.055	Beta (249,4789)	(*24*,*25*)
Adverse event, RIF	0.021	0.018–0.025	Beta (109,4877)	(*24*,*25*)
Adverse event hospitalization	0.01	0.0005–0.03	Beta (1,99)	(*25*)
Death, INH	0.00000988	0–0.00002	Beta (2,202495)	(*26*)
LTBI risk reduction, INH	0.90	0.78–0.95	Normal (−2.3,0.5)††	(*27*)
LTBI risk reduction, RIF	0.90	0.63–0.97	Normal (−2.3,0.8)††	(*28*,*24*)
Partial risk reduction, INH	0.346	0.267–0.490	Combination of normal distributions††, ‡‡	Expert opinion, (*25*)
Partial risk reduction, RIF	0.30	0.17–0.40	Normal (−0.35,0.1)††	Expert opinion, (*24*,*28*)
Adverse event duration	7 d	0–24	Gamma (0.7,10)	Expert opinion, (*25*)
TB parameters				
Death from TB	0.0476	0.0391–0.0566	Beta (76,1523)	(*3*)
Reactivation rate	0.0011	0.0009–0.0013	Beta (90.92,82545.55)	(*15*–*17*)
Abnormal CXR risk change	3.9	3.0–4.9	Normal (1.36,0.15)††	(*29*)
Extended therapy	0.124	0.029–0.264	Beta (2.366,16.713)	Expert opinion, (*30*)
Relapse rate	0.0359	0.0197–0.0654	Normal (−3.327,0.365)††	(*30*)
Hospitalization duration	17 d	Fixed	Fixed	Expert opinion, (*30*)
Model parameters				
BCG vaccination, <30 cases	0.605	0.60–0.61	Beta (45137,29502)	(*12*,*13*)
BCG vaccination, ≥30 cases	0.998	0.997–0.999	Beta (185381,384)	(*12*,*13*)
BCG vaccination uptake	0.837	Fixed	Fixed	(*14*)
Discount rate	0.03	Fixed	Fixed	(*23*)
Time horizon	25 y	Fixed	Fixed	NA

*AE, adverse event; BCG, bacillus Calmette-Guérin; IGRA, interferon-gamma release assay; INH, isoniazid; LTBI, latent tuberculosis infection; NA, not available; PSA, probabilistic sensitivity analysis; RIF, rifampin; TST, tuberculin skin test; TB, tuberculosis.
†Treated as a negative result if it occurred; was equally likely to occur in those with and without LTBI.
‡Without being mandatory, this value is 63.5% (imputed from 43.4% completing screening when 68.4% adhere with a follow-up appointment) (*5*).
§Without being mandatory, this value is 78% (imputed from 43.7 of 56 individuals completing medical evaluation) (*5*).
¶Very high incidence, ≥200 cases/100,000; high incidence, ≥100 and <200 cases/100,000; moderate incidence, ≥30 and <100 cases/100,000; low incidence, <30 cases/100,000.
#From a meta-analysis (*22*); see also Appendix (https://wwwnc.cdc.gov/EID/article/25/4/17-1630-App1.pdf).
**This model assumes all who report postarrival due to a positive preimmigration LTBI diagnostic test are offered treatment. Exploratory analysis adjusts this assumption so that only the number who would complete TST screening begin treatment.
††Results from this distribution are exponentiated.
‡‡Formula: 0.33 × (Normal(−1.168,0.228)) + 0.374 × (Normal(−0.381,0.169)) + 0.293 × 1.

cost per QALY gained of $16,291 compared with the base case. Sequential screening with rifampin treatment again was slightly cheaper, resulting in a cost per QALY gained of $20,165.

Sensitivity Analysis

Among migrants from low-incidence countries, sequential screening coupled with postarrival rifampin treatment was the most cost-effective option in deterministic analysis. In PSA, this intervention had a probability of cost-effectiveness of 49.1% at a WTP threshold of $50,000/QALY and 50.7% at a WTP threshold of $100,000/QALY. This probability did not substantially increase past these thresholds, however, resulting in a probability of cost-effectiveness of 52% at a WTP threshold of $200,000/QALY (Figure 2, panel A).

Among migrants from moderate-, high-, and very high–incidence countries, IGRA screening coupled with postarrival rifampin treatment was the most cost-effective option in deterministic analysis. This intervention strategy at WTP thresholds of $50,000/QALY gained had probabilities of cost-effectiveness of 57.5% among migrants from moderate-incidence countries (Figure 2, panel B), 68.2% among migrants from high-incidence countries (Figure 2, panel C), and of 73.2% among migrants from very high–incidence countries (Figure 2, panel D). At a WTP threshold of $100,000/QALY gained probabilities of cost-effectiveness were 59.8% among migrants from moderate-incidence countries, 70.6% among migrants from high-incidence countries, and 75.2% among migrants from very high–incidence countries.

Discussion

The intervention of preimmigration LTBI screening followed by postarrival treatment among new migrants from countries with a TB incidence ≥30 cases/100,000 persons appears to be an effective method for reducing TB incidence post-arrival. The use of IGRA screening coupled with postarrival rifampin treatment provided the lowest cost-effectiveness ratio in migrants from these countries. This intervention strategy reduced TB incidence by >45% and yielded costs <$50,000/QALY gained.

Table 3. Cost and QALY estimates and values used for sensitivity analysis of intervention strategies for screening and treatment of latent TB infection in immigrants*

Parameter	Estimate, $	Range evaluated in PSA	PSA distribution	References
Costs				
Full INH treatment	992	804–1,179	Triangular, 804–1,179	BCCDC, (*33*,*36*)
Drug costs	181			
Nurse and clinician costs	741			
Follow-up chest radiograph	42			
Routine tests	28			
Full RIF treatment	575	464–686	Triangular, 464–686	BCCDC, (*33*,*36*)
Drug costs	98			
Nurse and clinician costs	421			
Follow-up chest radiograph	42			
Routine tests	14			
Partial INH	462	174–804	Triangular, 174–804	BCCDC, (*33*,*36*)
Partial RIF	319	178–464	Triangular, 178–464	BCCDC, (*33*,*36*)
Complete TST	31	24–38	Triangular, 24–38	BCCDC, (*33*,*36*)
TST cost	11			
Nurse costs (2 visits)	20			
Incomplete TST	21	17–25	Triangular, 17–25	BCCDC, (*33*,*36*)
IGRA	54	31–62	Triangular, 31–62	BCCDC, (*33*,*36*)
Kit and technician cost	47			
Nurse costs	7			
Chest radiograph	42	32–52	Triangular, 32–52	BCCDC, (*33*,*36*)
Cost per radiograph	35			
Nurse costs	7			
TB	20,532	7,141–39,525	Gamma (4.1064,5,000)	Expert opinion, (*33*,*34*)
LTBI adverse event	732	549–916	Triangular, 549–916	(*33*)
Hospitalization	6,641	5,305–9,985	Triangular, 5,305–9,985	(*30*)
Death	26,933	13,079–40,788	Triangular, 13,079–40,788	(*37*)
QALYs				
LTBI	0.81		Assumed	(*38*)
Healthy	0.81	0.58–0.97	Beta (7.85,1.84)	(*38*)
Adverse event disutility	0.2	0.15–0.25	Triangular, ± 25%	(*30*,*33*)
TB	0.69	0.08–0.24†	Beta (9,51)	(*38*)
Hospitalization	0.5	0.28–0.51†	Beta (19.5,30.5)	(*30*)
Death	0	Fixed	Fixed	Standard

*All costs are in 2016 Can $. BCCDC, British Columbia Centre for Disease Control; IGRA, interferon-gamma release assay; INH, isoniazid; LTBI, latent tuberculosis infection; PSA, probabilistic sensitivity analysis; RIF, rifampin; TB, tuberculosis; TST, tuberculin skin test.
†Sampled as a percent decrement compared to healthy QALY.

Because prevalence of LTBI was low among migrants from countries with a TB incidence <30 cases/100,000 persons and specificities of LTBI diagnostic tests are imperfect, this intervention may result in a high number of uninfected persons receiving treatment unnecessarily. This finding suggests that with some strategies, the QALYs lost due to treatment side effects among those with false-positive diagnostic results may be greater than the QALYs gained by averted TB in those with true-positive diagnostic results. If screening and treatment must be performed in these low LTBI prevalence populations, more specific screening methods (i.e., sequential screening) are preferred to avoid inappropriate treatment.

Probabilistic sensitivity analysis suggests a certain degree of uncertainty in results. The behavior of CEACs as WTP thresholds increase suggests that the intervention offers small increases in population QALYs or large increases in cost in many replications. It is important to understand how well the model parameters represent the local setting when using the results of this analysis to inform evidence-based policy. These results suggest that intervention offers domestic benefits to the receiving country, but several factors need to be carefully examined. IGRA use in high-resource settings suffers from variability, in part related to several operational issues (*39*), and TST variability remains an issue (*40*). For both types of test, variability may be exacerbated in low-resource settings where LTBI prevalence rates are likely to be higher. In this model, we did not consider the costs of program initiation and maintenance; although they are outside the scope of this analysis, these costs merit careful evaluation when seeking to implement policy.

