

Cost-effectiveness of interferon-gamma release assays for tuberculosis screening in nursing homes

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SUMMARY

Tuberculosis (TB) in older people is a significant public health problem in low TB-incidence countries. Older persons have increased TB incidence, higher reactivation and mortality. A delay in diagnosis and initiation of TB treatment in patients with atypical clinical and radiological features is a significant factor of widespread transmission. This study aimed to evaluate the cost-effectiveness of interferon-gamma release assays [IGRAs; QuantiFERON[®]-TB Gold In-Tube (QFT) and T-SPOT[®].TB (T-SPOT)] compared to the tuberculin skin test (TST) and chest X-ray (CXR) examination for TB screening for nursing homes. Decision trees and Markov models were constructed using a societal perspective on a lifetime horizon. Seven strategies: no screening, TST, QFT, T-SPOT, TST followed by QFT, TST followed by T-SPOT, and CXR were considered. QFT [US\$ 401·9, 4·36 707 QALY (year 2014 values)] was the most cost-effective at the willingness-to-pay level of US\$ 50 000/QALY gained. TST followed by QFT was the most cost-effective in residents with comorbidities. CXR was less cost-effective. Cost-effectiveness was sensitive to latent TB infection (LTBI) rate and bacillus Calmette-Guérin vaccination rate. Effective LTBI screening using IGRA is recommended to prevent TB transmission not only in nursing homes but also in local communities in low-incidence countries.

Key words: Cost-effectiveness study, public health, screening programme, transmission, tuberculosis (TB).

INTRODUCTION

Tuberculosis (TB) in older people (aged ≥ 65 years) is a significant public health problem in low TB-incidence countries, especially in nursing homes and long-term care facilities [1–6]. Ageing is accompanied with TB risk factors; malnutrition, sarcopenia, progressive reduction in cell-mediated immune function and co-existing illnesses such as diabetes mellitus, chronic renal failure, malignancy and antineoplastic chemotherapy [1–4].

Elderly persons have increased incidence of TB, higher TB reactivation and higher TB mortality. Active TB at the time of arrival at the nursing home, reactivation of latent tuberculosis infection (LTBI) and transmission within the nursing home are causes of TB in the elderly. The low treatment completion proportion and high risk of adverse reaction due to LTBI treatment are also seen in the elderly population [3, 4]. A delay in diagnosis and initiation of TB treatment with atypical clinical and radiological features is a significant factor for widespread transmission in nursing homes and long-term care facilities [5]. A TB outbreak needs large-scale contact screening to detect LTBI and to control TB in nursing-home residents, healthcare workers, their staff

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and persons in the local community after prolonged TB exposure [1, 2, 6].

Two *Mycobacterium tuberculosis*-specific interferon-gamma release assays (IGRAs), QuantiFERON[®]-TB Gold In-Tube (QFT; Qiagen, Germany) and T-SPOT[®].TB (T-SPOT; Oxford Immunotec, UK), are available instead of the tuberculin skin test (TST) as new methods for diagnosing LTBI. IGRAs neither influence by bacillus Calmette-Guérin (BCG) vaccination nor have booster phenomenon, unlike TST. They have excellent accuracy with higher sensitivities and specificities than those of TST, especially in BCG-vaccinated individuals [7–9]. However, the purchase cost of IGRAs are higher than those of TST and chest X-ray (CXR) examination.

The global proportion of older people increased from 9.2% in 1990 to 11.7% in 2013 and will continue to grow as a proportion of the world's population, reaching 21.1% by 2050 [10]. Cost-effectiveness regarding the use of IGRAs for TB screening for nursing homes warrants evaluation as a TB policy control measure.

In this study, cost-effectiveness of TB screening using IGRA (QFT or T-SPOT), compared to TST, TST followed by QFT or T-SPOT, CXR for active TB screening, and no screening was assessed to evaluate the optimal entry method for older persons to nursing homes.

METHODS

Target population

The target population was a hypothetical cohort of 84-year-old residents and those with comorbidities such as HIV infection, diabetes mellitus and chronic kidney disease in nursing homes using a societal perspective on a lifetime horizon. Nursing homes are defined as institutions that provide healthcare to people who are unable to manage independently in the community. The average age at nursing-home entry is 84 years and the average time spent living there is 4 years [11]. In Japan almost all the elderly have received BCG vaccination.

As this was a modelling study with all inputs and parameters derived from published literature, ethical approval was not required.

