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Interferon-gamma release assays and TB screening in high-income countries: a cost-effectiveness analysis

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SUMMARY

OBJECTIVE: Interferon-gamma release assays (IGRA) are now available alternatives to tuberculin skin testing (TST) for detection of latent tuberculosis infection (LTBI). We compared the cost-effectiveness of TST and IGRA in different populations and clinical situations, and with variation of a number of parameters.

METHODS: Markov modelling was used to compare expected TB cases and costs over 20 years following screening for TB with different strategies among hypothetical cohorts of foreign-born entrants to Canada, or contacts of TB cases. The less expensive commercial IGRA, QuantiFERON®-TB Gold (QFT), was examined. Model inputs were derived from published literature.

RESULTS: For entering immigrants, screening with chest radiograph (CXR) would be the most and QFT the least cost-effective. Sequential screening with TST then QFT was more cost-effective than QFT alone in all scenarios, and more cost-effective than TST alone in selected subgroups. Among close and casual contacts, screening with TST or QFT would be cost saving; savings with TST would be greater than with QFT, except in contacts who were bacille Calmette-Guérin (BCG) vaccinated after infancy.

CONCLUSIONS: Screening for LTBI, with TST or QFT, is cost-effective only if the risk of disease is high. The most cost-effective use of QFT is to test TST-positive persons.

KEY WORDS: screening; quantiferon; tuberculosis control; tuberculosis prevention; economic analysis

THE DECLINE IN TUBERCULOSIS (TB) rates in the general population of high-income countries has shifted TB control efforts to high-risk subgroups[1,2] such as contacts of active cases. Screening migrants for TB as they enter high-income countries, although widely practised, remains controversial.[3,4] Current chest radiographic (CXR) screening is useful to detect prevalent active TB, but it is insensitive for latent TB infection (LTBI). Tuberculin skin test (TST) screening has been proposed to detect individuals with LTBI, who can be treated,[3] but it has a number of important limitations.[5,6]

Two ex vivo blood tests are now commercially available for the diagnosis of LTBI: QuantiFERON®-TB-Gold (QFT) (Cellestis, Carnegie, VIC, Australia) and T-Spot.*TB*® (T-Spot) (Oxford Immunotech, Oxford, UK). Both measure interferon-gamma (IFN-γ) produced by circulating lymphocytes in whole blood following in vitro exposure to antigens found in *Mycobacterium tuberculosis*.[7,8] Recent recommendations have suggested that these new tests can be used instead of the TST[9] or as adjunctive measures.[10] We have compared the cost-effectiveness of IFN-γ release assays (IGRA) and TST for TB screening in different populations and clinical situations. Given the manufacturers' current unit costs, including tax, of $19.00 (CDN—Canadian dollars) for QFT, and $63.25 CDN for the T-Spot, and equivalent performance,[11–13] we considered only QFT for this analysis.

METHODS

Study populations

We examined screening of immigrants at entry to Canada, or of close and casual contacts. To account for varying prevalence of LTBI we examined three cohorts from countries with low, intermediate and high incidence of TB. Their characteristics are summarised in Table 1. To examine the impact of TST specificity we stratified these analyses according to bacille Calmette-Guérin (BCG) vaccination status—an important cause of false-positive TST, but not false-positive QFT.[33] All cohort members were assumed to enter Canada as legal immigrants, in whom human immunodeficiency virus (HIV) seroprevalence is virtually nil (unpublished data from Citizenship and Immigration Canada). Prevalence of resistance to anti-tuberculosis drugs reflected average prevalence in foreign-born individuals in

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Table 1 Modeling inputs and assumptions: characteristics of legal immigrants entering Canada

