Original Article

A screening strategy for latent tuberculosis in healthcare workers: Cost-effectiveness and budget impact of universal versus targeted screening

May Ee Png PhD[1], Joanne Yoong PhD[2], Catherine Wei Min Ong FAMS, PhD[3,4], Dale Fisher FRACP[3,4] and Natasha Bagdasarian MD, MPH[3,4]

[1]Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore, [2]Center for Economic and Social Research East, University of Southern California, Washington, DC, United States, [3]Division of Infectious Disease, Department of Medicine, National University Health System, Singapore, Singapore and [4]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

Abstract

Objective: To evaluate the clinical, cost-efficiency, and budgetary implications of universal versus targeted latent tuberculosis infection (LTBI) screening strategies among healthcare workers (HCWs) in an intermediate tuberculosis (TB)-burden country.

Design: Pragmatic cost-effectiveness and budget impact analysis using decision-analytic modeling.

Setting: A tertiary-care hospital in Singapore.

Methods: We compared 7 potentially implementable LTBI screening programs including universal and targeted strategies with different screening frequencies. Feasible targeting methods included stratification by country of origin (a proxy for risk of prior TB exposure) and by high-risk occupation. The clinical and financial consequences of each strategy were estimated relative to "no screening" (current practice) and compared to locally appropriate cost-effectiveness thresholds. All analyses were conducted from the hospital's perspective over a 3-year time horizon, based on the typical hospital planning period. Parameter uncertainties were accounted for using sensitivity analyses.

Results: In our model, relative to current practice, screening new international hires and triennial screening of existing high-risk workers is most cost-effective (US$58 per quality adjusted life year [QALY]) and decreases active TB cases from 19 to 14. Screening all new hires combined with triennial universal screening, with or without annual high-risk screening or annual universal screening, reduced active TB to a range of 19 to 6 cases, but these strategies are less cost-effective and require substantially higher expenditures.

Conclusions: Targeted LTBI screening for HCWs can be highly cost-effective for hospitals in settings similar to Singapore. More inclusive screening strategies (including regular universal screening) can yield better outcomes but are less efficient and may even be unaffordable.

(Received 18 April 2018; accepted 24 November 2018)

The occupational risk of acquiring tuberculosis varies considerably in healthcare settings.[1] Although nosocomial transmission of tuberculosis (TB) has been relatively uncommon in low-TB-burden countries,[2] healthcare workers (HCWs) who routinely perform high-risk procedures (eg, bronchoscopy) are at increased risk of TB exposure.[3] In addition, international travel has facilitated TB outbreaks in healthcare settings. A recent report from the United Kingdom traced multidrug-resistant TB (MDR-TB) transmission between hospitalized patients in which the index patient was an HIV-positive HCW who had previously worked at a hospital in South Africa during a 2005 outbreak of MDR-TB.[4] Nosocomial TB transmission is thus no longer dependent solely on the TB burden of a single country.

Actively screening and treating latent TB infection (LTBI) can reduce the risk of progression to active TB in high-risk groups. On exposure and conversion to LTBI, ~10% of immunocompetent individuals with LTBI will develop active TB, of whom 5% will develop active disease in the first 2 years and the next 5% of whom will develop TB at some point in their lifetime.[5] LTBI screening for HCWs does not routinely take place in all countries. However, screening programs that focus on testing and treating HCWs who have been identified as high risk may still be valuable. For instance in the United States, the TB incidence rate in non–US-born HCWs was 10-fold higher than in their US-born counterparts.[6] Although universal screening for LTBI is recommended by the US Centers for Disease Control and Prevention,[7] intensified screening of HCWs from high TB-burden countries has also been proposed.[6]