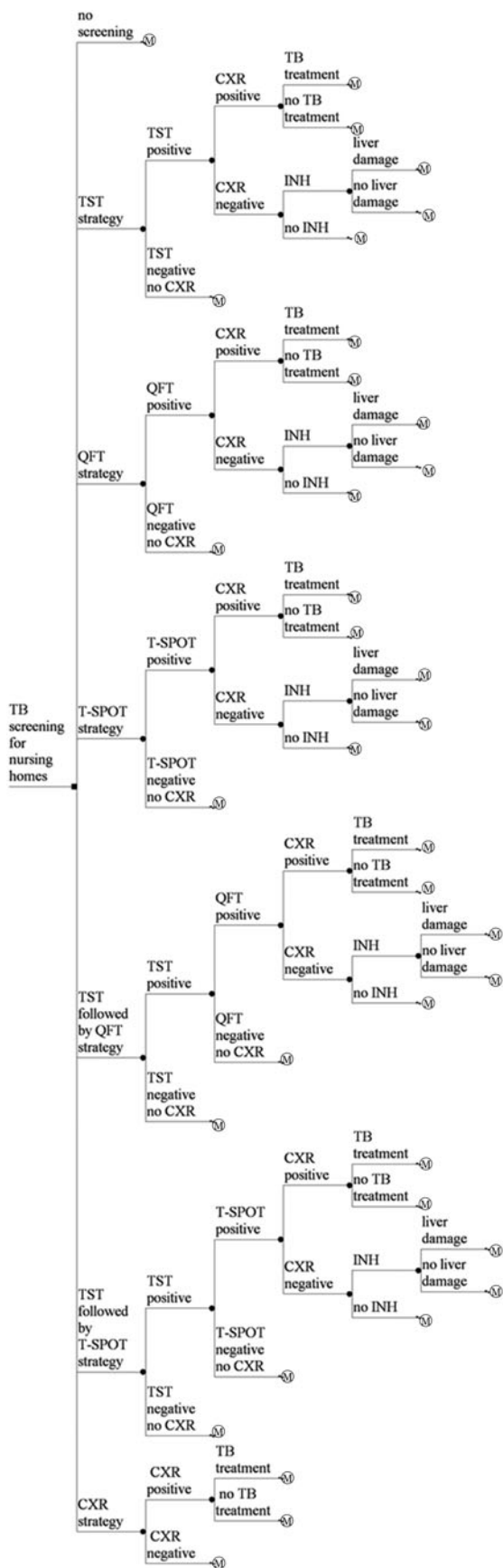
Decision trees and Markov models

The following seven clinical states were included in this model to represent the possible clinical states in

the target populations: (i) well (no LTBI, no TB); (ii) LTBI; (iii) LTBI, taking LTBI treatment without complication; (iv) LTBI, taking LTBI treatment with liver dysfunction; (v) drug-sensitive TB (DS-TB) during TB treatment and before; (vi) multidrug resistant tuberculosis (MDR-TB) during MDR-TB treatment and before; (vii) dead. Decision-analytical calculations were performed using TreeAge Pro Healthcare Module 2012 (TreeAge Software Inc., USA). Each cycle length was 1 year.

Decision trees and Markov models were developed for seven strategies; no screening, TST, QFT, T-SPOT, TST followed by QFT, TST followed by T-SPOT, and CXR (Fig. 1). Per-person cost and effectiveness were calculated. The incremental cost effectiveness ratio (ICER) of each screening arm was applied and compared. The rates of adherence of chemoprophylaxis, liver dysfunction induced by chemoprophylaxis, and completion of DS-TB and MDR-TB treatments were considered. Markov models that took into account comorbidities such as HIV infection, diabetes mellitus and chronic kidney disease were also constructed with the lower test sensitivities and their relative risks of reactivation rates.

- (1) No screening
- (2) *TST strategy*. A nursing-home resident undergoes TST testing. If TST induration diameter is ≥ 5 mm in those without BCG vaccination and ≥ 10 mm in those with BCG vaccination, the resident undergoes CXR. If active TB is suspected based on CXR, and subsequent smears, cultures and drug sensitivity test of sputum examination are performed, the resident is treated with the standard 6-month protocol for DS-TB or the protocol for MDR-TB. If active TB is not detected by CXR, the resident receives 9-month isoniazid (INH) chemoprophylaxis. If TST induration diameter is < 5 mm in those without BCG vaccination and < 10 mm in those with BCG vaccination, the resident does not require follow-up. The proportion of residents for whom the TST was performed and read was 1.0.
- (3) *IGRA (QFT or T-SPOT) strategy*. A nursing-home resident undergoes IGRA testing. If the IGRA is positive, active TB is suspected based on CXR and subsequent smears, and cultures and drug sensitivity test of sputum examination are performed, the resident is treated with the standard 6-month protocol for DS-TB or the protocol for MDR-TB. If the IGRA is positive and active TB is not



detected by CXR, the resident receives 9-month INH chemoprophylaxis. If the IGRA is negative, the resident does not require follow-up.

- (4) *TST followed by IGRA (QFT or T-SPOT) strategy.* A nursing-home resident undergoes TST testing. If TST induration diameter is ≥ 5 mm in those without BCG vaccination and ≥ 10 mm in those with BCG vaccination, the resident undergoes IGRA testing. If the IGRA is positive, active TB is suspected based on CXR and subsequent smears, and cultures and drug sensitivity test of sputum examination are performed, the resident is treated with the standard 6-month protocol for DS-TB or the protocol for MDR-TB. If the IGRA is positive and active TB is not detected by CXR, the resident receives 9-month INH chemoprophylaxis. If the IGRA is negative, the resident does not require follow-up. If TST induration diameter is < 5 mm in those without BCG vaccination and < 10 mm in those with BCG vaccination, the resident does not require follow-up.