Hypothetical cohorts of entrants represented by populations from:	Low incidence	Intermediate incidence	High incidence	Reference
Number entering each year	1000	1000	1000	Assumption
Mean age, years	35	35	35	Assumption
Incidence of smear-positive TB/100 000*	2	60	120	[14]
ARI in country of origin	0.04%	1.2%	2.4%	From [14,15]
Prevalence of LTBI				
Legal immigrants entering Canada				
Recent (<2 years)	0.08%	1.6%	2.1%	Calculated
Long standing (2+ years)	1.3%	33.4%	55.9%	
Close contacts (probability of infection = 0.4)				
Recent (<2 years)	39.4%	26%	16.8%	[16–18]
Long standing (2+ years)	1.4%	35.0%	58.0%	[19,20]
Casual contacts (probability of infection = 0.08)				
Recent (<2 years)	7.9%	5.2%	3.4%	
Long standing (2+ years)	1.4%	35.0%	58.0%	
Prevalence of active TB				
Legal immigrants at entry	0.05%	0.2%	0.3%	[21–25]
Close contacts	3%	3%	3%	[25]
Casual contacts	0.6%	0.6%	0.6%	[19,20]
Prevalence of underlying MDR	1.0%	1.0%	1.0%	[26]
Prevalence of underlying INH resistance	10%	10%	10%	[26]
Selected test characteristics	Parameter	Reference		
CXR				
Sensitivity — Detection of active TB	100%	Assumption		
Sensitivity — Detection of LTBI	11%	[27]		
TST				
Sensitivity — Detection of TB disease	82%	[28,29]		
Sensitivity — Detection of infection	95%	[30–32]		
Specificity — TB infection: not BCG-vaccinated	98%	From [33]		
Specificity — BCG-vaccinated in infancy	92%	From [33]		
Specificity — BCG-vaccinated in older childhood/adolescence	60%	From [33]		
QFT				
Sensitivity — Detection of TB disease	82%	[34–40]		
Sensitivity — Detection of infection	95%	Assumption		
Specificity — TB infection: non-vaccinated	98%			
Specificity — BCG vaccinated in infancy	98%	For all 3: [34–40]		
Specificity — BCG vaccinated in older childhood/adolescence	98%			
Selected cost estimates (costs in 2004 CDN$[41])				
CXR				
Screening radiograph	$25.74	[25]		
Medical evaluation if abnormal CXR†	$225.17			
TST				
Screening TST	$12.73	[42]		
Medical evaluation if positive TST‡	$154.40	[25]		
QFT				
Screening QFT: manufacturer's retail unit cost (+ tax)	$19.00	Quote from manufacturer		
All other costs (see text)	$22.32	[42]		
Medical evaluation if positive QFT‡	$154.40	[25]		
LTBI				
Cost of treatment	$433.37	[25]		
Cost of drug-induced hepatitis	$5,319.50	[43,44]		
Active TB				
General medical/follow-up visit	$29.94	[43]		
Total health system cost, active TB cases picked up by screening	$2,157.29	From [25]		
Total health system cost, active TB cases diagnosed passively	$21,599.44	From [44] and [45]		
Selected outcomes				
Likelihood of INH-induced hepatitis	1%	[46–48]		
Likelihood of hospitalisation if hepatitis develops	9%	[43]		
Likelihood that a positive reactor is medically evaluated, and is offered, accepts and completes LTBI treatment	21%	[24,25,49–54]		
Likelihood that a positive reactor who completes LTBI treatment is cured, if underlying organism is INH-sensitive	90%	[55]		
Likelihood that a positive reactor who completes LTBI treatment is cured, if underlying organism is INH-resistant	0%	[56]		
Likelihood of cure for a patient with active TB	80%	[1]		

* Rates taken from WHO [11] for USA, Dominican Republic and Sierra Leone as examples of low, intermediate and high TB incidence.
† Medical evaluation for abnormal CXR includes: initial clinic visit, consultation, repeat CXR, TST, three sputum AFB, blood tests and follow-up visit (clinic and physician charges). [25]
‡ Medical evaluation for positive TST or QFT includes: initial clinic visit, consultation, CXR and blood test. [25]
TB = tuberculosis; ARI = annual risk of infection; LTBI = latent tuberculosis infection; MDR = multidrug resistance; INH = isoniazid; CXR = chest X-ray; TST = tuberculin skin test; BCG = bacille Calmette-Guérin; QFT = QuantiFERON®-TB Gold; WHO = World Health Organization; AFB = acid-fast bacilli.

Canada in 2002.[26] For ease of calculation, all hypothetical cohorts were assumed to be of 1000 individuals each. This study did not require ethics review.

General description of model

A decision analysis model was constructed using Tree Age software (Health Care Edition, version 0.8, Tree Age Pro 2005, Williamstown, MA, USA). This model employed multiple Markov processes that allowed variables to change over time. A 20-year analytic horizon was used with 3% annual discounting for all costs and outcomes that occurred after Year 1.[57]

Year 1 was defined as the year that entering immigrants underwent screening, or of contact investigation. At the start all cohort members were in one of four underlying TB health states: non-infected, recent LTBI, long-standing LTBI and active TB disease (additional details of the modelling are shown in Figures 1–3 in an on-line supplement*). Health states at the end of Year 1 reflected all diagnostic and treatment activities—assumed to have been completed in Year 1. Those who survived Year 1 entered the next year in the same health state. For example, those with LTBI who were not diagnosed and/or not treated in Year 1, would begin Year 2 with LTBI.

Treatment outcomes of active TB detected through screening were as reported nationally.[1] LTBI treatment outcomes were taken from several large-scale screening programmes:[21,24,25,49–54] 81% of those with positive test results would complete medical evaluation, 51% of those eligible would be offered isoniazid (INH), of whom 71% would accept, and 50% (overall 21%) would finish 9 months of INH therapy. INH for 9 months would have 90% efficacy if the underlying organism was INH-susceptible[55] and 0% efficacy if INH-resistant.[56]

In subsequent years, the probability that persons with LTBI would develop active TB was based on data from published cohort studies and randomised controlled trials (summarised in the supplement Table*). Of those developing active TB after screening, 95% would be diagnosed passively and treated, with outcomes as above.[1] Outcomes of undiagnosed active TB would be as in the pre-antibiotic era.[58–60] Average age-specific background mortality rates from Canadian life tables were used for other-cause mortality.[61]

Neither new HIV infection, nor new TB infection nor LTBI treatment would occur after Year 1. These assumptions simplified the model, and did not affect the comparison of strategies.