Singapore has an intermediate TB incidence of 35–45 cases per 100,000 population among Singapore residents,[8] but a considerable number of HCWs are at higher risk. For instance, almost
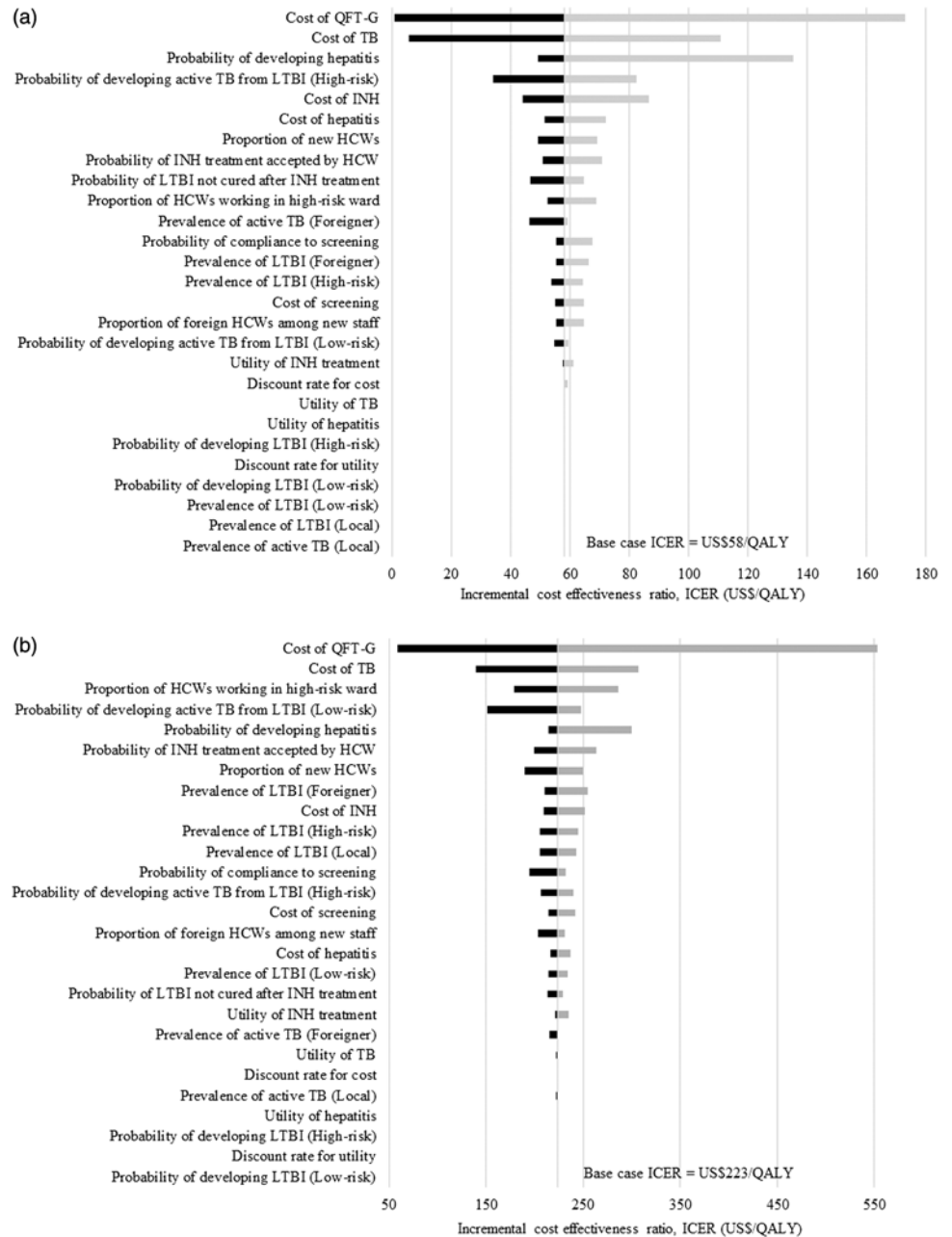
Fig. 1. One-way sensitivity analysis of model parameters on the incremental cost effectiveness ratio (ICER) of the (a) "new international + triennial high-risk", (b) "new + triennial universal", (c) "new + triennial universal + annual high-risk" and (d) "new + annual screening" relative to "no screening." HCW, healthcare worker; INH, isoniazid, LTBI, latent tuberculosis infection; QFT-G, QuantiFERON-TB Gold In-Tube; TB, tuberculosis.

25% of nurses in Singapore originate from high-TB–burden countries like the Philippines which has a TB incidence of 288 per 100,000 population.[9,10] Presently, LTBI screening for HCWs is neither mandated nor routinely practiced. Migrant workers in Singapore for >6 months, including HCWs, are only required to undergo a 1-time chest x-ray to screen for active TB.[11]

In November 2015, a pediatric nurse at the National University Hospital (NUH), a 1,225-bed tertiary-care hospital in Singapore, was diagnosed with pulmonary TB. The nurse had immigrated to Singapore from a high-TB-burden country and had been coughing for 5 months prior to diagnosis. In that time, she had cared for 481 pediatric patients. No secondary active TB disease was detected but 13 exposed HCWs and 8 exposed pediatric patients had LTBI, and this large-scale exposure resulted in a significant cost (>US $100,000 in direct costs[12]). Following this incident, we conducted a pragmatic cost-effectiveness and budget impact analysis to

evaluate potentially feasible LTBI screening strategies in newly hired and existing HCWs at the tertiary hospital in Singapore to determine the best strategy to implement in our intermediate TB-burden country.

Methods

Model

A decision-tree model (Supplemental Material Fig. 1 online) was designed to simulate various screening strategies and health outcomes among a hypothetical cohort of 30-year old, newly hired HCWs over 3 years, the approximate length for 1 budgetary cycle. Several assumptions, based on published literature or expert opinion, were adopted to simplify model construction.