- (5) *CXR strategy.* A nursing-home resident undergoes a CXR test. If CXR is positive, active TB is suspected based on CXR and subsequent smears, cultures and drug sensitivity test of sputum examination are performed, the resident is treated with the standard 6-month protocol for DS-TB or the protocol for MDR-TB. If CXR is negative, the resident does not require follow-up.

Probabilities, costs, effectiveness, utilities and other assumptions

All data were collected using Medline. A search of the literature published from 1980 to 2 April 2016 was undertaken to use incremental cost-effectiveness analysis.

Prevalence of LTBI and TB, probability of TB patients having MDR-TB, relative risk of TB in the

Fig. 1. Simplified illustration of the decision trees. A square node represents the decision node. A circular node represents a chance node. Branches from a chance node represent possible outcomes. An \textcircled{M} node represents a Markov node. QFT, QuantiFERON[®]-TB Gold In-Tube; TB, tuberculosis; T-SPOT, T-SPOT[®].TB; TST, tuberculin skin test; CXR, chest X-ray examination; INH, 9-month INH chemoprophylaxis protocol for latent tuberculosis infection.

elderly, adherence rate of chemoprophylaxis, probability of hepatotoxicity induced by chemoprophylaxis, efficacy of chemoprophylaxis protocol, the completion rates of DS-TB and MDR-TB treatments, recurrence rates of DS-TB and MDR-TB after treatment and mortality rates of DS-TB and MDR-TB were derived from the published literature [2, 12–23]. The BCG vaccination rate was 0.93 in Japan in 2012 [24]. Age-specific all-cause mortality rates were obtained from Japanese life tables. Data from the meta-analyses, which included studies from numerous low-incidence countries, were used to determine the sensitivities and specificities of TST, QFT and T-SPOT [7–9, 26–29]. The sensitivity and specificity of CXRs were obtained from the published literature [30]. The lower test sensitivities and the relative risks of reactivation rates in the elderly with comorbidities such as HIV infection, diabetes mellitus and chronic kidney disease were also obtained from the published literature [23, 26–29].

Cost data were collected using a societal perspective. All costs were adjusted to 2014 Japanese yen, using the medical care component of the Japanese consumer price index and were converted to US dollars (US\$), using the Organisation for Economic Cooperation and Development (OECD) purchasing power parity rate in 2014 (1 US\$ = ¥105.8) [31, 32]. The cost of TST screening included labour costs for two physician visits and the TST reagents. The costs of QFT and T-SPOT screening included the screening kits, one physician visit, and the labour costs for laboratory technicians [31, 33]. The cost of CXR screening included the material cost of CXR, one physician visit, and the labour costs for radiology technicians [31, 33]. The costs of TB treatment, 9-month INH chemoprophylaxis and treatment of liver dysfunction caused by chemoprophylaxis were determined from the national fee schedule in Japan [31] (Table 1). The costs of smears, cultures and drug sensitivity testing of sputum examinations were also considered [31]. All costs were discounted at a fixed annual rate of 3%. Per-person costs were calculated for each strategy.

The main outcome measure of effectiveness was quality-adjusted life-years (QALYs). Health state utilities were calculated by using a utility weight of 0.58 for MDR-TB, 0.80 for DS-TB, 0.85 for LTBI (taking chemoprophylaxis with complication), 0.95 for LTBI (taking chemoprophylaxis without complication) and 1 each for LTBI and well (Table 1) [34, 35]. All clinical benefits were discounted at a fixed annual rate

of 3%. Per-person QALYs were calculated for each strategy.

One-way sensitivity analyses and probability sensitivity analyses

One-way sensitivity analyses and probability sensitivity analyses were performed to determine which strategy yielded the greatest benefits and costs, using the ranges of probabilities, costs, relative risks and utilities. Each model variable was assigned a distribution based on the values in the literature and assumptions (Table 1). By Monte Carlo simulation distributions, the selected probabilities are in β distributions and the selected relative risks are in lognormal probabilities.

RESULTS

In the base-case analysis, QFT strategy was the most cost-effective at the willingness-to-pay level of US\$ 50 000/QALY gained (US\$ 401.9, 4.36 707 QALY; ICER 91.3 US\$/QALY, year 2014 values). TST followed by QFT strategy (US\$ 516.3, 4.36 900 QALY; ICER 59 129.9 US\$/QALY) was less cost-effective than QFT strategy. CXR strategy (US\$ 6683.3, 4.37 579 QALY; ICER 908 961.6 US\$/QALY) was less cost-effective (Table 2). In analyses considered with higher risk of TB reactivation due to comorbidities such as HIV infection, diabetes mellitus and chronic kidney disease, TST followed by QFT strategy was more cost-effective than QFT strategy. CXR strategy was also less cost-effective (Table 2).