This model considered only the costs of persons who became permanent residents. The data from Canada indicated that ≈50%–60% of those who begin the process of becoming a permanent resident successfully complete it (*3*,*15*). For migrants from very high–incidence countries, assuming only half of migrants receiving preimmigration

Table 4. Results in various TB incidence settings of implementing intervention strategies for screening and treatment of latent TB infection in immigrants*

Intervention	% Identified for postarrival followup	Cost/1,000 persons, $	No. QALYs/1,000 persons	No. TB cases/1,000 persons	% Reduction in TB incidence	Cost per QALY gained, $†
Low TB incidence countries						
Base case	0.82	9,681	13,761.03	0.41	NC	NC
SEQ/RIF	4.02	60,996	13,761.30	0.26	36.87	191,889
SEQ/INH	4.02	67,309	13,761.08	0.28	32.00	1,289,335‡
IGRA/RIF	6.43	80,107	13,761.22	0.22	46.16	373,773‡
IGRA/INH	6.43	91,056	13,761.07	0.25	39.07	2,315,425‡
TST/RIF	22.99	120,910	13,760.65	0.24	40.08	Dominated
TST/INH	22.99	162,233	13,760.59	0.27	34.12	Dominated
Moderate TB incidence countries						
Base case	2.88	58,301	13,735.03	2.47	NC	NC
SEQ/RIF	11.99	121,950	13,736.36	1.57	36.52	47,561
IGRA/RIF	14.52	129,036	13,736.66	1.33	46.36	43,343
SEQ/INH	11.99	142,739	13,735.71	1.72	30.55	122,821‡
IGRA/INH	14.52	154,804	13,736.69	1.50	39.47	58,154‡
TST/RIF	38.96	206,145	13,736.84	1.46	40.77	81,548‡
TST/INH	38.96	277,998	13,735.98	1.61	34.88	230,641‡
High TB incidence countries						
Base case	2.79	122,928	13,702.56	5.39	NC	NC
SEQ/RIF	19.13	194,289	13,704.93	3.44	36.06	29,997
IGRA/RIF	23.60	199,878	13,705.48	2.91	45.99	26,350
SEQ/INH	19.13	231,835	13,704.38	3.73	30.73	59,655‡
TST/RIF	44.24	247,488	13,704.35	3.28	39.21	69,421‡
IGRA/INH	23.60	263,572	13,704.93	3.22	40.18	59,154‡
TST/INH	44.24	348,686	13,704.15	3.54	34.36	141,336‡
Very high TB incidence countries						
Base case	3.87	184,357	13,666.32	8.12	NC	NC
SEQ/RIF	27.45	263,628	13,670.25	5.18	36.23	20,165
IGRA/RIF	33.86	268,840	13,671.50	4.41	45.61	16,291
TST/RIF	49.82	318,025	13,670.32	5.62	30.76	33,403‡
SEQ/INH	27.45	318,435	13,671.23	4.86	40.16	27,296‡
IGRA/INH	33.86	337,716	13,671.02	4.97	38.82	32,657‡
TST/INH	49.82	415,877	13,669.91	5.33	34.34	64,494‡

*Very high incidence, ≥200 cases per 100,000; high incidence: ≥100 and <200 cases/100,000; moderate incidence, ≥30 and <100 cases/100,000; low incidence: <30 cases/100,000. IGRA, interferon-gamma release assay; INH, isoniazid; NC, not calculable; QALY, quality-adjusted life year; RIF, rifampin; SEQ, sequential screening; TB, tuberculosis; TST, tuberculin skin test.

†*The cost per QALY gained is calculated in comparison to the base case. Dominated indicates that an intervention strategy has higher costs and worse outcomes compared to the base case. Costs are in CAD.

‡This intervention strategy is strictly dominated by another intervention strategy. It is more expensive and has worse outcomes.

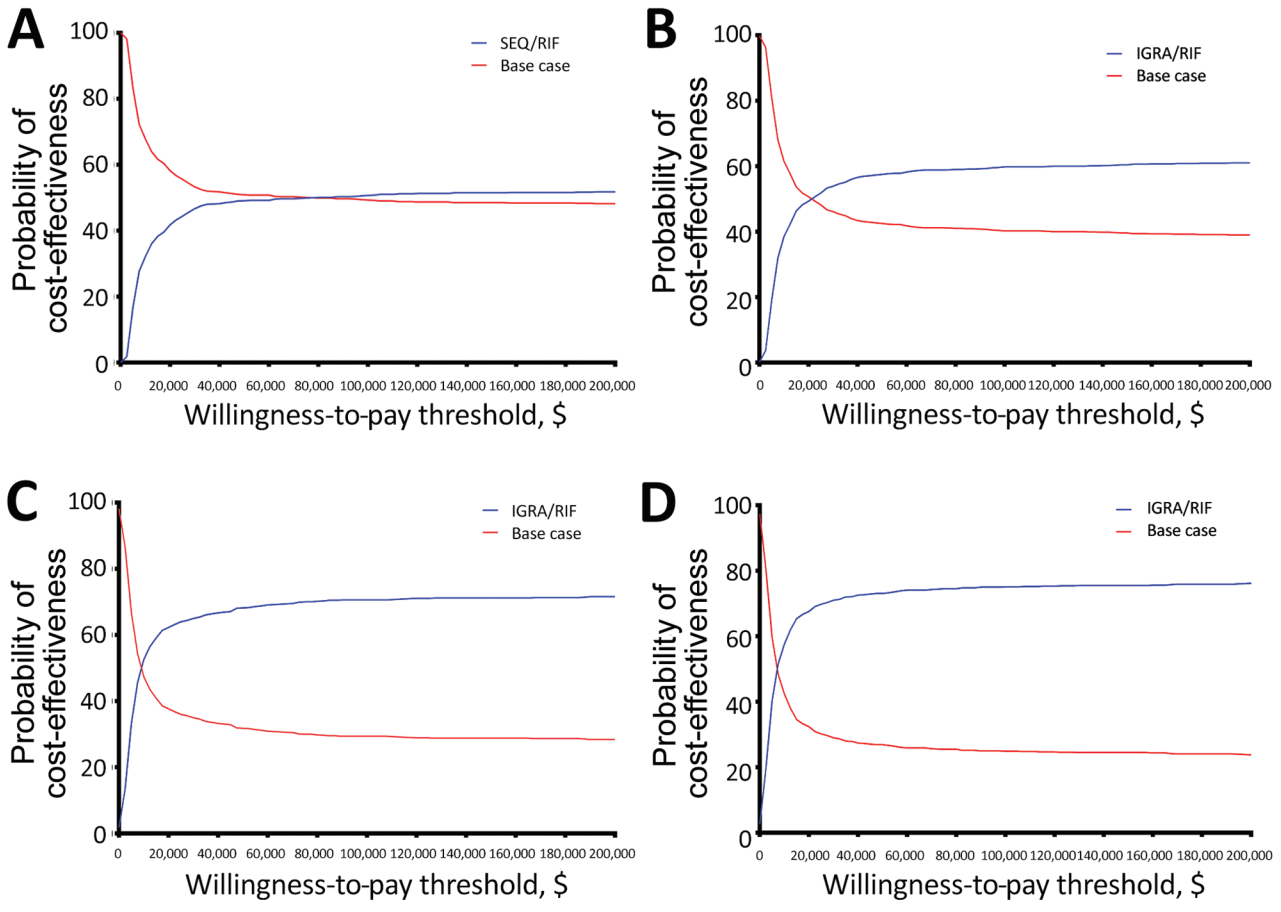

Figure 2. Cost-effectiveness acceptability curves of the base case of no intervention compared with intervention strategies in evaluation of screening and treatment of latent tuberculosis infection in immigrants. The graphs demonstrate the probability that an option is more cost-effective at various willingness-to-pay thresholds per quality adjusted life year gained. A) Comparison of the base case with the intervention strategy of preimmigration SEQ screening coupled with postarrival RIF treatment among migrants from low-incidence countries. B) Comparison of the base case with the intervention strategy of preimmigration IGRA screening coupled with postarrival rifampin treatment among migrants from moderate-incidence countries. C) Comparison of the base case with the intervention strategy of preimmigration IGRA screening coupled with postarrival RIF treatment among migrants from high-incidence countries. D) Comparison of the base case with the intervention strategy of preimmigration IGRA screening coupled with postarrival RIF treatment among migrants from very high–incidence countries. IGRA, interferon-gamma release assay; RIF, rifampin; SEQ, sequential.

screening became permanent residents, the cost-effectiveness ratio increased 60% to ≈$26,000 when the intervention strategy was IGRA coupled with rifampin. Another consideration is the feasibility of the intervention. In a country like Canada, 2%–3% of new permanent residents are requested to follow up postarrival based on preimmigration medical exams (*3*,*15*). If the country implemented preimmigration IGRA screening for migrants from moderate- to very high–incidence countries, 17.6% would be requested to follow up postarrival (*3*,*15*). However, coupling IGRA with postarrival rifampin treatment could prevent 3.9% of all TB cases in Canada in the first year (*3*,*12*,*15*). Applied to new permanent residents to Canada in 2014, this process would increase the number requested to follow up postarrival from 6,100 to 45,800 but would result in the prevention of 61 TB cases in the first year (1 case prevented/651 additional postarrival referrals). If this process were then consistently implemented in successive cohorts in the future, it could annually prevent ≈400 TB cases.