Newly hired HCWs were categorized as "Singaporean" or "International" (with a higher likelihood of having LTBI because
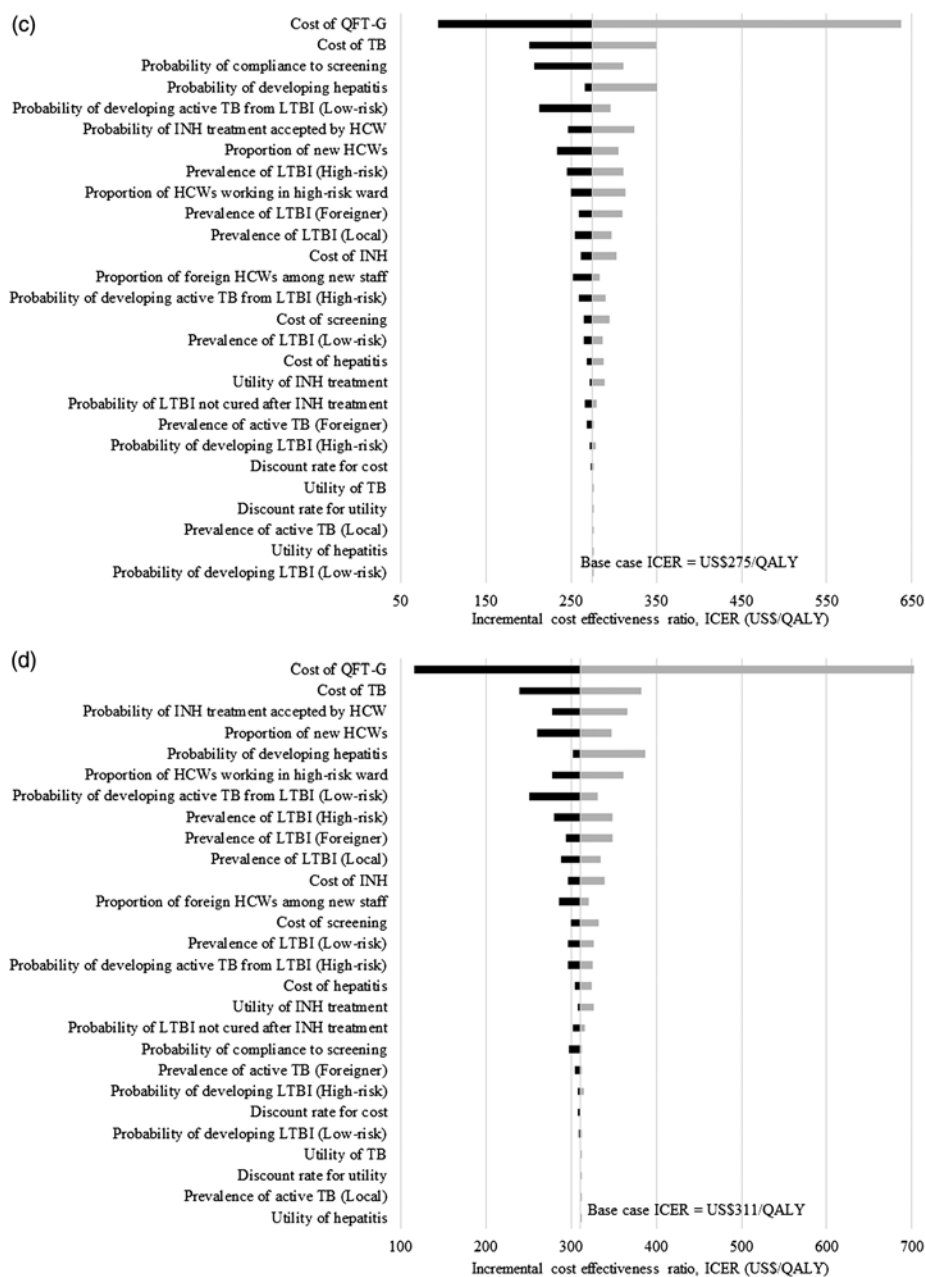
Fig. 1. (Continued)

most are from a high-TB-burden country). Existing HCWs were categorized according to the risk of exposure to TB based on their area of work (high- versus low-risk areas; which were mutually exclusive, assuming that HCWs do not work in >1 area concomitantly). High-risk areas were classified as emergency medicine, radiology, respiratory, general medicine, hematology-oncology, microbiology or pathology laboratories, medical intensive care or transplant units, based on the likelihood of encountering unrecognized pulmonary TB, performing aerosol-generating procedures, or encountering infectious specimens.[13–15]

Further assumptions included the following: (1) all HCWs had normal chest x-rays at each screening time point; (2) HCWs diagnosed with LTBI would be adherent to 6 months of isoniazid (INH) treatment; (3) no deaths and no transmission or recurrent TB; and (4) a stable level of occupational risk during the time horizon of 3 years.

Screening strategies

Based on discussion with hospital stakeholders regarding considerations of feasibility and acceptability, we considered the following screening strategies for new and current employees with levels of risk stratification (Table 1).

(1) "No screening" (current approach): No HCWs undergo screening for LTBI.
(2) "New": All newly hired HCWs undergo a triennial screening at the time of employment.
(3) "New international + triennial high-risk": Newly hired international staff undergo mandatory LTBI screening, while existing staff working in high-risk areas are screened once every 3 years. Partial adherence to screening among existing staff is assumed.