One-way sensitivity analyses

In the base-case analysis, cost-effectiveness was sensitive to LTBI rate and BCG vaccination rate. TST followed by QFT strategy was more cost-effective than QFT strategy when the LTBI rate was >0.35 and when the BCG vaccination rate was <0.57 at the willingness-to-pay level of US\$ 50 000/QALY gained (Tables 3, 4). In the analyses considered with the risk of TB reactivation due to comorbidities such as HIV infection, diabetes mellitus and chronic kidney disease, QFT strategy was more cost-effective than TST followed by QFT strategy when the LTBI rate was <0.18 in HIV-infected residents, 0.30 in diabetes mellitus residents, 0.26 in chronic kidney disease residents, and when the BCG vaccination rate was >0.95 in diabetes mellitus residents at the willingness-to-pay level of US\$ 50 000/QALY gained.

Table 1. *Baseline estimates for selected variables*

	Baseline value	One-way sensitivity analysis range	Distribution in probability sensitivity analysis	References
Prevalence of LTBI in nursing-home residents	0.30	0.13–0.61	Beta	[17, 18, 32]
Prevalence of active TB in nursing-home residents	0.00 114	0.001–0.003	Beta	[1, 17]
Probability of having MDR-TB in TB patients	0.006	0–0.01	Beta	[14]
Relative risk of TB in the elderly	2.25	2.20–2.31*	Lognormal	[1]
Probability of recurrence of DS-TB after TB treatment	0.0684	0.0182–0.1785*	Beta	[14, 15]
Probability of recurrence of MDR-TB after TB treatment	0.0836	0.0273–0.204*	Beta	[21]
Relative risk of reactivation rate with HIV infection	9.9	8.7–11.3	Lognormal	[23]
Relative risk of reactivation rate with poorly controlled diabetes mellitus	1.7	1.5–2.2*	Lognormal	[23]
Relative risk of reactivation rate with chronic kidney disease	2.4	2.1–2.8*	Lognormal	[23]
Prevalence of active TB with HIV infection	0.0113	0.0099–0.0129	Beta	[1, 17, 23]
Prevalence of active TB with poorly controlled diabetes mellitus	0.0019	0.0017–0.0025	Beta	[1, 17, 23]
Prevalence of active TB with chronic kidney disease	0.0027	0.0024–0.0032	Beta	[1, 17, 23]
Proportion of patients had the TST performed and read	1	–	–	Assumption
Efficacy of 9H chemoprophylaxis protocol	0.8	0.6–0.9	Beta	[13, 22]
Adherence rate of 9H chemoprophylaxis protocol	0.365	0–1	Beta	[16]
Completion rate of DS-TB treatment	0.5	0.3–0.7	Beta	Assumption
Completion rate of MDR-TB treatment	0.5	0.3–0.7	Beta	[21]
Probability of developing active TB from LTBI	0.0015	0.0004–0.0039	Beta	[23]
Probability of drug-related hepatotoxicity by 9H chemoprophylaxis	0.021	0.01–0.04	Beta	[12]
TB mortality	0.366	0.2–0.5	Beta	[19]
Sensitivity of TST for LTBI	0.77	0.71–0.82*	Beta	
Sensitivity of TST for LTBI with HIV infection	0.43	0.37–0.5	Beta	
Sensitivity of TST for LTBI with diabetes mellitus	0.73	0.64–0.78	Beta	
Sensitivity of TST for LTBI with chronic kidney disease	0.68	0.58–0.78	Beta	[7, 26–29]
Specificity of TST for LTBI (BCG-vaccinated)	0.59	0.46–0.73*	Beta	
Specificity of TST for LTBI (non-BCG-vaccinated)	0.97	0.95–0.99*	Beta	
Sensitivity of QFT for LTBI	0.84	0.81–0.87*	Beta	
Sensitivity of QFT for LTBI with HIV infection	0.61	0.54–0.67*	Beta	
Sensitivity of QFT for LTBI with diabetes mellitus	0.80	0.71–0.83	Beta	
Sensitivity of QFT for LTBI with chronic kidney disease	0.75	0.65–0.85	Beta	
Specificity of QFT for LTBI	0.99	0.98–1.00*	Beta	
Sensitivity of T-SPOT for LTBI	0.89	0.86–0.91*	Beta	[8, 9, 26–29]
Sensitivity of T-SPOT for LTBI with HIV infection	0.65	0.56–0.74*	Beta	
Sensitivity of T-SPOT for LTBI with diabetes mellitus	0.84	0.71–0.87	Beta	
Sensitivity of T-SPOT for LTBI with chronic kidney disease	0.79	0.69–0.89	Beta	
Specificity of T-SPOT for LTBI	0.98	0.94–0.99*	Beta	
Sensitivity of QFT for active TB	0.80	0.75–0.84*	Beta	
Specificity of QFT for active TB	0.79	0.75–0.82*	Beta	[25]
Sensitivity of T-SPOT for active TB	0.81	0.78–0.84*	Beta	
Specificity of T-SPOT for active TB	0.59	0.56–0.62*	Beta	
Sensitivity of CXR for active TB	0.70	0.59–0.82	Beta	
Specificity of CXR for active TB	0.60	0.52–0.63	Beta	[30]

Table 1 (cont.)