Details of screening strategies

Immigration entry screening

On entry, the prevalence of active TB was based on published reports,[21–25] and prevalence of LTBI was based on age at immigration[62] and incidence of smear-positive TB in the country of origin,[14] using the Styblo formula.[15]

STRATEGY 1: No screening.

STRATEGY 2: CXR. All immigrants would first undergo CXR. If normal, they would have no further follow-up. All immigrants with abnormal CXR would have specialist consultation, repeat CXR and other tests as appropriate.[25] Immigrants with active TB would be treated appropriately, while those with abnormal CXR and positive TST (often termed 'inactive TB') would receive INH (see Strategy 3). These represent about 11% of all patients with LTBI,[25,63] and they have an increased risk of reactivation.[24,64,65]

STRATEGY 3: TST. All immigrants would first undergo TST; if negative (<10 mm) they would have no further follow-up. Those with active TB and false-negative TST would be diagnosed passively during Year 1. Those with a positive TST (10+ mm) would be referred for specialist consultation, CXR and further testing. Patients with active TB would receive full therapy, and the remainder INH. The sensitivity of TST would be 95% for LTBI[32] and 82% for active disease.[28,29] Specificity would depend on non-tuberculous mycobacterial prevalence in the region of origin and BCG vaccination, including age at vaccination.[33]

STRATEGY 4: QFT. In this strategy, the first test would be a QFT; immigrants with a negative QFT would have no further testing, nor visits. Immigrants with a positive QFT would have the same evaluation and management as for a positive TST.[9] The sensitivity of QFT would be 82% for active disease[34–40] and 95% for LTBI—equal to TST. The specificity of QFT of 98% was from studies in populations with very low expected prevalence of LTBI.[34–38,66] (Summary test characteristics for QFT were calculated by pooling data from the above studies, using Meta-DiSc® software.[67])

STRATEGY 5: TST followed by QFT if TST-positive. Subjects first undergo a TST. If negative, they have no further testing, but if positive, a QFT is done. If the QFT is negative they have no further testing, but if positive they would be evaluated as in Strategies 3 and 4.

Contact investigations

Close contacts would have a 40% chance of new infection,[16–18] and 3% would have prevalent active disease.[25] Casual contacts would have an 8% chance of new infection, and 0.6% would have active disease.[19,20] Contacts with prior long-standing LTBI could be re-infected, but would have an 80% lower risk of disease.[68,69]

STRATEGY 1: No screening.

STRATEGY 2: TST. Contacts would have a single TST 8 weeks after TB exposure; if negative (<5 mm) they would receive no further follow-up. A single test was modelled for both strategies because there is no published information regarding serial QFT testing for detection of new TB infection. TST positive (≥5

* Available from the authors at http://www.respdiv.mcgill.ca/respepi/Menzies.htm

mm) contacts would undergo medical evaluation and appropriate treatment for active disease or LTBI, as described above.

STRATEGY 3: QFT. This strategy had the same testing protocols and outcomes as the TST strategy for contacts, except that QFT-negative subjects would need only one visit.

Costs

We included all government and health system costs as well as patients' out-of-pocket expenditures,[70] but not TB-related death or disability. Health system costs were derived from earlier micro-costing studies[25,27,43] and patient expenditures from earlier patient surveys.[71] All costs were expressed in 2004 Canadian dollars (average rate of exchange in 2004: $1.30 CDN = $1.00 US[72]); values from earlier years were adjusted using appropriate inflation indices.[41,73]

The most important cost was for the treatment of active TB. If passively diagnosed (i.e., after screening), the total cost per case was $21 599,[44,45,74] but it was only $2160 (10%) for cases diagnosed actively by screening.[25,75] This difference reflects the much higher probability and longer duration of hospitalisation for passively diagnosed cases.[25,75] QFT cost included the manufacturer's current unit costs, plus costs for clinical personnel, transportation, laboratory personnel and reporting.[42]

RESULTS

As shown in Table 2, all strategies for screening immigrants at entry to Canada had a modest impact. CXR screening was the least costly of all three screening strategies, with incremental cost per case prevented ranging from $875 for immigrants from high-incidence

Table 2 Effect of BCG vaccination at different ages (hence TST specificity) and prevalence of LTBI on expected cases and costs with different immigration screening strategies. 35-year-old legal immigrants entering Canada from countries with different TB incidence (1000 from each country—all costs in Canadian $ 2004)