Table 1. Description of Screening Strategies

| | Year 1 | | | | Year 2 and 3 | |
| | New Staff | | Existing Staff | | Existing Staff | |
Strategy Name	International	Singaporean	High-Risk Ward	Low-Risk Ward	High-Risk Ward	Low-Risk Ward
No screening	None	None	None	None	None	None
New	Mandatory	Mandatory	None	None	None	None
New international + triennial high risk	Mandatory	None	Partial adherence	None	None	None
New international + annual high risk	Mandatory	None	Partial adherence	None	If QFT-G tested negative or no screening was done, screening was repeated but with partial adherence assumed	None
New + triennial universal	Mandatory	Mandatory	Partial adherence	Partial adherence	None	None
New + triennial universal + annual high risk	Mandatory	Mandatory	Partial adherence	Partial adherence	If QFT-G tested negative or no screening was done, screening was repeated but with partial adherence assumed	None
New + annual universal	Mandatory	Mandatory	Partial adherence	Partial adherence	If QFT-G tested negative or no screening was done, screening was repeated but with partial adherence assumed	If no screening was done previously, screening would be conducted but with partial adherence assumed

Note. QFT-G, QuantiFERON-TB Gold In-Tube. Partial adherence refers to adherence rate of screening as defined in Table 2.

(4) "New international + annual high risk": Newly hired international staff undergo mandatory LTBI screening, whereas existing staff working in high-risk areas are screened annually (unless previously tested positive) with partial adherence assumed.

(5) "New + triennial universal": All newly hired HCW undergo mandatory LTBI screening, whereas all existing staff are screened once every three years. Partial adherence to screening is assumed among existing staff.

(6) "New + triennial universal + annual high-risk": All newly hired HCW undergo mandatory LTBI screening, whereas all existing staff are screened once every three years. Existing staff in high-risk areas are screened annually (unless previously tested positive) and partial adherence is assumed.

(7) "New + annual universal": All newly hired HCW undergo mandatory LTBI screening whereas all existing staff are screened annually (unless previously tested positive) and partial adherence is assumed.

Quantiferon-TB Gold-In-Tube (QFT-G) was the selected screening test for LTBI because Bacille Calmette-Guérin (BCG), which is included in childhood vaccination schedule in Singapore, would interfere with the interpretation of tuberculin skin test. Based on past observation, we assumed that newly hired HCWs would be fully adherent to screening, with 80% adherence rate for existing HCWs. HCWs with prior history of TB or LTBI would not be screened since these populations would have a positive result, and existing guidelines do not recommend treating again with INH.

Effectiveness and cost-effectiveness analysis

A cost effectiveness analysis (CEA) of 7 screening strategies for LTBI was conducted from the hospital's perspective in a hypothetical cohort of 5,000 frontline healthcare workers employed at the start of the baseline year of 2016, comprising 500 new and 4,500 existing employees. The main outcomes of measure were number of active TB cases averted and ultimately quality adjusted life years (QALYs).

Probabilities and outcomes associated with testing and treatment were obtained from published literature and expert opinions, whereas the HCW population characteristics were assumed to be similar to our own hospital setting. Costs included the direct medical costs of screening (inclusive of tests and labor/overhead costs, converted to a per-head value) and treatment of TB and LTBI, as well as indirect costs related to productivity losses from absenteeism based on average hospital wages obtained from published sources and the hospital finance department. Most newly hired international HCWs come from regional high-burden TB countries (eg, China and the Philippines); thus, estimates for the prevalence of LTBI and active TB were based on these countries. In addition, the quality-adjusted life years (QALY) attributed to an individual with LTBI were assumed to be the same as that of a TB-free individual.[16] Costs were adjusted to 2016 Singapore dollars and converted to 2016 US dollars (US$1=S$1.3815)[17]. Both costs and outcomes were discounted at an annual rate of 3%, a commonly used value for discounting in cost-effective analysis.

We simulated the development, detection, and treatment of TB in the hypothetical cohort under each strategy, and we estimated clinical effectiveness by comparing the number of active TB cases

Table 2. Estimates for Model Parameters of a Hypothetical Cohort of 30-Year Old Healthcare Workers (HCWs)

Parameters	Base Case	Sensitivity Range	References
HCW at entry, year 1			
Workforce characteristics			
Total number of HCWs eligible for screening	5,000	4,000–6,000	NUH
Proportion of new HCWs	0.10	0.05–0.20	NUH
Proportion of international HCWs	0.50	0.40–0.80	
Proportion of HCWs working in high-risk ward	0.20	0.10–0.30	NUH
Retention rate	0.90	0.80–1.00	NUH
Annual probability			
Prevalence of LTBI			
International	0.63	0.33–0.79	Menzies et al, 2007[20]
Singaporean	0.24	0.04–0.46	Menzies et al, 2007[20]
High-risk	0.30	0.225–0.375	Salpeter et al, 2004[21]
Low-risk	0.04	0.03–0.05	Salpeter et al, 2004[21]
Prevalence of active TB			
International	0.00089	0.00067–0.00395	WHO Global Tuberculosis Report[22]
Singaporean	0.00040	0.00035–0.00045	MOH, 2015[8]
HCW from year 2 onward			
Annual probability			
Develop active TB			
High-risk	0.0057	0.004275–0.007125	Salpeter, 2004[21]
Low-risk	0.0023	0.001725–0.004	Salpeter, 2004[21]
Develop LTBI			
High-risk	0.03	0.0225–0.0375	Salpeter, 2004[21]
Low-risk	0.003	0.00225–0.01	Salpeter, 2004[21]
LTBI not cured after INH treatment	0.35	0.07–0.5	del Campo et al, 2012[23]
INH treatment accepted by HCW	0.64	0.375–0.85	Pathak et al, 2016[24]
INH-induced hepatitis	0.003	0.001–0.02	del Campo et al, 2012[23]; Kowada et al, 2015[16]
Hepatitis resolved after INH treatment	0.95	0.80–0.99	Assumed based on del Campo et al, 2012[23]
Adherence with screening	0.80	0.40–1.00	Assumed
Cost, per person (USD)			
Screening program	4	2–8	NUH
QFT-G	72	36–144	NUH
6-month INH	72	36–144	NUH
Treatment of INH-induced hepatitis	11,607	5,804–23,214	NUH
Treatment of active TB	12,305	6,153–19,688	NUH
Discount rate, %	3	3–5	Assumed
QOL (QALY)			
During 6-month INH treatment	0.975	0.85–1.00	Dobler et al, 2015[25]
INH-induced hepatitis	0.667	0.4–0.8	Dobler et al, 2015[25]
During treatment of active TB	0.827	0.50–0.98	Dobler et al, 2015[25]
Discount rate, %	3	1–5	Assumed