Regardless of how preimmigration LTBI screening is implemented, investment in LTBI infrastructure in high TB incidence settings will be essential for global TB elimination. Evidence suggests that introduction of routine preimmigration TB screening in many high-income, low-incidence countries has played a role in improving infrastructure for TB programs in low-resource areas (*41*). Further introducing LTBI screening as part of these routine medical exams may have similar impact.

The cost-effectiveness of preimmigration LTBI screening and postarrival treatment has not been evaluated since 2003. Previously, Schwartzman and Menzies (*42*) examined the idea of preimmigration TST screening in addition to

standard preimmigration chest radiograph coupled with postarrival isoniazid treatment. They found the cost per TB case prevented was approximately Can $94,500. In our study, using this intervention strategy in very high incidence countries resulted in a cost per TB case prevented of approximately Can $83,000. Schwartzman et al. (*43*) later investigated the cost associated with performing a TST in all new legal immigrants from Mexico, a low-incidence country, and coupling it with postarrival isoniazid treatment. This resulted in a cost per TB case prevented of $1.2 million (2016 Can $). Using this same intervention strategy in our study resulted in a cost per TB case prevented of $1.1 million (2016 Can $). By evaluating new strategies applied to a variety of TB incidence settings, our study represents a much-needed update to the literature.

Our analysis has several strengths. Use of discrete event simulation enabled realistic modeling of time spent in various health states, which is difficult to implement in Markov models. This type of model also allowed age-representative modeling of new migrants for application of age-adjusted LTBI prevalence. The source of most of the cost data was the British Columbia Center for Disease Control, which handles most TB cases in the province of British Columbia. This analysis estimated LTBI prevalence and abnormal chest radiograph prevalence using several years of immigration and TB data from Ontario. The data are likely to be generalizable, because Ontario accepts 40% of new permanent residents (*12*) and the data fit well with reported LTBI prevalence estimates (*16*), suggesting these parameters are reflective of long-term TB trends.

In this study, we assumed that all migrants were recommended postarrival LTBI treatment when they had a positive LTBI diagnostic test, which is not necessarily true; for some persons, the risk for serious adverse events may outweigh the benefit of treatment. Social factors and concurrent conditions may increase the risk for reactivation of LTBI. We have shown that the benefits of rifampin treatment for migrants from moderate- to very high–incidence countries who test positive by IGRA preimmigration outweigh the potential risks of adverse events. However, in practice, individual adverse-event risk is considered, and treatment may not be offered to all migrants. Further research designed to identify the specific populations who should be offered treatment would help inform future analyses.

We derived the reactivation rate of LTBI from the literature, but because many of those studies were based on TB incidence in those who were positive by TST, it is possible that the predictive value of the TST caused underestimation of true reactivation rates. Our analysis did not consider 3 months of once-weekly isoniazid and rifapentine as an LTBI treatment modality because it was not universally available. Literature data, however, suggest this modality may yield similar results to rifampin treatment (*44*).

Our analysis used a healthcare system perspective, which does not consider costs incurred by persons experiencing the intervention (*45*). It is possible that consideration of costs and benefits from a societal perspective would change the results of this analysis; however, it is also likely that this difference would strengthen the preference for screening with IGRA, which requires only 1 visit, instead of TST, which requires 2, due to reduced absenteeism associated with IGRA testing. Costs per QALY gained may increase for all strategies if the time costs for migrants to follow up for LTBI treatment were considered. Finally, we assumed that TB reactivation was constant, which, while demonstrated previously (*18*), contradicts the common paradigm of decreasing risk over time (*46*). Where possible, we performed sensitivity analyses to view the effects our limitations may have on our results to better inform decision makers.

In conclusion, preimmigration IGRA screening coupled with postarrival rifampin treatment among migrants from countries with moderate to very high incidence of TB resulted in the lowest cost-effectiveness ratios. This evidence can be used to support policy decisions surrounding preimmigration LTBI screening in high-income, immigrant-receiving countries, when coupled with evaluations on program implementation, acceptability, and sustainability. Next steps in research should be to identify subgroups at highest risk for progression to TB disease to limit individual risk associated with LTBI treatment and improve the likelihood of feasibility and sustainability.

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J.R.C., J.C.J., and F.M. were involved in development of the study objective and design. J.R.C. performed data collection, created the model, performed data analysis and interpretation, and drafted the manuscript. J.C.J. provided expert input on the data informing the model, data interpretation, and performed manuscript editing. M.S. reviewed the model for errors, provided expert input for data analysis, and edited the manuscript. V.J.C. provided expert input on the data informing the model and edited the manuscript. R.K.E. provided expert input on the data interpretation and edited the manuscript. F.M. reviewed the model inputs collected and the data analysis, provided expert input for data interpretation, and edited the manuscript. All authors approved the study objective, design, and final manuscript.

About the Author

Dr. Campbell received his PhD from the University of British Columbia in Vancouver and is currently a postdoctoral fellow at McGill University in Montreal, Quebec, Canada. His primary research interests include health economics, evidence-based public health policy, and infectious disease.

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Address for correspondence: Fawziah Marra, University of British Columbia, 2405 Wesbrook Mall, Vancouver, BC V6T 1Z3, Canada; email: fawziah@mail.ubc.ca

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Cost-effectiveness of Latent Tuberculosis Infection Screening before Immigration to Low-Incidence Countries

Appendix

Cost-effectiveness Ratio Calculation

To calculate the incremental cost-effectiveness ratio (ICER), the difference in costs between an intervention strategy ($Cost_i$) and the base case ($Cost_b$) is divided by the difference in quality-adjusted life years (QALYs) between an intervention strategy ($QALY_i$) and the base case ($QALY_b$). This is calculated through the formula:

$$ICER = \frac{Cost_i - Cost_b}{QALY_i - QALY_b}$$

This value can then be compared to a policy maker's willingness-to-pay (WTP) threshold. A value below this threshold is considered cost-effective and can be used as a component supporting new policies.

Efficiency Frontier

The efficiency frontier plots the costs and QALYs of each intervention and connects interventions that provide the next best option in terms of costs and QALYs. Interventions not on the frontier are either dominated by other interventions (i.e., they have higher costs and lower QALYs than other interventions) or are excluded due to extended dominance (i.e., a more expensive intervention provides a lower ICER). The values listed adjacent to lines along the frontier represent the ICER of going from one intervention to the next and can be used to support policy makers decisions on optimal intervention strategies.

Probability of Creating a Secondary Tuberculosis Case Calculation

We assumed that 85% of tuberculosis (TB) cases from our data source were due to reactivation of previously acquired latent TB infection (LTBI). To account for the remaining cases, we modeled the creation of secondary cases when a case of reactivation TB occurred. The formula based on this assumption is:

$$Probability\ of\ Creating\ a\ Secondary\ Case = \left(\frac{1}{0.85}\right) - 1 = 17.6\%$$

In this way, all TB cases are accounted for in this model and we minimize underestimation of overall longitudinal TB burden. Further to this, the method of modeling secondary cases will result in reductions in TB transmission as incidence of TB reactivation is reduced – in this way TB transmission was directly tied to incidence of TB reactivation.

Meta-Analysis of Reported Rates of Post-Arrival Reporting for Passive Follow-Up

A meta-analysis was performed using Stata software, version 12.1 (StataCorp, www.stata.com). To complete this, logit-transformed proportions were meta-analyzed using random-effects. The weighted pooled point estimate was back transformed into a proportion for ease of interpretation (Appendix Figure 1). The result of this meta-analysis is that 68.4% (95% CI: 64.6% to 72.1%) of those referred for passive (unenforced) post-arrival follow-up actually attend the clinic post-arrival.

Additional Sensitivity Analysis

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) was performed to assess the uncertainty in parameters and their impact on decisions. To complete this, probabilistic distributions are created and sampled each replication. When detailed cost data was available and known to fall within well-defined ranges, costs were modeled with a triangular distribution; when cost data was more uncertain, a gamma distribution, which can accommodate skewed cost data, was used. Beta distributions were used for most probabilities. When literature data was available and exact proportions of persons experiencing an event could be calculated, β distributions parameters

were defined as: α = number of persons experiencing event; β = number of persons not experiencing event. If this level of detail was not known, a β distribution was fit to represent reported 95% CI or means and standard deviations. In the case of treatment effect, lognormal distributions were used based on 2x2 tables of effectiveness or fit to our perceived level of uncertainty. For sampling health state utilities, we first sampled from the distribution of the healthy QALY. We assumed those with LTBI would have the same value. For TB and hospitalization QALYs, we sampled from distributions to decrement these QALYs based on the sampled healthy QALY.

The average results of the PSA are reported in Appendix Table 1. Variability can be seen through plots of the differences in costs and QALYs on a cost-effectiveness plane for the PSA of select strategies (Appendix Figure 2). The results of the PSA support the findings from the deterministic analysis: the intervention strategy of preimmigration interferon-gamma release assay (IGRA) screening coupled with postarrival follow-up and treatment with rifampin was the preferred strategy in migrants from moderate- to very high–incidence countries. Further analysis of the relationship between decisions is provided below in efficiency frontiers.