	Incidence smear-positive TB in countries of origin		
	Low (2/100 000) $CDN	Intermediate (60/100 000) $CDN	High (120/100 000) $CDN
No screening			
Expected future active TB cases over 20 years	0.4	9.8	15.7
Total costs	8 810	204 510	327 490
CXR screening			
Future active TB cases prevented*	0.02	0.5	0.8
Total costs	52 553	219 850	328 190
Costs (savings) relative to no screen†	43 743	15 340	700
Incremental cost per case prevented	2 187 167	30 680	875
QFT or TST screening—future active TB cases prevented*	0.05	1.3	2.1
QFT screening (all BCG status—QFT specificity 98%)			
Total cost	64 920	303 020	459 040
Total cost (savings) relative to no screen†	56 110	98 510	131 550
Incremental cost per case prevented‡	1 122 200	75 777	62 643
TST screening—no BCG (TST specificity 98%)			
Total costs with TST screening	30 320	267 250	423 250
Total costs (savings) with TST relative to no screen†	21 510	62 740	95 760
Incremental cost per case prevented with TST§	430 200	48 262	45 600
Total costs (savings) with TST relative to QFT¶	(34 600)	(35 770)	(35 790)
TST screening—BCG in infancy (TST specificity 92%)			
Total costs with TST screening	48 810	279 390	431 060
Total costs (savings) with TST relative to no screen†	40 000	74 880	103 570
Incremental cost per case prevented with TST§	800 000	58 961	49 319
Total costs (savings) with TST relative to QFT¶	(16 110)	(23 630)	(27 980)
TST screening—BCG older (TST specificity 60%)			
Total costs with TST screening	129 660	332 520	465 260
Total costs (savings) with TST relative to no screen†	120 850	128 010	137 770
Incremental cost per case prevented with TST§	2 417 000	100 050	65 605
Total costs (savings) with TST relative to QFT¶	64 740	29 500	6 220
TST screening—mixture of BCG (TST specificity 85%)‡			
Total costs with TST screening	69 597	293 053	439 857
Total costs (savings) with TST relative to no screen†	60 787	88 543	112 367
Incremental cost per case prevented with TST§	1 215 733	68 110	53 508
Total costs (savings) with TST relative to QFT¶	4 677	(9 967)	(19 183)

* Future active TB cases prevented by the screening strategy, compared to no screening programme.
† Costs in parentheses ($) indicate net savings.
‡ Assumes that one-third of population will have received BCG in infancy, one-third received BCG after infancy and one-third was never vaccinated.
§ Added costs for screening per incident case prevented by screening compared to no screening.
¶ Difference in total costs between screening strategies shown. (Costs in parentheses indicate net savings.) There is no difference in the number of cases prevented with TST or QFT strategy.
BCG = bacille Calmette-Guérin; TST = tuberculin skin test; LTBI = latent tuberculosis infection; TB = tuberculosis; CXR = chest X-ray; QFT = QuantiFERON®-TB Gold.

Table 3 Summary of cost-effectiveness of screening strategies in three populations with three BCG vaccination states and in three clinical situations

Clinical situation	Population from country with TB incidence that is	BCG vaccination*	Preferred strategy†	Costs relative to no screening: Cost per incremental case prevented‡ $CDN	Costs relative to no screening: Added costs or (savings) per person screened $CDN
Immigration entry screening§	Low	All¶	CXR	2 187 167	43.74
	Intermediate	All	CXR	30 680	15.34
	High	All	CXR	875	0.70
Close contacts§	Low	None	TST	Savings	(340.84)
		Infancy	TST	Savings	(331.24)
		Older	QFT	Savings	(305.60)
	Intermediate	None	TST	Savings	(297.99)
		Infancy	TST	Savings	(290.68)
		Older	QFT	Savings	(262.20)
	High	None	TST	Savings	(256.35)
		Infancy	TST	Savings	(251.68)
		Older	QFT	Savings	(231.16)
Casual contacts§	Low	None	TST	Savings	(53.09)
		Infancy	TST	Savings	(43.08)
		Older	QFT	Savings	(18.40)
	Intermediate	None	TST	5 540	11.08
		Infancy	TST	22 530	22.53
		Older	QFT	23 425	46.85
	High	None	TST	28 020	56.04
		Infancy	TST	31 800	63.60
		Older	QFT	45 915	91.03

* TST specificity: No BCG—98%, BCG infancy—92%, BCG older—60%. From [33].
† Preferred—strategy with lowest incremental cost per case prevented, or greatest savings.
‡ Added costs for screening per incident case prevented by screening—compared to no screening.
§ For entry screening CXR was compared to TST and QFT, because CXR is the current strategy for many high-income countries. Each strategy compared separately to no screening. For close and casual contacts, TST and QFT were compared to no screening; CXR screening was not considered because this is *not* used for initial screening in contact investigations in high-income countries.
¶ All—means holds true for all BCG vaccination histories—none, or BCG in infancy or BCG after infancy.
BCG = bacille Calmette-Guérin; TB = tuberculosis; CXR = chest X-ray; TST = tuberculin skin test; QFT = QuantiFERON®-TB Gold.

countries to $2.2 million for those from low-incidence countries. Initial screening with QFT was the most expensive strategy, except in populations BCG-vaccinated after infancy, where TST was more expensive because of low specificity. Additional sensitivity analyses varied the QFT sensitivity for active disease from 70% to 90%, the case detection rate for passively diagnosed cases from 80% to 100%, and discount rate from 0 to 6%. These variations did not have a major impact on the findings, nor did they change the relative order of the screening strategies in any of the populations or scenarios (data not shown in tabular form). Finally, adding TST or QFT screening to ongoing CXR screening would cost $73 000–$101 000 per *additional* case prevented, even in immigrants from high-incidence countries.