Note. HCW, healthcare worker; INH, isoniazid; LTBI, latent tuberculosis infection; NUH, National University Hospital; QALY, quality-adjusted life-year; QFT-G, QuantiFERON-TB Gold In-Tube; QOL, quality of life; TB, tuberculosis.

Table 3. Base Case Effectiveness and Cost-Effectiveness Analysis Results of Screening Strategies Among Initial Cohort Compared With No Screening

Strategy	No. of TB cases (per 5,000 HCWs)	No. of TB cases averted (per 5,000 HCWs)	Incr. cost (US$) per TB case averted	QALYs (per HCW)	Incr. QALYs	Cost (US$ per HCW)	Incr. cost (US$)	ICER (US$/ QALY)
No screening	19			2.91		46		
New	18	1	53,926[a]	2.98	0.07	55	9	122
New international + triennial high risk	14	5	6,745	3.03	0.12	53	7	58
New international + annual high risk	13	6	21,482[a]	3.07	0.15	70	24	157
New + triennial universal	7	12	16,298	3.09	0.18	86	40	223
New + triennial universal + annual high risk	6	13	22,657	3.12	0.21	103	57	275
New + annual universal	6	13	26,646	3.13	0.22	113	67	311

Note. HCW, healthcare worker; ICER, incremental cost-effectiveness ratio; Incr., incremental; QALYs, quality-adjusted life-years; TB, tuberculosis.
[a]Dominated.

and total QALYs experienced by the cohort over the model horizon, relative to the benchmark of "no-screening." We calculated the total direct and indirect costs related to TB control, treatment, and the incremental cost-effectiveness ratio (ICER) for each strategy (ie, the difference in total discounted costs over the difference in discounted QALYs), relative to the benchmark of "no screening." To determine whether an intervention was cost-effective, we compared the cost per QALY gained from each strategy to a locally appropriate willingness-to-pay threshold of US$50,000 per QALY, based on World Health Organization CHOICE guidelines.[18] Interventions below this threshold represent an efficient allocation of healthcare resources. TreeAge software (TreeAge Pro Healthcare Williamstown, MA) was used to conduct the cost-effectiveness analysis.

Budget impact analysis

An intervention can be cost-effective but still unaffordable if the total cost required exceeds available resources. In addition to the CEA, we conducted a budget impact analysis (BIA) to estimate the net cumulative cost of implementing the various strategies including the cost of treating potential adverse events (eg, INH-induced hepatitis) and/or the development of active TB. To capture the budgetary obligations of the hospital at full-scale implementation, we assumed a dynamic cohort with a turnover rate of 10% across all areas and an annual inflow of 500 new HCWs while maintaining the same initial cohort size. With a BIA, costs remain undiscounted to assess the actual dollar impact expected at each time point.[19] The BIA was performed using Microsoft Excel (Microsoft, Redmond, WA).

Sensitivity analysis

Because the model incorporates many assumptions, we included sensitivity analyses to evaluate the likely impact of parameter uncertainty. We conducted one-way sensitivity analysis, determining plausible ranges for the values of all parameters used in the baseline scenario (Table 2) based on the underlying literature or expert opinions. For each parameter individually, holding all others fixed, we then recalculated ICERs for all the strategies at the extreme ends of the range, quantifying the sensitivity of the ICER estimates to the values assumed. Results were presented in

standard tornado diagrams, graphically ranking the model parameters by their impact on the ICER estimate. Likewise, for the BIA, key characteristics like total number of HCWs, proportion of new HCWs, proportion of international HCWs, proportion of HCWs working in high-risk areas and retention rate were varied (Table 2), and the range of resulting total budget estimates were reported.