Efficiency frontiers are displayed in Appendix Figure 3. In each of the plotted frontiers, only one intervention was included on the frontier, with others excluded due to strict or extended dominance. Among migrants from low-incidence countries, only SEQ/RIF fell on the frontier, while among migrants from moderate high and very high–incidence countries, only IGRA/RIF fell on the frontier.

Exploratory Sensitivity Analysis

Various exploratory sensitivity analyses were performed. We analyzed the impact of limiting LTBI screening by age on outcomes. We then analyzed the impact certain parameters may have on cost-effectiveness including: modeling low LTBI therapy uptake postarrival, ensuring 100% adherence in postarrival follow-up, ensuring 100% adherence and participation in all steps of the LTBI cascade of care, extending the time horizon, altering TB reactivation rate, and modeling high and low estimates of costs.

Parameter changes evaluated for exploratory sensitivity analysis are listed in Appendix Table 2. In the case of varying the reactivation rate, LTBI prevalence estimates were also adjusted to reflect the expected TB incidence based on data used to calibrate these parameters in

the base analysis. This would result in nearly identical number of overall TB cases over the time horizon, but costs due to increasing or decreasing LTBI prevalence will change.

Results of exploratory analyses are presented in Appendix Tables 3–6. Only screening certain portions of new migrants based on age did not significantly impact cost per QALY gained but did lessen the overall reductions in TB incidence seen. Mandating postarrival follow-up improved the reduction in TB incidence by 40% compared with a passive system. On the contrary, if we modeled initiation of LTBI therapy at an extreme low value of 63.5%, reduction in TB incidence was reduced by ≈30%. This further impacted decisions on which intervention strategy was likely to be the most cost-effective. Fully mandating all parts of the LTBI cascade of care (i.e., all those test-positive must follow-up postarrival and complete treatment, except in cases of adverse events) increased overall costs of intervention strategies ≈40%, but overall reductions in TB incidence exceeded 80%.

Using a lifetime time horizon significantly improved cost-effectiveness of intervention strategies. Adjusting reactivation rate or costs did not significantly impact cost-effectiveness but did impact the overall cost of intervention strategies. In the case of adjusting reactivation rate, this was due to increasing or decreasing the number of persons with LTBI.

Appendix Table 1. Average PSA results of implementing intervention strategies in various TB incidence settings

Intervention	Cost/1,000, $	No. QALYs/1,000	No. TB cases/1,000	% Reduction in TB incidence	Cost/QALY gained, $†
Low TB incidence					
Base case	9,653	13,797.86	0.40	NC	NC
SEQ/RIF	60,425	13,798.51	0.27	33.76	77,885
SEQ/INH	67,006	13,798.11	0.29	28.41	228,858‡
IGRA/RIF	75,449	13,798.32	0.23	43.35	143,563‡
IGRA/INH	86,579	13,798.19	0.25	37.03	233,564‡
TST/RIF	121,260	13,798.08	0.25	38.07	498,153‡
TST/INH	163,467	13,798.06	0.27	33.63	751,114‡
Moderate TB incidence					
Base case	59,131	13,770.72	2.51	NC	NC
SEQ/RIF	121,736	13,771.95	1.62	35.45	50,590§
IGRA/RIF	125,439	13,772.73	1.38	44.92	32,938
SEQ/INH	142,037	13,772.33	1.72	31.53	51,332‡
IGRA/INH	151,623	13,772.54	1.53	39.12	50,769‡
TST/RIF	207,659	13,772.66	1.52	39.47	76,512‡
TST/INH	281,239	13,772.58	1.64	34.53	119,301‡
High TB incidence					
Base case	124,384	13,733.54	5.43	NC	NC
SEQ/RIF	195,166	13,737.25	3.52	35.16	19,047§
IGRA/RIF	198,604	13,738.15	3.04	44.01	16,093
SEQ/INH	232,435	13,736.49	3.76	30.82	36,612‡
IGRA/INH	245,804	13,737.39	3.31	38.98	31,501‡
TST/RIF	266,307	13,737.79	3.31	38.99	33,343‡
TST/INH	352,574	13,737.35	3.58	34.05	59,891‡
Very high TB incidence					
Base case	184,977	13,696.10	8.13	NC	NC
SEQ/RIF	265,405	13,701.78	5.31	34.66	14,163§

Intervention	Cost/1,000, $	No. QALYs/1,000	No. TB cases/1,000	% Reduction in TB incidence	Cost/QALY gained, $†
IGRA/RIF	268,953	13,702.93	4.58	43.67	12,299
SEQ/INH	320,020	13,700.59	5.68	30.12	30,062‡
TST/RIF	322,422	13,702.09	5.00	38.48	22,941‡
IGRA/INH	337,776	13,701.61	5.03	38.12	27,709‡
TST/INH	420,458	13,701.09	5.39	33.70	47,149‡

*All costs in 2016 CAD. Dominated: This intervention strategy has higher costs and worse outcomes compared to the base case.
CI, confidence interval; IGRA, interferon-gamma release assay; INH, isoniazid; NC, not calculable; QALY, quality-adjusted life year; RIF, rifampin; SEQ, sequential screening; TB, tuberculosis; TST, tuberculin skin test.
Very high incidence, ≥200 cases per 100,000; high incidence: ≥100 and <200 cases/100,000; moderate incidence, ≥30 and <100 cases/100,000; low incidence: <30 cases/100,000.
†The cost per QALY gained is calculated in comparison to the base case.
‡This intervention strategy is strictly dominated by another intervention strategy. It is more expensive and has worse outcomes.
§This intervention strategy is extendedly dominated by another intervention strategy. While it increases QALYs, it has a higher ICER than a more expensive intervention strategy

Appendix Table 2. Parameter changes for the exploratory sensitivity analysis*

Parameter	Original estimate	Exploratory sensitivity analysis estimate(s), range
Full INH treatment	$992	$804, $1,179
Full RIF treatment	$575	$464, $686
Partial INH treatment	$462	$174, $804
Partial RIF treatment	$319	$178, $464
Complete TST	$31	$24, $38
Incomplete TST	$21	$17, $25
IGRA	$54	$31, $62
Tuberculosis	$20,532	$7,141, $39,525
LTBI adverse event	$732	$549, $916
Hospitalization	$6641	$5,305; $9,985
Death	$26,933	$13,079; $40,788
Initiate treatment	93.8%	100%
Complete INH	61.6%	100%
Complete RIF	81.4%	100%
Annual reactivation rate†	0.11%	0.09%; 0.13%
Time horizon	25 y	Lifetime
Adherence to post-arrival follow-up	68.4%	100%

*All costs in 2016 Can $. INH, isoniazid; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; RIF, rifampin; TST, tuberculin skin test.
†Also changes the prevalence of LTBI.

Appendix Table 3. Results of exploratory sensitivity analyses in TB screening in migrants from low TB incidence countries*

Intervention	Cost/1,000, $	No. QALYs/1,000	No. TB cases/1,000	% Reduction in TB incidence	Cost/QALY gained, $†
Only screen persons ≤60 y of age					
Base case	9,681	13,761.03	0.41	NC	NC
SEQ/RIF	58,830	13,761.33	0.26	35.00	166,639
SEQ/INH	65,133	13,761.11	0.29	28.20	767,845‡
IGRA/RIF	77,220	13,761.25	0.23	44.02	312,764‡
IGRA/INH	87,622	13,761.10	0.26	37.10	1,243,726‡
TST/RIF	116,550	13,760.62	0.25	38.07	Dominated
TST/INH	156,102	13,760.67	0.27	33.35	Dominated
Only screen persons ≤35 y of age					
Base case	9,681	13,761.03	0.41	NC	NC
SEQ/RIF	45,484	13,761.34	0.34	16.46	118,623
SEQ/INH	49,337	13,761.11	0.35	12.80	501,351‡
IGRA/RIF	59,255	13,761.26	0.33	19.69	222,482‡
IGRA/INH	66,138	13,761.10	0.34	15.84	811,778‡
TST/RIF	89,077	13,760.62	0.35	14.71	Dominated
TST/INH	117,358	13,760.68	0.34	16.50	Dominated
Only screen persons 10–60 y of age					
Base case	9,681	13,761.03	0.41	NC	NC
SEQ/RIF	50,922	13,761.33	0.28	31.13	138,216
SEQ/INH	55,929	13,761.11	0.29	29.15	611,279‡
IGRA/RIF	66,222	13,761.25	0.24	39.86	257,727‡
IGRA/INH	75,153	13,761.10	0.27	34.48	990,386‡