Investigation of close contacts with QFT or TST would actually result in savings (Table 3). Savings would be somewhat less among contacts originally from high-incidence countries, because of the high prevalence of prior LTBI, with its associated protective effect against disease following re-infection. QFT would be more cost-effective than TST in close and casual contacts who had received BCG vaccination after infancy because of reduced TST specificity. The balance between the differences in costs and specificities of QFT and TST is demonstrated by the cost-minimisation analysis shown in Figure 1. If TST is $70 cheaper than the more specific IGRA test (as for the T-Spot currently), then screening with the IGRA test will be less expensive only if TST specificity is less than 40%.

As seen in Table 4, screening immigrants for LTBI would be more cost-effective in the presence of medi-

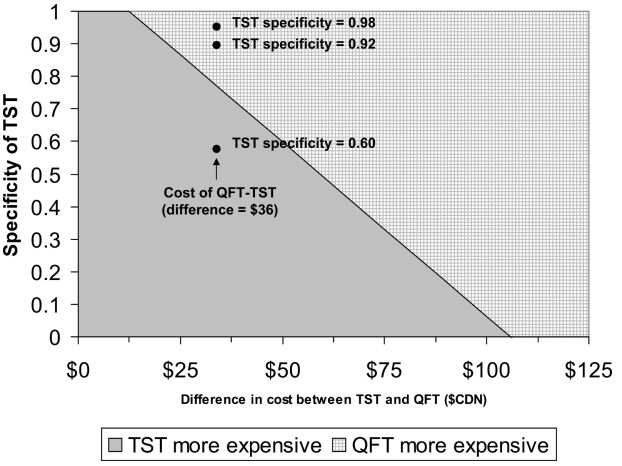

Figure 1 Cost minimisation analysis—varying the difference in cost between TST and QFT, and the specificity of TST. Grey shading = TST more expensive; cross-hatch shading = QFT more expensive. TST = tuberculin skin test; QFT = QuantiFERON®-TB Gold.

Table 4 Effect of risk of reactivation in long-standing TB infection and sensitivity of TST on expected cases and costs with different screening strategies. Hypothetical cohorts of 1000 non-BCG-vaccinated legal immigrants aged 35 from an intermediate-incidence country entering Canada with medical conditions that increase the risk of reactivation. (All costs in Canadian $ 2004)

	Annual risk of TB reactivation*		
	Healthy low risk 0.1% $CDN	High risk 1.2% $CDN	Very high risk 5% $CDN
No screening			
Expected future active TB cases over 20 years	9.8	70.0	181.7
Total cost	204 510	1 464 490	3 800 310
CXR screening			
Future active TB cases prevented†	0.5	3.3	4.3
Total costs	219 610	1 419 780	3 734 820
Total costs (savings) relative to no screen‡	15 100	(44 710)	(65 490)
Incremental cost per case prevented§	30 200	(22 355)	Savings
QFT screening (sensitivity = 95%)			
Future active TB cases prevented†	1.3	10.7	27.0
Total costs	303 020	1 364 000	3 359 760
Total costs (savings) relative to no screen‡	98 510	(100 490)	(440 550)
Incremental cost per case prevented§	77 567	(16 748)	Savings
TST screening (sensitivity = 95%)			
Future active TB cases prevented†	1.3	10.7	27.0
Total costs	267 250	1 328 230	3 323 990
Total costs (savings) relative to no screen‡	62 740	(136 260)	(476 320)
Incremental cost per case prevented§	49 402	(17 033)	Savings
Total costs (savings) relative to QFT¶	(35 770)	(35 770)	(35 770)
Effect of reduction in TST sensitivity			
TST sensitivity 90%			
Reduction in cases prevented (compared to sensitivity of 95%)	0.1	0.5	1.5
Cost (savings) relative to QFT	(39 491)	(29 021)	(11 122)
TST sensitivity 85%			
Reduction in cases prevented (compared to sensitivity of 95%)	0.2	1.1	2.9
Cost (savings) relative to QFT	(43 212)	(22 300)	13 529
TST sensitivity 80%			
Reduction in cases prevented (compared to sensitivity of 95%)	0.2	1.7	4.3
Cost (savings) relative to QFT	(46 933)	(15 500)	38 179
TST sensitivity 75%			
Reduction in cases prevented (compared to sensitivity of 95%)	0.3	2.2	5.8
Cost (savings) relative to QFT	(50 655)	(8 800)	62 830