	Baseline value	One-way sensitivity analysis range	Distribution in probability sensitivity analysis	References
Cost (\$US 2014, 1 \$US = ¥105·8)				
QFT	59·5	22·5–97·1		[31–33]
T-SPOT	59·5	22·5–97·1		
TST	15·1	10·9–31·5		
CXR	35·6	17·8–71·2		
Smears, cultures and drug sensitivity test of sputum examination	156·8	78·4–313·6	n.a.	
9H chemoprophylaxis	1219·3	390·2–1817·2		
Treatment of drug-induced hepatitis by chemoprophylaxis	11 689	5845–23 378		
Treatment of DS-TB for 6 months	14 612	7306–29 224		
Treatment of MDR-TB	1 89 457	94 729–378 914		
Average physician income per hour	49·4	24·7–98·8		
Average nurse income per hour	14·1	7·1–28·2	n.a.	
Average income per hour for radiology technician	23·8	11·9–47·6		
Average income per hour for laboratory technician	21·3	10·7–42·6		
Utility				
Well	1			
LTBI	1			
LTBI taking LTBI treatment without complication	0·95			
LTBI taking LTBI treatment with liver dysfunction	0·85		n.a.	[34, 35]
DS-TB during treatment and before	0·80			
MDR-TB during treatment and before	0·58			
Dead	0			

* 95% confidence interval.

BCG, Bacillus Calmette-Guérin; CXR, chest X-ray examination; DS-TB, drug-sensitive tuberculosis; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; MDR-TB, multidrug-resistant tuberculosis; QFT, QuantiFERON[®]-TB Gold In-Tube; TB, tuberculosis; T-SPOT, T-SPOT[®].TB; TST, tuberculin skin test; 9H, 9-month isoniazid.

Hepatotoxicity by 9-month INH chemoprophylaxis had little impact on cost-effectiveness.

Probabilistic sensitivity analyses

According to the Monte Carlo simulations for 10 000 trials, the cost-effectiveness acceptability curve in 84-year-old nursing-home residents demonstrated that the QFT strategy had more chance of being cost-effective than TST followed by QFT with 65% probability at the US\$ 50 000 willingness-to-pay level (Fig. 2).

DISCUSSION

This study demonstrated that using IGRA was more cost-effective for LTBI screening for nursing homes at the willingness-to-pay level of US\$ 50 000/QALY gained. Highest specificity of QFT, and cost savings

due to effective chemoprophylaxis by preventing TB reactivation in the elderly are the main reasons for the higher cost-effectiveness result of the QFT strategy. Cost-effectiveness was sensitive to LTBI rate and BCG vaccination rate. Hepatotoxicity by 9-month INH chemoprophylaxis had little impact on cost-effectiveness.

In this study, the main outcome measure of effectiveness was QALYs gained. The use of QALYs can combine the effects of quantity of life with quality of life in a single measure. ICER, which is calculated by using incremental costs and incremental QALYs gained can be compared to the willingness-to-pay level. Willingness to pay provides a measure of the societal value attached to a given health benefit when the values from a population are aggregated. Even if the differences in effectiveness between IGRA and TST on LTBI screening are very small, as in this case,

Table 2. Results of seven strategies for TB screening of elderly nursing-home residents

Strategy	Cost (\$US 2014)	Incremental Cost (\$US)	Effectiveness (QALY)	Incremental effectiveness (QALY)	ICER (US\$/QALY)
Base case					
No screening	123.5	0	1.31 737	0	0
QFT	401.9	278.5	4.36 707	3.04 970	91.3
T-SPOT	419.3	17.3	4.36 646	-0.00 061	Dominated
TST/QFT	516.3	114.4	4.36 900	0.00 193	59 129.9
TST/T-SPOT	527.6	11.3	4.36 857	-0.00 043	Dominated
TST	666.2	149.9	4.36 418	-0.00 482	Dominated
CXR	6683.3	6167.0	4.37 579	0.00 678	908 961.6
HIV infection					
TST/QFT	491.7	0	4.34 437	0	0
TST/T-SPOT	499.0	7.3	4.34 419	-0.00 019	Dominated
QFT	559.8	68.1	4.34 376	-0.00 062	Dominated
T-SPOT	577.4	85.7	4.34 331	-0.00 106	Dominated
TST	687.7	196.1	4.33 961	-0.00 476	Dominated
No screening	761.7	270.0	1.34 383	-3.00 054	Dominated
CXR	6801.0	6309.3	4.34 950	0.00 512	1 231 827.4
Diabetes mellitus					
No screening	171.2	0	1.31 935	0	0
QFT	408.4	237.2	4.36 556	3.04 621	77.9
T-SPOT	423.6	15.2	4.36 506	-0.00 050	Dominated
TST/QFT	510.2	101.8	4.36 761	0.00 205	49 599.9
TST/T-SPOT	519.4	9.2	4.36 728	-0.00 033	Dominated
TST	669.9	159.7	4.36 262	-0.00 499	Dominated
CXR	6692.1	6181.9	4.37 382	0.00 621	995 725.1
Chronic kidney disease					
No screening	221.4	0	1.32 143	0	0
QFT	413.5	192.0	4.36 405	3.04 263	63.1
T-SPOT	428.9	15.4	4.36 356	-0.00 049	Dominated
TST/QFT	499.7	86.3	4.36 619	0.00 213	40 410.5
TST/T-SPOT	508.6	8.9	4.36 588	-0.00 031	Dominated
TST	669.7	170.0	4.36 100	-0.00 519	Dominated
CXR	6701.4	6201.7	4.37 175	0.00 556	1 115 156.1