Intervention	Cost/1,000, $	No. QALYs/1,000	No. TB cases/1,000	% Reduction in TB incidence	Cost/QALY gained, $†
TST/RIF	99,155	13,760.62	0.26	34.80	Dominated
TST/INH	132,435	13,760.68	0.28	31.05	Dominated
Only 63.5% initiate therapy after arrival					
Base case	9,459	13,760.96	0.41	NC	NC
SEQ/RIF	58,376	13,761.30	0.30	25.75	143,147
SEQ/INH	62,759	13,761.20	0.32	21.79	224,620‡
IGRA/RIF	75,049	13,761.22	0.28	32.26	255,693‡
IGRA/INH	82,340	13,761.16	0.29	27.98	362,842‡
TST/RIF	96,641	13,760.75	0.29	29.46	Dominated
TST/INH	124,688	13,760.68	0.31	23.79	Dominated
100% Adherence to post-arrival follow-up					
Base case	9,937	13,761.12	0.40	NC	NC
SEQ/RIF	65,283	13,761.84	0.19	52.25	77,011
SEQ/INH	74,688	13,761.48	0.23	44.11	178,931‡
IGRA/RIF	88,258	13,761.73	0.14	64.91	129,787‡
IGRA/INH	104,144	13,761.66	0.18	55.75	176,541‡
TST/RIF	158,280	13,761.05	0.17	58.17	Dominated
TST/INH	218,474	13,761.03	0.20	50.85	Dominated
No losses in the LTBI cascade of care					
Base case	10,173	13,761.32	0.39	NC	NC
SEQ/RIF	65,488	13,762.28	0.15	60.59	57,335
SEQ/INH	79,499	13,762.13	0.17	57.04	85,831‡
IGRA/RIF	88,899	13,762.27	0.08	78.12	82,958‡
IGRA/INH	112,814	13,762.16	0.10	75.41	122,324‡
TST/RIF	164,894	13,762.19	0.12	68.64	176,445‡
TST/INH	258,857	13,762.15	0.13	65.48	299,189‡
Reactivation rate is 0.9 cases/1,000 PY					
Base case	9,709	13,760.03	0.41	NC	NC
SEQ/RIF	61,978	13,760.30	0.25	38.35	195,474
SEQ/INH	68,898	13,760.08	0.28	31.52	1,324,360‡
IGRA/RIF	81,411	13,760.22	0.22	45.03	380,575‡
IGRA/INH	92,642	13,760.07	0.24	40.56	2,359,934‡
TST/RIF	121,635	13,759.59	0.24	40.74	Dominated
TST/INH	163,310	13,759.64	0.27	35.05	Dominated
Reactivation rate is 1.3 cases/1,000 PY					
Base case	9,533	13,761.67	0.40	NC	NC
SEQ/RIF	60,332	13,761.94	0.26	35.38	189,954‡
SEQ/INH	66,632	13,761.72	0.29	27.67	1,277,446‡
IGRA/RIF	79,335	13,761.86	0.22	45.67	370,447‡
IGRA/INH	89,844	13,761.71	0.25	37.93	2,285,044‡
TST/RIF	120,192	13,761.23	0.24	41.31	Dominated
TST/INH	161,282	13,761.28	0.26	34.15	Dominated
Lifetime time horizon					
Base case	13,375	20,735.49	0.57	NC	NC
SEQ/RIF	63,180	20,735.79	0.35	38.24	161,566§
SEQ/INH	69,518	20,735.76	0.39	30.40	203,916‡
IGRA/RIF	82,257	20,736.47	0.32	44.05	69,939
IGRA/INH	93,122	20,735.95	0.35	37.45	173,790‡
TST/RIF	123,069	20,734.57	0.34	40.34	Dominated
TST/INH	164,387	20,735.02	0.37	33.97	Dominated
Minimum estimated costs					
Base case	7,709	13,761.03	0.41	NC	NC
SEQ/RIF	45,709	13,761.30	0.26	36.87	142,099
SEQ/INH	51,306	13,761.08	0.28	32.00	975,411‡
IGRA/RIF	52,694	13,761.22	0.22	46.16	238,752‡
IGRA/INH	62,376	13,761.07	0.25	39.07	1,555,483‡
TST/RIF	99,230	13,760.59	0.24	40.08	Dominated
TST/INH	135,984	13,760.65	0.27	34.12	Dominated
Maximum estimated costs					
Base case	11,653	13,761.03	0.41	NC	NC
SEQ/RIF	72,938	13,761.30	0.26	36.87	229,171
SEQ/INH	79,963	13,761.08	0.28	32.00	1,528,335‡
IGRA/RIF	92,536	13,761.22	0.22	46.16	429,269‡
IGRA/INH	104,750	13,761.07	0.25	39.07	2,648,963‡
TST/RIF	142,655	13,760.59	0.24	40.08	Dominated
TST/INH	188,544	13,760.65	0.27	34.12	Dominated

Intervention	Cost/1,000, $	No. QALYs/1,000	No. TB cases/1,000	% Reduction in TB incidence	Cost/QALY gained, $†

*All costs in 2016 Can $. Dominated: This intervention strategy has higher costs and worse outcomes compared with the base case. IGRA, interferon-gamma release assay; INH, isoniazid; NC, not calculable; QALY, quality-adjusted life year; RIF, rifampin; SEQ, sequential screening; TB, tuberculosis; TST, tuberculin skin test.
†The cost per QALY gained is calculated in comparison to the base case.
‡This intervention strategy is strictly dominated by another intervention strategy. It is more expensive and has worse outcomes.
§This intervention strategy is extendedly dominated by another intervention strategy. While it increases QALYs, it has a higher ICER than a more expensive intervention strategy.

Appendix Table 4. Results of exploratory sensitivity analyses in migrants from moderate TB incidence countries*

Intervention	Cost/1,000, $	No. QALYs/1,000	No. TB cases/1,000	% Reduction in TB incidence	Cost/QALY gained, $†
Only screen persons ≤60 y of age					
Base case	58,301	13,735.03	2.47	NC	NC
SEQ/RIF	118,834	13,736.66	1.64	33.66	37,076‡
IGRA/RIF	125,579	13,736.95	1.41	42.91	34,924
SEQ/INH	137,416	13,736.01	1.74	29.41	80,574§
IGRA/INH	149,533	13,736.94	1.56	36.67	47,669§
TST/RIF	199,887	13,737.13	1.54	37.55	67,186§
TST/INH	268,497	13,736.27	1.67	32.52	168,567§
Only screen persons ≤35 y of age					
Base case	58,301	13,735.03	2.47	NC	NC
SEQ/RIF	98,543	13,736.30	2.09	15.25	31,697‡
IGRA/RIF	103,655	13,736.59	2.00	18.90	29,012
SEQ/INH	107,793	13,735.65	2.13	13.94	79,979§
IGRA/INH	116,023	13,736.58	2.07	16.28	37,222§
TST/RIF	159,486	13,736.77	2.04	17.56	58,010§
TST/INH	206,294	13,735.91	2.11	14.55	167,437§
Only screen persons 10–60 y of age					
Base case	58,301	13,735.03	2.47	NC	NC
SEQ/RIF	108,704	13,736.57	1.68	31.89	32,638‡
IGRA/RIF	114,669	13,736.88	1.49	39.59	30,343
SEQ/INH	125,466	13,735.94	1.79	27.63	73,548§
IGRA/INH	135,916	13,736.87	1.63	34.05	42,064§
TST/RIF	176,404	13,737.07	1.59	35.78	57,931§
TST/INH	235,861	13,736.21	1.75	29.27	150,695§
Only 63.5% initiate therapy after arrival					
Base case	58,301	13,734.92	2.50	NC	NC
SEQ/RIF	117,154	13,736.00	1.84	26.33	54,608‡
IGRA/RIF	123,323	13,736.33	1.70	32.08	46,250
SEQ/INH	130,963	13,735.79	1.93	22.58	83,767§
IGRA/INH	140,730	13,736.09	1.81	27.61	70,514§
TST/RIF	170,321	13,736.57	1.78	28.69	67,777§
TST/INH	218,771	13,736.42	1.87	25.25	107,079§
100% Adherence to post-arrival follow-up					
Base case	58,301	13,734.93	2.45	NC	NC
SEQ/RIF	130,209	13,737.12	1.18	51.75	32,935‡
IGRA/RIF	139,318	13,738.23	0.83	66.10	24,577
SEQ/INH	159,527	13,736.93	1.36	44.67	50,690§
IGRA/INH	177,134	13,737.59	1.09	55.63	44,712§
TST/RIF	262,181	13,737.91	1.02	58.50	68,474§
TST/INH	367,557	13,737.10	1.23	49.65	142,888§
No losses in the LTBI cascade of care					
Base case	60,621	13,735.17	2.33	NC	NC
SEQ/RIF	127,849	13,737.68	0.92	60.38	26,863‡
IGRA/RIF	136,690	13,738.68	0.52	77.51	21,717
SEQ/INH	169,175	13,737.77	0.98	57.87	41,819§
IGRA/INH	188,938	13,738.41	0.60	74.47	39,639§
TST/RIF	269,509	13,738.19	0.76	67.35	69,219§
TST/INH	429,117	13,737.59	0.81	65.19	152,307§
Reactivation rate is 0.9 cases/1,000 PY					
Base case	59,005	13,729.18	2.50	NC	NC
SEQ/RIF	127,864	13,730.85	1.57	37.06	41,217‡
IGRA/RIF	135,775	13,731.33	1.34	46.46	35,627
SEQ/INH	150,721	13,730.75	1.71	31.77	58,282§
IGRA/INH	164,567	13,731.44	1.50	40.17	46,683§