* Annual risk of reactivation in person with LTBI: low risk from [76,77]. High risk: conditions such as Infliximab therapy[78] or renal failure.[79,80] Very high risk: transplant[81–84] or asymptomatic HIV infection.[85]
† Incident cases in the cohort prevented with the screening strategy compared to no screening.
‡ Values in parentheses indicate savings.
§ Added costs for screening per incident case prevented by screening compared to no screening.
¶ Difference in cost per case prevented is shown because there is no difference in the number of cases prevented with the TST and QFT strategy, making the incremental effectiveness zero.
TB = tuberculosis; TST = tuberculin skin test; BCG = bacille Calmette-Guérin; CXR = chest X-ray; QFT = QuantiFERON®-TB Gold.

cal problems that increase reactivation risk. Generally, TST would be more cost-effective than QFT unless TST sensitivity was less than 90% and risk of reactivation was very high (see also Figure 2).

All screening strategies would be much more cost-effective if a higher proportion of those with positive screening tests completed medical evaluation and LTBI therapy (Table 5).

By improving programme performance, the public health impact of close contact investigation could be quadrupled, and incremental cost per case prevented halved, for example from $48 262 to $22 494 in one group.

Sequential testing (QFT only in TST-positive persons) would result in savings in populations with a low prevalence of true TB infection or a high likelihood of false-positive TST due to BCG (Table 6). For example, TST screening alone of immigrants from a low-incidence country who were BCG-vaccinated

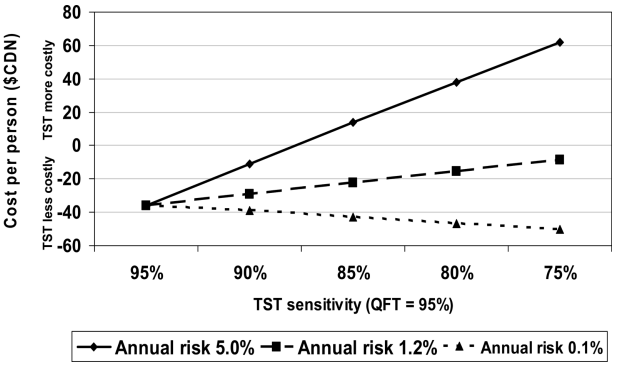

Figure 2 Total costs or savings with TST relative to QFT screening with varying TST sensitivity, and different annual risks of reactivation of disease. Straight line with diamond = annual risk 5.0%; dashed line with square = annual risk 1.2%; dotted line with triangle = annual risk 0.1%. TST = tuberculin skin test; QFT = QuantiFERON®-TB Gold.

Table 5 Effect of programme efficiency* on expected cases and costs with immigration screening or contact investigations with different strategies. For hypothetical cohorts of 1000 non-BCG-vaccinated immigrants, average age 35 years, from countries with intermediate TB incidence. (All costs in Canadian $ 2004)

	Programme performance	
	Routine (21% complete treatment)	Excellent* (78% complete treatment)
Immigrants entering Canada		
No screening		
Expected future active TB cases over 20 years	9.8	9.8
Expected total costs	$204 510	$204 510
CXR screening—future active TB cases prevented†	0.5	1.8
Costs (savings) relative to no screen‡	$15 340	$580
Incremental cost per case prevented	$30 680	$322
QFT screening—future active TB cases prevented†	1.3	4.7
Costs (savings) relative to no screen‡	$98 510	$142 360
Incremental cost per case prevented§	$75 777	$30 289
TST screening—future active TB cases prevented†	1.3	4.7
Costs (savings) relative to no screen‡	$62 740	$105 720
Incremental cost per case prevented§	$48 262	$22 494
Total costs (savings) with TST relative to QFT¶	($35 770)	($36 640)
Close contacts		
No screening		
Expected future active TB cases over 20 years	52.1	52.1
Expected total costs	$1 085 840	$1 085 840
QFT screening—future active TB cases prevented†	3.8	14
Costs (savings) relative to no screen‡	($262 200)	($290 320)
Incremental cost per case prevented§	Savings	Savings
TST screening—future active TB cases prevented†	3.8	14
Costs (savings) relative to no screen‡	($297 990)	($326 630)
Incremental cost per case prevented with TST§	Savings	Savings
Total costs (savings) with TST relative to QFT¶	($35 790)	($36 310)

* If the overall programmatic efficiency were improved so that 100% of those eligible completed screening, 100% reported for medical evaluation, 100% were prescribed, 100% accepted to begin LTBI and 78% completed LTBI therapy. Routine programme results taken from [69].
† Incident cases prevented by the screening strategy, compared to no screening programme.
‡ Numbers in parentheses ($) indicate net savings.
§ Added costs for screening per incident case prevented by screening—compared to no screening.
¶ Difference in total costs between screening strategies shown. (Costs in parentheses indicate net savings.) There is no difference in the number of cases prevented with TST or QFT strategy.
BCG = bacille Calmette-Guérin; TB = tuberculosis; CXR = chest X-ray; QFT = QuantiFERON®-TB Gold; TST = tuberculin skin test; LTBI = latent tuberculosis infection.

after infancy would cost $131 per person screened, compared to $46 using the sequential strategy. However, if the prevalence of true positive TST is higher—as in close contacts or immigrants from intermediate- or high-incidence countries—the sequential strategy would be more expensive than TST alone.