CXR, Chest X-ray examination; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; QFT, QuantiFERON®-TB Gold In-Tube; T-SPOT, T-SPOT®.TB; TST, tuberculin skin test.

the willingness-to-pay method using QALYs gained is very useful to evaluate cost-effectiveness.

Current entry TB screening is conducted by CXR as active TB screening in Japan. There is no data regarding the prevalence of hepatotoxicity by 9-month INH chemoprophylaxis in nursing-home residents in Japan. We derived the prevalence of hepatotoxicity and efficacy of the chemoprophylaxis protocol from the published literature. CXR examination only can detect active TB. When TB is detected by CXR screening for symptoms of TB in nursing-home residents, TB infection spreads in nursing residents and healthcare staff [36, 37]. Large-scale contact screening in nursing homes is needed [36, 37]. Some residents may die due to transmission of

TB in nursing homes [5, 6, 36, 37]. This study demonstrates that active case-finding was not cost-effective and that preventive strategy with the diagnosis and treatment of LTBI was the most efficient strategy to control TB in nursing homes despite its hepatotoxicity in low TB-incidence countries.

A previous study reported the cost-effectiveness of QFT compared to CXR, and no screening compared to TB screening of the BCG-vaccinated elderly general population and demonstrated that the no-screening strategy offered the greatest cost saving for elderly populations in Japan [38]. In that study for the elderly general population, the results also demonstrated that the QFT strategy was more cost-effective than no

Table 3. Sensitivity analysis of LTBI rate

LTBI rate	Strategy	Cost (US\$ 2014)	Effectiveness (QALY)	Incremental cost (US\$)	Incremental effectiveness (QALY)	ICER (US\$/QALY)
0.13	No screening	106.9	0.86 278	0.0	0.00 000	0.0
0.13	QFT	292.6	4.37 178	185.7	3.50 900	52.9
0.13	T-SPOT	304.7	4.37 144	12.1	-0.00 034	Dominated
0.13	TST/QFT	420.0	4.37 260	127.3	0.00 082	156 009.1
0.13	TST/T-SPOT	426.7	4.37 238	6.7	-0.00 021	Dominated
0.13	TST	615.3	4.36 761	195.3	-0.00 499	Dominated
0.13	CXR	6683.3	4.37 560	6263.3	0.00 300	2 086 461.0
0.226	No screening	110.7	0.99 315	0.0	0.00 000	0.0
0.226	QFT	354.4	4.36 912	243.7	3.37 597	72.2
0.226	T-SPOT	369.4	4.36 863	15.0	-0.00 049	Dominated
0.226	TST/QFT	474.4	4.37 057	120.0	0.00 145	82 906.6
0.226	TST/T-SPOT	483.6	4.37 023	9.3	-0.00 034	Dominated
0.226	TST	644.0	4.36 567	169.7	-0.00 490	Dominated
0.226	CXR	6683.3	4.37 571	6208.9	0.00 514	1 208 423.0
0.322	No screening	127.3	1.41 375	0.0	0.00 000	0.0
0.322	QFT	416.1	4.36 646	288.8	2.95 270	97.8
0.322	T-SPOT	434.1	4.36 582	18.0	-0.00 064	Dominated
0.322	TST/QFT	528.8	4.36 854	112.7	0.00 208	54 208.0
0.322	TST/T-SPOT	540.6	4.36 808	11.9	-0.00 046	Dominated
0.322	TST	672.8	4.36 374	144.0	-0.00 480	Dominated
0.322	CXR	6683.3	4.37 581	6154.5	0.00 727	846 076.9
0.418	No screening	143.8	1.83 436	0.0	0.00 000	0.0
0.418	QFT	477.8	4.36 380	333.9	2.52 944	132.0
0.418	T-SPOT	498.8	4.36 300	21.0	-0.00 079	Dominated
0.418	TST/QFT	583.2	4.36 651	105.4	0.00 271	38 880.5
0.418	TST/T-SPOT	597.6	4.36 593	14.4	-0.00 058	Dominated
0.418	TST	701.5	4.36 180	118.4	-0.00 471	Dominated
0.418	CXR	6683.3	4.37 592	6100.1	0.00 941	648 236.1
0.514	No screening	160.4	2.25 497	0.0	0.00 000	0.0
0.514	QFT	539.5	4.36 114	379.1	2.10 617	180.0
0.514	T-SPOT	563.5	4.36 019	24.0	-0.00 095	Dominated
0.514	TST/QFT	637.6	4.36 448	98.1	0.00 334	29 345.1
0.514	TST/T-SPOT	654.6	4.36 377	17.0	-0.00 070	Dominated
0.514	TST	730.3	4.35 986	92.7	-0.00 461	Dominated
0.514	CXR	6683.3	4.37 602	6045.7	0.01 155	523 598.1
0.61	No screening	177.0	2.67 558	0.0	0.00 000	0.0
0.61	QFT	601.2	4.35 847	424.2	1.68 290	252.1
0.61	T-SPOT	628.2	4.35 738	26.9	-0.00 110	Dominated
0.61	TST/QFT	692.0	4.36 245	90.8	0.00 397	22 840.3
0.61	TST/T-SPOT	711.6	4.36 162	19.6	-0.00 083	Dominated
0.61	TST	759.0	4.35 793	67.1	-0.00 452	Dominated
0.61	CXR	6683.3	4.37 613	5991.3	0.01 368	437 877.4