Intervention	Cost/1,000, $	No. QALYs/1,000	No. TB cases/1,000	% Reduction in TB incidence	Cost/QALY gained, $†
TST/RIF	209,711	13,731.83	1.47	41.11	56,717§
TST/INH	283,226	13,731.15	1.62	35.31	113,602§
Reactivation rate is 1.3 cases/1,000 PY					
Base case	57,807	13,738.64	2.45	NC	NC
SEQ/RIF	117,950	13,741.03	1.56	36.30	25,192‡
IGRA/RIF	124,326	13,741.33	1.33	45.98	24,716
SEQ/INH	136,278	13,740.49	1.68	31.34	42,500§
IGRA/INH	147,736	13,740.48	1.49	39.45	48,846§
TST/RIF	203,596	13,740.95	1.46	40.40	63,063§
TST/INH	274,258	13,740.54	1.60	34.62	114,013§
Lifetime time horizon					
Base case	80,521	20,589.15	3.42	NC	NC
SEQ/RIF	135,403	20,591.19	2.21	35.31	26,834‡
IGRA/RIF	141,253	20,592.00	2.42	29.17	21,301
SEQ/INH	155,841	20,591.14	1.89	44.81	37,751§
IGRA/INH	166,455	20,591.74	2.11	38.38	33,183§
TST/RIF	219,818	20,591.06	2.07	39.51	72,744§
TST/INH	291,198	20,590.12	2.26	33.75	215,855§
Minimum estimated costs					
Base case	46,426	13,735.03	2.47	NC	NC
IGRA/RIF	92,622	13,736.66	1.33	46.36	28,307
SEQ/RIF	93,356	13,736.36	1.57	36.52	35,068§
SEQ/INH	111,521	13,735.71	1.72	30.55	94,686§
IGRA/INH	115,204	13,736.65	1.50	39.47	42,470§
TST/RIF	169,528	13,736.84	1.46	40.77	67,901§
TST/INH	233,240	13,735.98	1.61	34.88	196,119§
Maximum estimated costs					
Base case	70,178	13,735.03	2.47	NC	NC
SEQ/RIF	144,900	13,736.36	1.57	36.52	55,836‡
IGRA/RIF	150,482	13,736.66	1.33	46.36	49,206
SEQ/INH	168,312	13,735.71	1.72	30.55	142,743
IGRA/INH	179,434	13,736.65	1.50	39.47	67,465§
TST/RIF	242,876	13,736.84	1.46	40.77	95,258§
TST/INH	322,868	13,735.98	1.61	34.88	265,276§

*All costs in 2016 Can $. IGRA, interferon-gamma release assay; INH, isoniazid; NC, not calculable; QALY, quality-adjusted life year; RIF, rifampin; SEQ, sequential screening; TB, tuberculosis; TST, tuberculin skin test.
†The cost per QALY gained is calculated in comparison to the base case.
‡ This intervention strategy is extendedly dominated by another intervention strategy. While it increases QALYs, it has a higher ICER than a more expensive intervention strategy.
§This intervention strategy is strictly dominated by another intervention strategy. It is more expensive and has worse outcomes.

Appendix Table 5. Results of exploratory sensitivity analyses in migrants from high TB incidence countries*

Intervention	Cost/1,000, $	No. QALYs/1,000	No. TB cases/1,000	% Reduction in TB incidence	Cost/QALY gained, ($)†
Only screen persons ≤60 y of age					
Base case	122,928	13,702.56	5.39	NC	NC
SEQ/RIF	189,766	13,703.94	3.57	33.80	48,452‡
IGRA/RIF	195,130	13,705.08	3.08	42.80	28,627
SEQ/INH	223,538	13,703.44	3.80	29.51	113,251§
IGRA/INH	239,543	13,704.43	3.43	36.35	62,167§
TST/RIF	256,075	13,705.02	3.34	38.07	54,092*
TST/INH	336,983	13,704.39	3.66	32.05	117,017§
Only screen persons ≤35 y of age					
Base case	122,928	13,702.56	5.39	NC	NC
SEQ/RIF	162,376	13,703.32	4.56	15.42	51,575‡
IGRA/RIF	166,890	13,703.57	4.36	19.13	43,327
SEQ/INH	177,765	13,703.19	4.64	13.78	86,006§
IGRA/INH	186,811	13,703.28	4.49	16.73	88,102§
TST/RIF	213,873	13,703.41	4.44	17.59	107,073§
TST/INH	263,567	13,703.20	4.60	14.65	219,339§
Only screen persons 10–60 y of age					
Base case	122,928	13,702.56	5.39	NC	NC
SEQ/RIF	179,377	13,704.28	3.70	31.33	32,716‡
IGRA/RIF	183,730	13,705.06	3.24	39.78	24,321
SEQ/INH	210,766	13,703.81	3.94	26.87	70,087§

Intervention	Cost/1,000, $	No. QALYs/1,000	No. TB cases/1,000	% Reduction in TB incidence	Cost/QALY gained, ($)†
IGRA/INH	223,488	13,704.55	3.56	33.89	50,319§
TST/RIF	235,007	13,704.25	3.50	34.96	66,195§
TST/INH	304,261	13,704.11	3.77	30.10	116,849§
Only 63.5% initiate therapy after arrival					
Base case	123,493	13,701.90	5.46	NC	NC
SEQ/RIF	187,956	13,703.54	4.02	26.37	39,248
IGRA/RIF	192,897	13,703.54	3.70	32.24	42,170
SEQ/INH	213,393	13,703.21	4.22	22.66	68,782§
IGRA/INH	224,618	13,703.45	3.93	28.10	65,044§
TST/RIF	230,606	13,703.38	3.91	28.37	72,197§
TST/INH	287,689	13,703.11	4.12	24.65	135,974§
100% adherence to post-arrival follow-up					
Base case	123,590	13,701.71	5.32	NC	NC
SEQ/RIF	205,198	13,705.26	2.57	51.59	22,981‡
IGRA/RIF	213,881	13,706.71	1.82	65.71	18,066
SEQ/INH	260,097	13,704.83	3.01	43.49	43,784§
IGRA/INH	283,398	13,705.64	2.35	55.82	40,719§
TST/RIF	316,894	13,706.31	2.24	57.87	42,089§
TST/INH	441,135	13,705.29	2.71	49.10	88,850§
No losses in the LTBI cascade of care					
Base case	123,337	13,702.66	5.13	NC	NC
SEQ/RIF	199,723	13,706.07	2.05	59.95	22,403‡
IGRA/RIF	206,838	13,707.94	1.16	77.37	15,795
SEQ/INH	274,295	13,705.94	2.19	57.32	45,942§
IGRA/INH	301,381	13,706.97	1.32	74.20	41,269§
TST/RIF	318,782	13,706.36	1.66	67.68	52,776§
TST/INH	501,470	13,705.89	1.80	64.93	116,949§
Reactivation rate is 0.9 cases/1,000 PY					
Base case	123,878	13,689.10	5.42	NC	NC
SEQ/RIF	207,013	13,692.31	3.44	36.44	25,889‡
IGRA/RIF	215,001	13,692.95	2.93	45.93	23,645
SEQ/INH	249,627	13,691.78	3.72	31.35	46,868§
IGRA/INH	269,077	13,691.92	3.26	39.73	51,459§
TST/RIF	271,148	13,692.32	3.21	40.72	45,759§
TST/INH	359,562	13,691.89	3.51	35.11	84,512§
Reactivation rate is 1.3 cases/1,000 PY					
Base case	122,759	13,710.67	5.38	NC	NC
SEQ/RIF	185,440	13,713.34	3.43	36.21	23,481‡
IGRA/RIF	190,194	13,713.62	2.92	45.75	22,844
SEQ/INH	218,459	13,712.71	3.69	31.42	47,077§
IGRA/INH	232,647	13,713.21	3.28	39.10	43,315§
TST/RIF	257,754	13,713.51	3.20	40.65	47,589§
TST/INH	340,390	13,713.27	3.52	34.57	83,627§
Lifetime time horizon					
Base case	170,849	20,402.30	7.49	NC	NC
SEQ/RIF	224,283	20,407.15	4.82	35.70	11,020‡
IGRA/RIF	225,833	20,408.27	4.06	45.77	9,210
SEQ/INH	261,944	20,405.53	5.24	30.06	28,166§
TST/RIF	275,189	20,405.94	4.61	38.44	28,678§
IGRA/INH	291,260	20,406.55	4.51	39.84	28,311§
TST/INH	377,756	20,404.24	4.97	33.69	106,493§
Minimum estimated costs					
Base case	97,691	13,702.56	5.39	NC	NC
IGRA/RIF	150,526	13,705.48	2.91	45.99	18,093
SEQ/RIF	151,483	13,704.93	3.44	36.06	22,612§
SEQ/INH	184,273	13,704.38	3.73	30.73	47,426§
IGRA/INH	192,125	13,704.35	3.28	39.21	52,631§
TST/RIF	215,987	13,704.93	3.22	40.18	49,754§
TST/INH	291,076	13,704.15	3.54	34.36	121,070§
Maximum estimated costs					
Base case	148,167	13,702.56	5.39	NC	NC
SEQ/RIF	230,715	13,704.93	3.44	36.06	34,699‡
IGRA/RIF	234,294	13,705.48	2.91	45.99	29,493
SEQ/INH	273,020	13,704.38	3.73	30.73	68,389§
IGRA/INH	287,910	13,704.35	3.28	39.21	77,883§
TST/RIF	311,276	13,704.93	3.22	40.18	68,602§
TST/INH	406,415	13,704.15	3.54	34.36	161,677§

Intervention	Cost/1,000, $	No. QALYs/1,000	No. TB cases/1,000	% Reduction in TB incidence	Cost/QALY gained, ($)†

*All costs in 2016 Can $. IGRA, interferon-gamma release assay; INH, isoniazid; NC, not calculable; QALY, quality-adjusted life year; RIF, rifampin; SEQ, sequential screening; TB, tuberculosis; TST, tuberculin skin test.
†The cost per QALY gained is calculated in comparison to the base case.
‡This intervention strategy is extendedly dominated by another intervention strategy. While it increases QALYs, it has a higher ICER than a more expensive intervention strategy.
§This intervention strategy is strictly dominated by another intervention strategy. It is more expensive and has worse outcomes.