DISCUSSION

Our analysis suggests that TST or QFT screening of entering immigrants will have little impact on the subsequent incidence of TB, despite considerable costs. On the other hand, screening of contacts with either test is predicted to have much greater impact and create savings. For all cohorts considered, the impact and costs with TST or QFT screening are similar, although QFT will be less costly in populations where BCG was given after infancy.

Strengths of the analysis include the analysis of two common screening situations, in populations with three different epidemiological backgrounds and three BCG vaccination histories. The modelling approach allowed the input of published parameter estimates and considered all plausible outcomes. Estimates of the effects of BCG and non-tuberculous mycobacteria on TST specificity were based on a recent extensive literature review.[33] Estimates of QFT sensitivity for active disease and specificity were also based on all available studies.

This analysis has a number of limitations. The sensitivity, specificity and feasibility of QFT in different populations and settings are being actively investigated. Hence our parameter estimates, although based on an extensive literature review, may be considered inaccurate in the future. We therefore examined a range of values to demonstrate how changes in test characteristics, programme performance or risk of reactivation of TB can affect the cost-effectiveness of different strategies. For example, the cost-minimisation analysis demonstrated the trade-off between the specificities and costs of TST and QFT. As the sensitivity of QFT for LTBI remains uncertain, it was assumed to

Table 6 Cases prevented and costs if QFT were performed only following a positive TST result.* In hypothetical cohorts of 1000 immigrants aged 35 entering Canada from countries with different TB incidence (all costs in Canadian $ 2004)

	Screening strategy*		
BCG vaccination status (hence TST specificity)	TST alone $CDN	QFT alone $CDN	TST then QFT $CDN
Immigrants from low TB incidence country			
No BCG			
Total programme costs	30 320	64 920	27 369†
Added (or reduced) costs relative to TST alone‡	—	34 600	(2 951)
BCG in infancy			
Total programme costs	48 810	64 920	30 793
Added (or reduced) costs relative to TST alone‡	—	16 110	(18 017)
BCG when older			
Total programme costs	129 660	64 920	45 827
Added (or reduced) costs relative to TST alone‡	—	(64 740)	(83 833)
Immigrants from intermediate TB incidence country			
No BCG			
Total programme costs	267 250	303 020	283 022
Added (or reduced) costs relative to TST alone‡	—	35 770	15 772
BCG in infancy			
Total programme costs	279 390	303 020	285 281
Added (or reduced) costs relative to TST alone‡	—	23 630	5 891
BCG when older			
Total programme costs	332 520	303 020	295 164
Added (or reduced) costs relative to TST alone‡	—	(29 500)	(37 356)
Immigrants from high TB incidence country			
No BCG			
Total programme costs	423 250	459 040	450 662
Added (or reduced) costs relative to TST alone‡	—	35 790	27 412
BCG in infancy			
Total programme costs	431 060	459 040	452 115
Added (or reduced) costs relative to TST alone‡	—	27 980	21 055
BCG when older			
Total programme costs	465 260	459 040	458 475
Added (or reduced) costs relative to TST alone‡	—	(6 220)	(6 785)

* As presently recommended by the UK National Institute for Clinical Excellence (NICE).[70] Investigation and management the same if subject had positive TST only, positive QFT only or positive TST AND positive QFT. CXR screening not considered for this analysis.

† Least expensive strategy for each population group.

‡ Difference in total costs between screening strategies shown. (Costs in parentheses indicate lower costs.) There is no difference in the number of cases prevented with TST alone or QFT alone strategies. QFT following TST results in a 5% reduction in cases prevented (see text).

QFT = QuantiFERON®-TB Gold; TST = tuberculin skin test; TB = tuberculosis; BCG = bacille Calmette-Guérin; CXR = chest X-ray.

equal the TST. To date, all studies of QFT have been cross-sectional—an inherently weak design, given the lack of a gold standard for LTBI. The true sensitivity of QFT to identify persons at risk for active TB disease will be known only when large-scale longitudinal studies have been completed. This analysis also did not account for HIV infection, because there is currently insufficient published information regarding performance of QFT in HIV-infected populations.

The most striking finding in this analysis was that screening with TST or QFT was much more cost-effective in contacts than entering immigrants. This is because prevalence of active disease is much higher in contacts, and cases detected through screening are much cheaper to treat.[25] The prevalence of recent infection is also higher; as their risk is also much higher,[19,86] the potential benefit of LTBI therapy is greater as long as those screened complete LTBI therapy.