We also conducted probabilistic sensitivity analysis (PSA), varying all parameters simultaneously according to an assumed probability distribution for each, using a Monte Carlo simulation with 1,000 runs and calculating the realized ICER for each strategy in each one. A gamma distribution was assumed for the cost parameters, whereas β distributions were assumed for probabilities and utilities. Base case values were used as the mean, and the standard deviation was computed by taking 25% of the difference between the low and high values defined in the one-way sensitivity analysis.[26] PSA results were presented as a cost-effectiveness acceptability curve (CEAC). This curve shows the empirically determined probability that each strategy is cost-effective (horizontal axis) compared with "no screening" over a range of possible values of the willingness-to-pay thresholds, which is the percentage of simulated runs in which ICER falls below the threshold value (vertical axis).

The National Healthcare Group Domain Specific Review Board exempted this study from full ethics review (reference no.: 2016/01000).

Results

In the "no-screening" benchmark, our model predicted ~19 cases of active TB over 3 years among the HCWs, close to the 21 cases that were extrapolated from the recorded 7 cases in our hospital in 2015.

Table 3 lists the clinical outcomes and cost-effectiveness analyses results. The most intensive screening strategy (all new hires and annual universal screening) is the most effective in terms of total TB cases averted and QALYs gained but also the most expensive.

All screening strategies were found to be cost-effective by local standards relative to "no screening." Hence, if any other strategy was implemented, the cost per QALY would be <US$50,000 per QALY. A highly targeted strategy of screening new international employees and high-risk workers once ("new international + triennial high-risk") was the most cost-effective (US$6,745 per TB case averted; US$58/QALY; reduces active TB cases from 19 to 14).
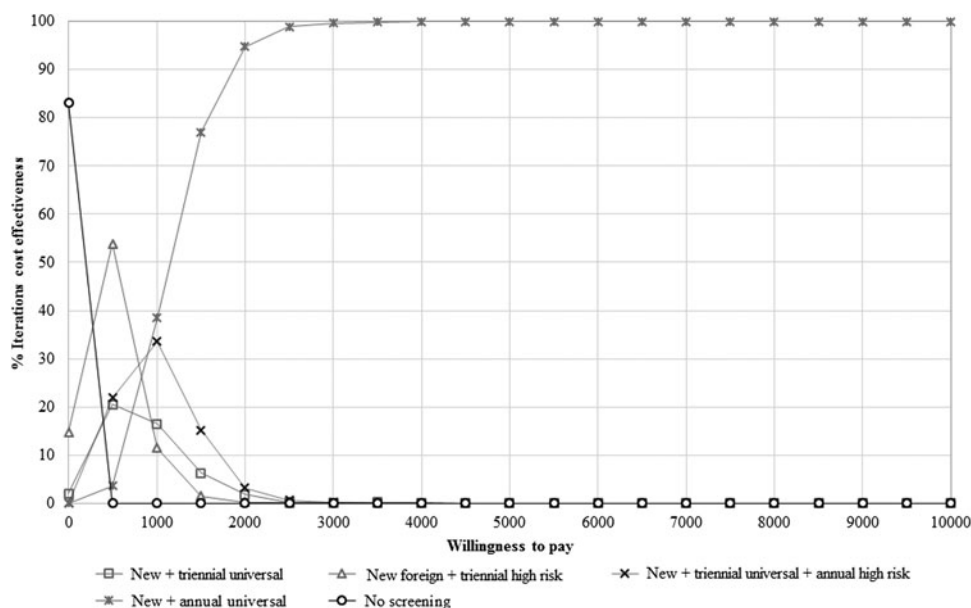
Fig. 2. Probabilistic sensitivity analysis on cost effectiveness of "no screening," "new international + triennial high-risk," "new + triennial universal," "new + triennial universal + annual high-risk," and "new + annual universal" screening strategies.

Annual universal screening for all employees ("new + annual universal") was the least cost-effective (US$26,646 per TB case averted; US$311/QALY). Screening new hires alone ("new") was more costly and less effective than screening only new international employees and high-risk workers once ("new international + triennial high-risk"), and screening of new international hires combined with annual high-risk screening ("new international + annual high risk") was also more costly and less effective than screening all newly employed and existing employees once ("new + triennial universal"). These 2 strategies ("new" and "new international + annual high risk") were therefore considered dominated and were removed from further analyses.

The base case 3-year total budget for TB control under "no screening" was US$238,379, which is the cost of diagnosing and managing active TB cases. Under the most cost-effective strategy of "new international + triennial high risk," the total hospital budget would be US$332,571, or an additional US$95,000 over 3 years. To decrease the overall cost, the cost of QFT-G (which accounted for majority of the budget in all strategies) could be targeted for reduction.

The one-way sensitivity analysis for undominated screening strategies relative to "no screening" (Fig. 1) shows that ICERs are most sensitive to the cost of QFT-G. However, since all the ranges of recalculated ICER values fall well below US$50,000 per QALY, our cost-effectiveness findings are robust (ie, our conclusions remained unchanged across a realistic range of possible parameters). One-way sensitivity analysis on the BIA results (Supplemental Material Fig. 2 online) showed that in general, the budget would be most sensitive to changes in the total number of HCWs and the retention rate.

Finally, the CEAC (Fig. 2) showed that at lower willingness-to-pay thresholds, the targeted screening strategy is most likely to be cost-effective. However, if willingness-to-pay is sufficiently high, a policy of universal screening can most likely be cost-effective.