Appendix Table 6. Results of exploratory analyses in migrants from very high TB incidence countries*

Intervention	Cost/1,000, $	No. QALYs/1,000	No. TB cases/1,000	% Reduction in TB incidence	Cost/QALY gained, $†
Only screen persons ≤60 y of age					
Base case	184,357	13,666.32	8.12	NC	NC
SEQ/RIF	257,138	13,670.07	5.36	33.99	19,422‡
IGRA/RIF	262,010	13,671.02	4.64	42.77	16,507
SEQ/INH	307,723	13,669.52	5.78	28.79	38,514§
TST/RIF	310,389	13,670.59	5.05	37.82	29,494§
IGRA/INH	325,585	13,669.95	5.16	36.45	38,909§
TST/INH	402,151	13,669.61	5.52	32.05	66,187§
Only screen persons ≤35 y of age					
Base case	184,357	13,666.32	8.12	NC	NC
SEQ/RIF	223,125	13,668.52	6.89	15.08	17,593‡
IGRA/RIF	226,103	13,668.80	6.55	19.29	16,848
SEQ/INH	244,909	13,667.52	7.03	13.44	50,260§
IGRA/INH	255,309	13,668.30	6.80	16.28	35,749§
TST/RIF	265,651	13,668.53	6.74	16.94	36,847§
TST/INH	316,918	13,667.99	6.92	14.77	79,512§
Only screen persons 10–60 y of age					
Base case	184,357	13,666.32	8.12	NC	NC
SEQ/RIF	246,752	13,670.05	5.57	31.33	16,711‡
IGRA/RIF	250,991	13,671.01	4.93	39.31	14,206
TST/RIF	290,406	13,670.58	5.28	34.94	24,898§
SEQ/INH	292,011	13,669.51	5.94	26.85	33,753§
IGRA/INH	307,714	13,669.93	5.35	34.05	34,114§
TST/INH	370,423	13,669.60	5.65	30.38	56,781§
Only 63.5% initiate therapy after arrival					
Base case	183,165	13,667.06	8.14	NC	NC
SEQ/RIF	255,496	13,669.71	6.08	25.22	27,222‡
IGRA/RIF	260,008	13,670.45	5.61	31.07	22,661
TST/RIF	286,279	13,669.35	5.85	28.10	44,932§
SEQ/INH	291,905	13,669.14	6.36	21.85	52,130§
IGRA/INH	305,683	13,669.01	5.94	26.93	62,670§
TST/INH	352,634	13,669.30	6.19	23.92	75,655§
100% Adherence to post-arrival follow-up					
Base case	185,064	13,667.21	8.01	NC	NC
SEQ/RIF	277,526	13,672.40	3.86	51.83	17,814‡
IGRA/RIF	286,742	13,673.59	2.75	65.72	15,931
SEQ/INH	356,943	13,671.03	4.50	43.88	45,057§
TST/RIF	369,167	13,673.42	3.36	58.09	29,667§
IGRA/INH	386,849	13,672.66	3.53	56.00	37,031§
TST/INH	512,140	13,672.17	4.08	49.11	65,978§
No losses in the LTBI cascade of care					
Base case	184,268	13,668.16	7.73	NC	NC
SEQ/RIF	269,103	13,674.32	3.10	59.97	13,783‡
IGRA/RIF	275,614	13,675.78	1.75	77.33	11,997
TST/RIF	366,839	13,675.63	2.52	67.46	24,447§
SEQ/INH	376,306	13,674.18	3.27	57.66	31,918§
IGRA/INH	411,237	13,675.57	1.97	74.47	30,634§
TST/INH	571,667	13,674.53	2.71	65.00	60,899§
Reactivation rate is 0.9 cases/1,000 PY					
Base case	185,203	13,646.81	8.14	NC	NC
SEQ/RIF	283,301	13,651.14	5.19	36.26	22,626‡
IGRA/RIF	291,983	13,651.90	4.43	45.51	20,962
TST/RIF	330,139	13,651.84	4.85	40.39	28,775§
SEQ/INH	346,376	13,650.64	5.63	30.82	42,038§
IGRA/INH	370,889	13,651.29	4.96	39.11	41,386§
TST/INH	433,739	13,651.04	5.34	34.41	58,669§
Reactivation rate is 1.3 cases/1,000 PY					
Base case	181,988	13,680.54	8.02	NC	NC

Intervention	Cost/1,000, $	No. QALYs/1,000	No. TB cases/1,000	% Reduction in TB incidence	Cost/QALY gained, $†
SEQ/RIF	250,392	13,684.51	5.19	35.28	17,215‡
IGRA/RIF	252,612	13,684.78	4.39	45.28	16,672
SEQ/INH	297,483	13,682.75	5.57	30.53	52,289§
TST/RIF	309,989	13,684.00	4.84	39.65	36,943§
IGRA/INH	313,436	13,683.69	4.91	38.75	41,738§
TST/INH	403,690	13,683.21	5.32	33.63	83,081§
Lifetime time horizon					
Base case	257,337	20,201.68	11.34	NC	NC
SEQ/RIF	309,830	20,208.76	7.29	35.77	7,415‡
IGRA/RIF	309,977	20,212.11	6.23	45.09	5,046
TST/RIF	362,091	20,207.77	7.90	30.38	17,210§
SEQ/INH	364,532	20,208.76	6.84	39.70	15,141§
IGRA/INH	378,284	20,208.92	7.00	38.33	16,718§
TST/INH	459,696	20,207.51	7.48	34.03	34,692§
Minimum estimated costs					
Base case	146,557	13,666.32	8.12	NC	NC
IGRA/RIF	206,883	13,671.50	4.41	45.61	11,632
SEQ/RIF	207,111	13,670.25	5.18	36.23	15,404§
SEQ/INH	254,658	13,670.32	5.62	30.76	27,013§
TST/RIF	260,362	13,671.23	4.86	40.16	23,169§
IGRA/INH	267,040	13,671.02	4.97	38.82	25,656§
TST/INH	346,126	13,669.91	5.33	34.34	55,593§
Maximum estimated costs					
Base case	222,159	13,666.32	8.12	NC	NC
SEQ/RIF	313,033	13,670.25	5.18	36.23	23,117‡
IGRA/RIF	315,886	13,671.50	4.41	45.61	18,073
SEQ/INH	374,284	13,670.32	5.62	30.76	38,015§
TST/RIF	376,642	13,671.23	4.86	40.16	31,450§
IGRA/INH	393,477	13,671.02	4.97	38.82	36,481§
TST/INH	485,765	13,669.91	5.33	34.34	73,432§

*All costs in 2016 Can $. IGRA, interferon-gamma release assay; INH, isoniazid; NC, not calculable; QALY, quality-adjusted life year; RIF, rifampin; SEQ, sequential screening; TB, tuberculosis; TST, tuberculin skin test.

†The cost per QALY gained is calculated in comparison to the base case.

‡This intervention strategy is extendedly dominated by another intervention strategy. While it increases QALYs, it has a higher ICER than a more expensive intervention strategy.