In several large-scale TB screening programmes only 21% of subjects with LTBI completed therapy because of failure to complete screening or medical evaluation for positive screening tests, plus physician and patient non-compliance with recommendations for LTBI therapy.[21,24,25,49–54] This will reduce the benefits of screening, while the costs remain the same. We found that if nearly 80% of those with LTBI completed treatment, the benefits of screening could be quadrupled and cost-effectiveness very substantially improved, for all the screening strategies and populations considered.

Our analysis also suggests that the strategy of using QFT only to test TST-positive persons should be cost-saving in populations where true infection is unlikely[14] but false-positive TSTs are common—such as in low-incidence countries where BCG vaccination was given in primary school or early adolescence.[87] However, this strategy will not be cost-saving if the prevalence of true LTBI is high. Given the sub-optimal sensitivity of TST and QFT for detection of active TB, sequential testing would also further reduce sensitivity.

In conclusion, important determinants of the relative cost-effectiveness of TST or QFT screening are risk of reactivation and differences between TST and QFT in specificity and cost. However, the selection of screening strategy is less important than programme performance. Programmes considering these new ex vivo tests for LTBI should thus first ensure that a high proportion of those with positive tests will be medically evaluated, prescribed and complete therapy.

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RÉSUMÉ

OBJECTIF : Les tests de libération d'interféron-gamma (IGRA) sont actuellement des alternatives disponibles au test cutané tuberculinique (TST) pour la détection de l'infection tuberculeuse latente (LTBI). Nous avons comparé le rapport coût-efficience du TST et de l'IGRA dans diverses populations et diverses situations cliniques tout en faisant varier un certain nombre de paramètres.

MÉTHODES : On a utilisé la modélisation de Markov pour comparer les cas de TB attendus avec les coûts au cours des 20 années faisant suite au dépistage pour TB au moyen de diverses stratégies dans des cohortes hypothétiques de sujets nés à l'étranger et immigrants au Canada ou de sujets-contact de cas TB. On a examiné le test QuantiFERON®-TB Gold (QFT), l'IGRA commercial le moins coûteux. Les données introduites dans le modèle ont été prélevées dans la littérature publiée.

RÉSULTATS : Pour les immigrants entrant au Canada, le dépistage par le cliché thoracique (CXR) aurait le rapport coût-efficience le plus élevé et le QFT le rapport le plus bas. Le dépistage séquentiel par le TST suivi du QFT a eu un rapport coût-efficience meilleur que le seul QFT dans tous les scénarios et s'est avéré avoir un rapport coût-efficience meilleur que le seul TST dans des sous-groupes sélectionnés. Pour les contacts étroits et occasionnels, le dépistage par TST ou QFT pourrait être le moins coûteux ; les sommes épargnées par le TST seraient plus élevées que par le QFT, sauf chez les contacts qui auraient été vaccinés par le BCG après la prime enfance.

CONCLUSIONS : Le dépistage pour la LTBI, que ce soit par TST ou QFT, n'a un rapport coût-efficience satisfaisant que si le risque de maladie est élevé. L'utilisation du QFT dont le rapport coût-efficience est le meilleur est le test des sujets positifs pour le TST.

RESUMEN

OBJETIVO : Actualmente, los ensayos de liberación de interferón-gama (IGRA) constituyen opciones a la prueba cutánea de la tuberculina (TST) en la detección de la infección tuberculosa latente (LTBI). Se comparó el rendimiento diagnóstico de ambas pruebas en poblaciones y situaciones clínicas diferentes, modificando una serie de variables.

MÉTODOS : Se utilizó el modelo de Markov con el fin de comparar los casos previstos de TB y el costo del tratamiento en un período de 20 años, siguiendo diferentes estrategias de detección de la TB en cohortes hipotéticas de inmigrantes al Canadá o de contactos de casos de TB. Se analizó el estuche comercial de menor costo de IGRA, el QuantiFERON-TB Gold® (QFT). Los datos introducidos al modelo se tomaron de la literatura científica publicada.

RESULTADOS : En los inmigrantes que llegan al Canadá, el método más rentable de detección sistemática sería la radiografía de tórax y el menos rentable la QFT. La detección secuencial con la TST y la QFT fue más rentable que la detección exclusiva con la QFT en todas las hipótesis consideradas y más rentable que la TST aislada en determinados subgrupos. La detección sistemática en los contactos cercanos o casuales con la TST o con la QFT ahorraría costos, comparada con la ausencia de detección ; este ahorro sería mayor con la TST que con la QFT, con la excepción de los contactos con antecedente de vacuna BCG después de 1 año de edad.

CONCLUSIÓN : La detección de la LTBI con la TST o la QFT es rentable únicamente cuando el riesgo de enfermedad es alto. La utilización más rentable de la QFT es su aplicación en personas con reacción positiva a la TST.