CXR, Chest X-ray examination; ICER, incremental cost-effectiveness ratio; LTBI, latent tuberculosis infection; QALY, quality-adjusted life-year; QFT, QuantiFERON[®]-TB Gold In-Tube; T-SPOT, T-SPOT[®].TB; TST, tuberculin skin test.

screening when TB prevalence was >0.00 047 on the sensitivity analysis. The superiority of the QFT strategy in the present study is consistent with those results.

To the best of our knowledge, this study is the first cost-effectiveness analysis of IGRAs for TB screening of elderly nursing-home residents, compared to TST,

TST followed by IGRAs, CXR and no screening using a Markov model.

Katsenos *et al.* showed that QFT had a significant additive value to single TST for detecting LTBI in institutionalized older adults [20]. Verma *et al.* demonstrated that LTBI screening with TST for the

Table 4. Sensitivity analysis of BCG vaccination rate

BCG vaccination rate	Strategy	Cost (US\$ 2014)	Effectiveness (QALY)	Incremental cost (US\$)	Incremental effectiveness (QALY)	ICER (US\$/QALY)
0	No screening	123.5	1.31 737	0.0	0.00 000	0.0
0	QFT	401.9	4.36 707	278.5	3.04 970	91.3
0	T-SPOT	419.3	4.36 646	17.3	-0.00 061	Dominated
0	TST/QFT	470.5	4.36 904	68.6	0.00 197	34 853.5
0	TST	474.9	4.36 758	4.4	-0.00 146	Dominated
0	TST/T-SPOT	480.1	4.36 864	9.5	-0.00 040	Dominated
0	CXR	6683.3	4.37 579	6212.8	0.00 675	920 317.9
0.2	No screening	123.5	1.31 737	0.0	0.00 000	0.0
0.2	QFT	401.9	4.36 707	278.5	3.04 970	91.3
0.2	T-SPOT	419.3	4.36 646	17.3	-0.00 061	Dominated
0.2	TST/QFT	480.4	4.36 903	78.4	0.00 196	40 003.2
0.2	TST/T-SPOT	490.3	4.36 863	9.9	-0.00 040	Dominated
0.2	TST	516.0	4.36 685	35.7	-0.00 218	Dominated
0.2	CXR	6683.3	4.37 579	6202.9	0.00 676	917 866.1
0.4	No screening	123.5	1.31 737	0.0	0.00 000	0.0
0.4	QFT	401.9	4.36 707	278.5	3.04 970	91.3
0.4	T-SPOT	419.3	4.36 646	17.3	-0.00 061	Dominated
0.4	TST/QFT	490.2	4.36 902	88.3	0.00 195	45 191.5
0.4	TST/T-SPOT	500.5	4.36 861	10.3	-0.00 041	Dominated
0.4	TST	557.2	4.36 612	67.0	-0.00 290	Dominated
0.4	CXR	6683.3	4.37 579	6193.1	0.00 677	915 419.5
0.6	No screening	123.5	1.31 737	0.0	0.00 000	0.0
0.6	QFT	401.9	4.36 707	278.5	3.04 970	91.3
0.6	T-SPOT	419.3	4.36 646	17.3	-0.00 061	Dominated
0.6	TST/QFT	500.1	4.36 901	98.1	0.00 195	50 418.7
0.6	TST/T-SPOT	510.7	4.36 860	10.6	-0.00 042	Dominated
0.6	TST	598.3	4.36 539	98.3	-0.00 363	Dominated
0.6	CXR	6683.3	4.37 579	6183.2	0.00 677	912 978.2
0.8	No screening	123.5	1.31 737	0.0	0.00 000	0.0
0.8	QFT	401.9	4.36 707	278.5	3.04 970	91.3
0.8	T-SPOT	419.3	4.36 646	17.3	-0.00 061	Dominated
0.8	TST/QFT	509.9	4.36 901	108.0	0.00 194	55 685.3
0.8	TST/T-SPOT	520.9	4.36 858	11.0	-0.00 043	Dominated
0.8	TST	639.5	4.36 465	129.6	-0.00 435	Dominated
0.8	CXR	6683.3	4.37 579	6173.4	0.00 678	910 542.2
1	No screening	123.5	1.31 737	0.0	0.00 000	0.0
1	QFT	401.9	4.36 707	278.5	3.04 970	91.3
1	T-SPOT	419.3	4.36 646	17.3	-0.00 061	Dominated
1	TST/QFT	519.8	4.36 900	117.8	0.00 193	60 991.7
1	TST/T-SPOT	531.1	4.36 857	11.4	-0.00 043	Dominated
1	TST	680.6	4.36 392	160.8	-0.00 508	Dominated
1	CXR	6683.3	4.37 579	6163.6	0.00 679	908 111.4