Discussion

Nosocomial TB exposures are inevitable in moderate to high-TB-burden countries where screening of LTBI in HCWs is not routinely practiced. Policy makers contemplating a LTBI screening program for HCWs need to consider trade-offs among the additional number of active TB cases prevented, resources used, and budget limitations. A risk-stratified approach to LTBI screening in HCWs may be a novel, pragmatic, and cost-effective strategy, especially in countries like Singapore, where a large proportion of HCWs originate from high TB-burden countries.[9]

Although regular universal screening can be most effective, it is most expensive and likely to be cost-effective only at high levels of willingness-to-pay. The total cost of instituting universal LTBI screening for all new and existing HCWs is $26,646 per active TB case averted, and policy makers would need to decide its worth. Our results showed that in this setting, targeted screening is likely to be highly cost-effective. The most cost-effective approach in our model involved screening of all new HCWs from high-risk countries of origin, and triennial screening every 3 years for existing HCWs in high-risk clinical areas, costing $6,745 per active TB cases averted (reducing active TB cases from 19 to 14). Our conclusions differ from a recent study published by Mullie et al,[27] possibly because that analysis was conducted with relatively high frequency screening in a low-incidence TB country from the healthcare system perspective.

Ultimately, decision makers need to weigh the inevitable trade-off of greater cost-effectiveness against the greater risk of missed cases. On the one hand, missed TB cases can have heavy clinical, legal, and financial consequences for a healthcare system[28] particularly because whole-genome sequencing has enabled more precise tracing of index cases in outbreak scenarios.[29] On the other hand, screening of existing employees in high-risk clinical areas requires additional resources to ensure adherence to LTBI testing and treatment, and resource constraints may be binding or systemic priorities may lie elsewhere.

Wherever possible, decision makers should also consider the use of innovative strategies to increase the efficiency of screening itself. To improve adherence, LTBI screening could be added to existing routine pre-employment screening (ie, screening for hepatitis B, verifying immunity to varicella and measles) and implementing a system to ensure regular LTBI screening for existing workers.

Finally, our results are most sensitive to the cost of QFT-G, which is the most expensive item. Reducing the cost of QFT-G could make all screening strategies more cost-effective, and even

cost-saving if the price is lower than the $36 in our model. This could be achieved by negotiating with manufacturers to lower the cost with bulk orders.

This study has certain limitations. Firstly, for simplicity, we assumed 100% specificity and sensitivity of QFT-G, although the documented specificity of QFT-G ranges from 98% to 100%,[16] and sensitivity ranges between 81% and 87%.[16,30] This could reduce the cost-effectiveness of screening, due to fewer positive tests and fewer HCWs treated for LTBI.[31] However, no existing LTBI test meets 100% sensitivity and specificity, whereas the other option, a tuberculin test, has an even lower sensitivity and specificity. However, reports of nosocomial TB in the literature tend to involve large-scale or drug-resistant cases, which limits the relevance to our Singapore setting. Furthermore, it is challenging to determine the duration and extent of exposure required for transmission in the community, let alone in a hospital setting, where shift work is prevalent. Secondly, neither nosocomial active TB transmission nor death due to INH-induced hepatitis/active TB were included in the model. However, the incidence of death due to INH-hepatitis is very low in the general literature[32] and has been historically zero among HCWs in this hospital, as with deaths from active TB.

Altogether, our study provides insights on the effectiveness, efficiency, and budget impact of LTBI screening strategies among HCWs. We found that LTBI screening strategies can be cost-effective if HCWs are risk-stratified according to their country of origin and area of work. Furthermore, the efficiency of screening could be further improved if health systems ensure adherence to LTBI testing and treatment, and could even be cost-saving if the cost of QFT-G were decreased. These strategies targeting LTBI screening in HCWs in intermediate-TB burden countries should be considered in the effort to prevent nosocomial TB transmission.[27,31]