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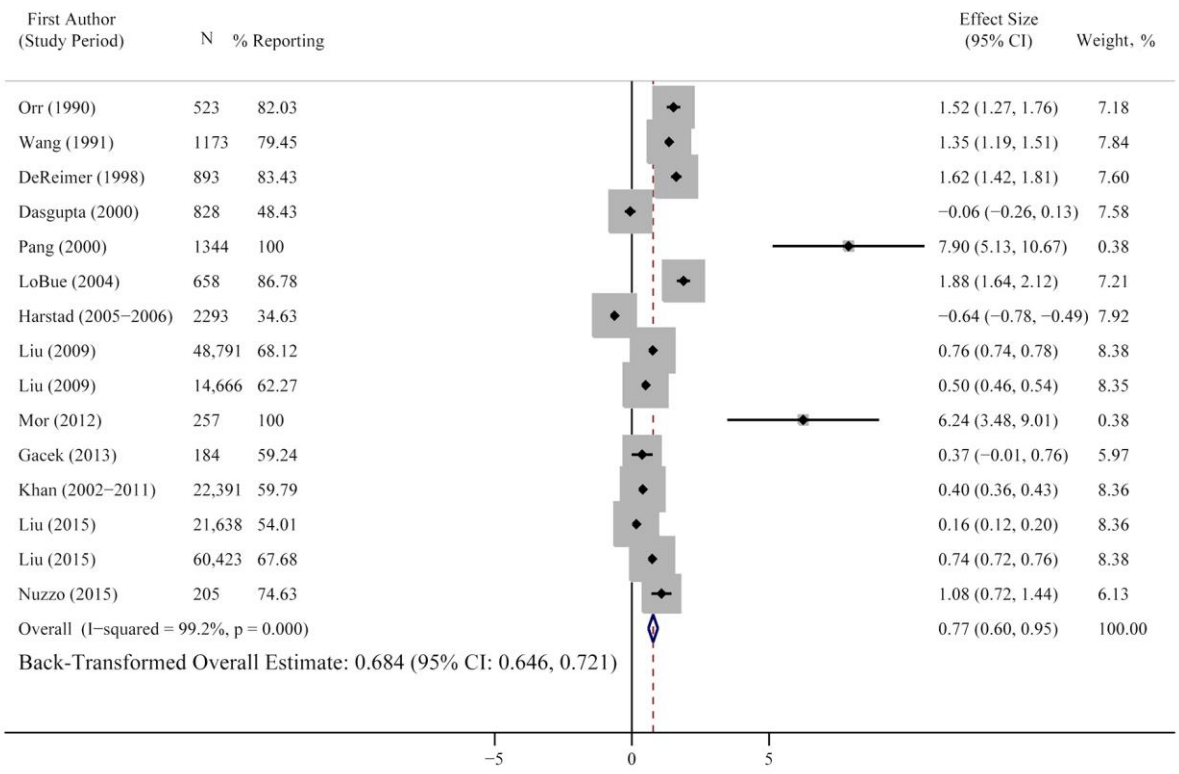
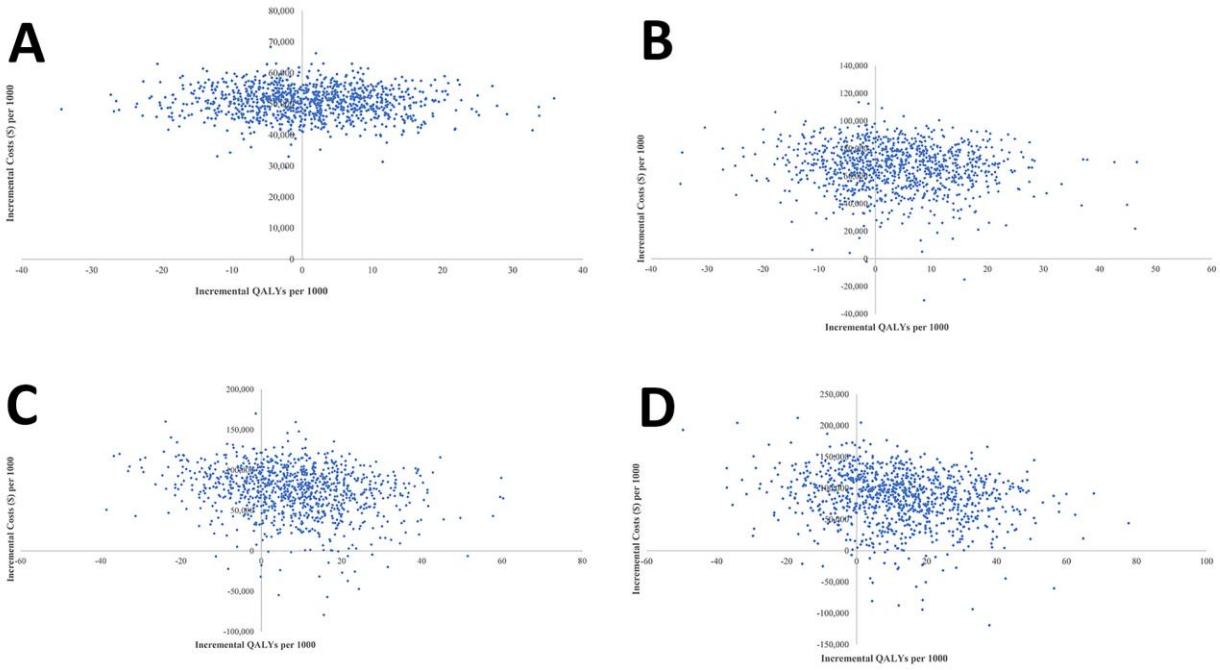
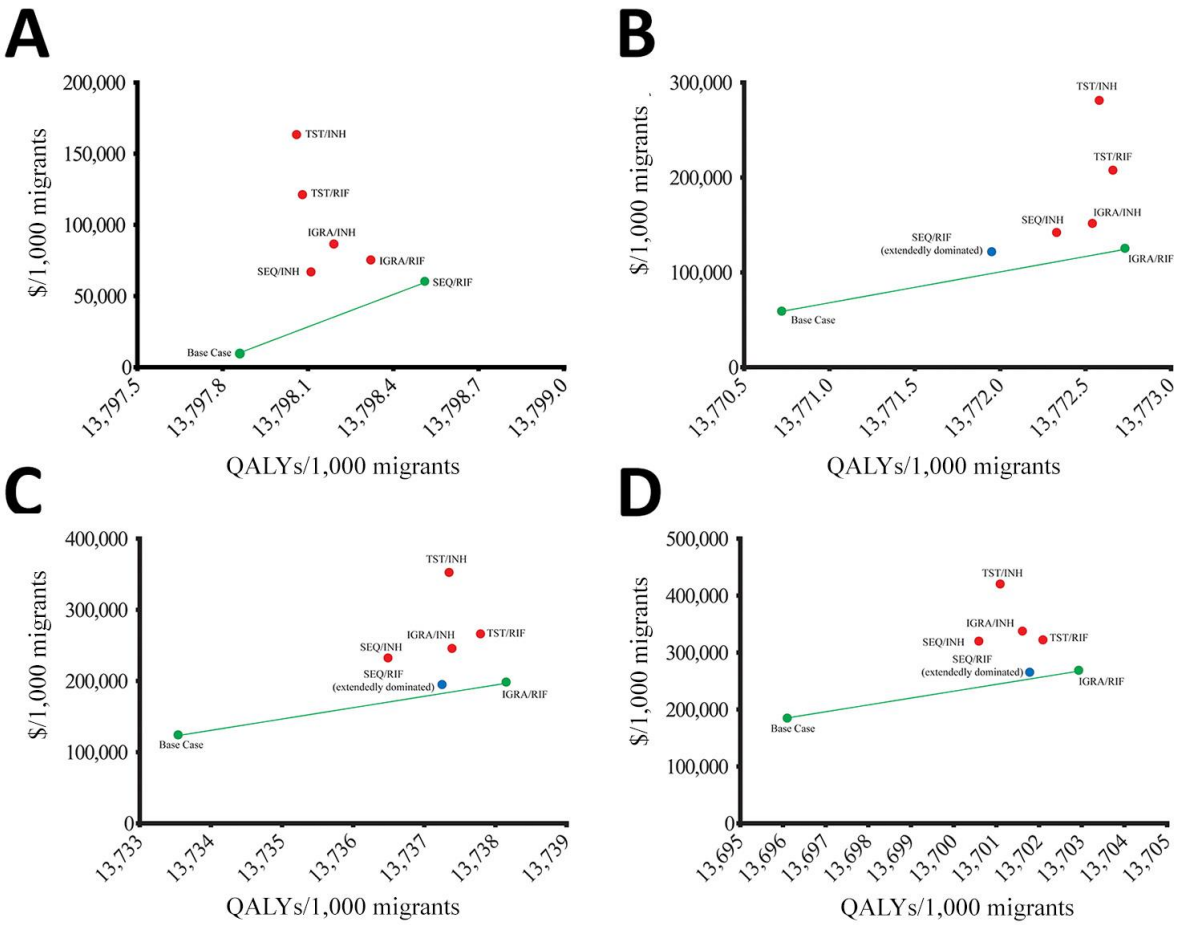


Appendix Figure 1. Meta-analysis of adherence with a request for post-arrival follow-up. This was used to inform the proportion who report for LTBI treatment post-arrival.



Appendix Figure 2. Cost-effectiveness planes demonstrating the variability in probabilistic sensitivity analysis replications for select intervention strategies in migrants from low incidence (A), moderate incidence (B), high incidence (C), and very high TB incidence (D) countries.



Appendix Figure 3. Efficiency frontier of population QALYs versus population costs among migrants from low (A), moderate (B), high (C), and very high (D) TB incidence countries. The frontier is read from left to right, with intervention strategies connected if they fall on the frontier. Those subsequent to the initial intervention strategy have an increased cost, but an increased benefit, and represent the next best value at increasing funding thresholds. The slope between 2 connected intervention strategies represents cost-effectiveness: a steeper slope represents poorer cost-effectiveness, while a shallow slope represents better cost-effectiveness. An intervention strategy that is extendedly dominated has a higher cost-per QALY gained and fewer population QALYs than the subsequent intervention on the frontier and is therefore less efficient. IGRA, interferon-gamma release assay; INH, isoniazid; QALY, quality-adjusted life year; RIF, rifampin; SEQ, sequential screening; TST, tuberculin skin test.