BCG, Bacillus Calmette-Guérin; CXR, chest X-ray examination; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; QFT, QuantiFERON®-TB Gold In-Tube; T-SPOT, T-SPOT®.TB; TST, tuberculin skin test.

elderly was more cost-effective than CXR screening in long-term care facilities in Canada and concluded that TB screening strategies on entry to long-term care are costly [18]. We first demonstrated that using IGRA was more cost-effective than TST and CXR for entry TB screening to a nursing home.

There are several limitations to this study. First, sensitivities and specificities of TB screening kits (IGRA and TST), were obtained from meta-analyses of immunocompetent individuals, but not for older people with waning immunity. Further study of test sensitivities with waning immunity of the elderly is needed. Second,

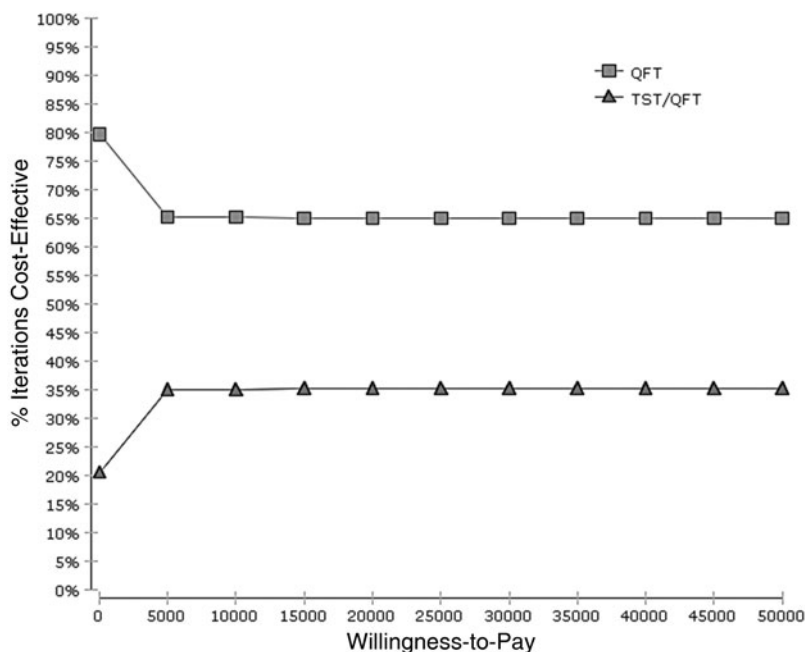


Fig. 2. Cost-effectiveness acceptability curve. QFT, QuantiFERON[®]-TB Gold In-Tube strategy; TST/QFT, tuberculin skin test followed by QuantiFERON[®]-TB Gold In-Tube strategy.

there is little data on LTBI rates using IGRAs in nursing-home residents. Further studies of the elderly based on IGRA testing are needed. Third, the harm from radiation exposure by repeating CXR was not considered in this model. Fourth, the use of rifapentine plus isoniazid for 3 months, which had a higher treatment completion rate, was not considered for chemoprophylaxis regimen of nursing-home residents in this model. Further, long-term safety monitoring research and a cost-effectiveness study using rifapentine plus isoniazid for 3 months is required. Fifth, the epidemiology of TB in the elderly needs to be dealt with in much more detail in order to make a more convincing case for TB policy change. Sixth, there is no method for diagnosing whether LTBI differentiates first infection with TB from reinfection. Seventh, there are little epidemiological studies of TB outbreaks in nursing homes. Finally, there are different costs and medical systems in each country. Further cost-effectiveness studies will be needed for each country using each cost.

CONCLUSIONS

QFT [US\$ 401·9, 4·36 707 QALY (year 2014 values)] was the most cost-effective at the willingness-to-pay level of US\$ 50 000/QALY gained. TST followed by QFT was the most cost-effective in residents with comorbidities. CXR was less cost-effective. Effective

LTBI screening using IGRA is recommended to prevent TB transmission not only in nursing homes but also in local communities in low-incidence countries.

DECLARATION OF INTEREST

None.

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