References

1. Menzies D, Fanning A, Yuan L, Fitzgerald M. Tuberculosis among health care workers. *N Engl J Med* 1995;332:92–98.
2. Davidson JA, Lalor MK, Anderson LF, Tamne S, Abubakar I, Thomas HL. TB in healthcare workers in the UK: a cohort analysis 2009–2013. *Thorax* 2017;72:654–659.
3. Sydnor ERM, Perl TM. Hospital epidemiology and infection control in acute-care settings. *Clin Microbiol Rev* 2011;24:141–173.
4. Martin Williams O, Abeel T, Casali N, *et al*. Fatal nosocomial MDR TB identified through routine genetic analysis and whole-genome sequencing. *Emerg Infect Dis* 2015;21:1082–1084.
5. Schluger NW. The pathogenesis of tuberculosis: the first one hundred (and twenty-three) years. *Am J Respir Cell Mol Biol* 2005;32:251–256.
6. Lambert LA, Pratt RH, Armstrong LR, Haddad MB. Tuberculosis among healthcare workers, United States, 1995–2007. *Infect Control Hosp Epidemiol* 2012;33:1126–1132.
7. Jensen PA, Lambert LA, Iademarco MF. *Guidelines for Preventing the Transmission of Mycobacterium Tuberculosis in Health-Care Settings*. Atlanta, GA: CDC; 2005.
8. Tuberculosis. Singapore Ministry of Health website. https://www.moh.gov.sg/content/moh_web/home/diseases_and_conditions/t/tuberculosis.html. Published 2017. Accessed October 1, 2017.
9. Demographics of nursing professionals in Singapore. Singapore Ministry of Health website. https://www.moh.gov.sg/content/moh_web/home/pressRoom/Parliamentary_QA/2012/demographics_of_nursingprofessionalsinsingapore.html. Published 2012. Accessed October 1, 2017.
10. Global HIV and Tuberculosis. Centers for Disease Control and Prevention website. https://www.cdc.gov/globalhivtb/where-we-work/philippines/philippines.html. Published 2016. Accessed June 1, 2017.
11. Chee CBE, Wang YT. TB control in Singapore: Where do we go from here? *Singapore Med J* 2012;53:236–238.
12. Bagdasarian N, Chan H, Ang S, Isa M, Chan S, Fisher D. A" Stone in the pond" approach to contact tracing: responding to a large-scale, nosocomial tuberculosis exposure in a moderate TB-burden setting. *Infect Control Hosp Epidemiol* 2017;38:1–3.
13. Casas I, Esteve M, Guerola R, *et al*. Incidence of tuberculosis infection among healthcare workers: risk factors and 20-year evolution. *Respir Med* 2013;107:601–607.
14. Baussano I, Bugiani M, Carosso A, *et al*. Risk of tuberculin conversion among healthcare workers and the adoption of preventive measures. *Occup Environ Med* 2007;64:161–166.
15. Cook S, Maw KL, Munsiff SS, Fujiwara PI, Frieden TR. Prevalence of tuberculin skin test positivity and conversions among healthcare workers in New York City during 1994 to 2001. *Infect Control Hosp Epidemiol* 2003;24:807–813.
16. Kowada A, Takasaki J, Kobayashi N. Cost-effectiveness of interferon-gamma release assay for systematic tuberculosis screening of healthcare workers in low-incidence countries. *J Hosp Infect* 2015;89:99–108.
17. Exchange rates. Monetary Authority of Singapore website. https://secure.mas.gov.sg/msb/ExchangeRates.aspx. Published 2016. Accessed June 1, 2017.
18. Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. *Expert Rev Pharmacoecon Outcomes Res* 2008;8:165–178.
19. Sullivan SD, Mauskopf JA, Augustovski F, *et al*. Budget impact analysis principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Heal* 2014;17:5–14.
20. Menzies D, Joshi R, Pai M. Risk of tuberculosis infection and disease associated with work in health care settings. *Int J Tuberc Lung Dis* 2007;11:593–605.
21. Salpeter SR, Salpeter EE. Screening and treatment of latent tuberculosis among healthcare workers at low, moderate, and high risk for tuberculosis exposure: a cost-effectiveness analysis. *Infect Control Hosp Epidemiol* 2004;25:1056–1061.
22. World Health Organization. Global tuberculosis report 2016. http://www.who.int/tb/publications/global_report/en/. Published 2017. Accessed April 1, 2017.
23. del Campo MT, Fouad H, Solis-Bravo MM, Sanchez-Uriz MA, Mahillo-Fernandez I, Esteban J. Cost-effectiveness of different screening strategies (single or dual) for the diagnosis of tuberculosis infection in healthcare workers. *Infect Control Hosp Epidemiol* 2012;33:1226–1234.
24. Pathak V, Harrington Z, Dobler CC. Attitudes towards preventive tuberculosis treatment among hospital staff. *PeerJ* 2016;4:e1738.
25. Dobler ACC, Martin A, Marks GB, *et al*. Benefit of treatment of latent tuberculosis infection in individual patients. *Eur Respir J* 2015;46:1397–1406.
26. Singer ME. Advanced sensitivity analyses: probabilistic, correlated and scenario. Veterans Affairs Health Services and Research and Development website. http://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/Slides_Singer.ppt. Published 2006. Accessed April 1, 2017.
27. Mullie GA, Schwartzman K, Zwerling A, N'Diaye DS. Revisiting annual screening for latent tuberculosis infection in healthcare workers: a cost-effectiveness analysis. *BMC Med* 2017;15:104.
28. Teichert E. Tenet Healthcare sued for $1.5 billion over tuberculosis exposure. Modern Healthcare website. http://www.modernhealthcare.com/article/20161108/NEWS/161109926. Published 2016. Accessed April 1, 2017.

29. Walker TM, Ip CLC, Harrell RH, *et al.* Whole-genome sequencing to delineate Mycobacterium tuberculosis outbreaks: A retrospective observational study. *Lancet Infect Dis* 2013;13:137–146.

30. Eralp MN, Scholtes S, Martell G, Winter R, Exley AR. Screening of healthcare workers for tuberculosis: development and validation of a new health economic model to inform practice. *BMJ Open* 2012;2:e000630.

31. Zwerling A, van den Hof S, Scholten J, Cobelens F, Menzies D, Pai M. Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review. *Thorax* 2012;67:62–70.

32. Saukkonen JJ, Cohn DL, Jasmer RM, *et al.* An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174:935–952.