

## **TITLE**

A Screening Strategy for Latent Tuberculosis in Healthcare Workers: Cost-effectiveness and Budget Impact of Universal versus Targeted Screening

## **ABBREVIATED TITLE**

LTBI Screening Strategies among HCWs

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## 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 hospital in Singapore.

**Methods.** Seven potentially implementable LTBI screening programs were compared, 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/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, reduces 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.

## INTRODUCTION

The occupational risk of acquiring tuberculosis varies considerably in health care settings<sup>1</sup>. While nosocomial transmission of tuberculosis (TB) has been relatively uncommon in low TB-burden countries<sup>2</sup>, healthcare workers (HCWs) who routinely perform high-risk procedures such as bronchoscopy, are at increased risk of TB exposure<sup>3</sup>. In addition, international travel has facilitated TB outbreaks in health-care settings. A recent report from the United Kingdom traced multi-drug resistant TB (MDR-TB) transmission between hospitalized patients, in which the index patient was a HIV-positive HCW, who had previously worked at a hospital in South Africa during a 2005 outbreak of MDR-TB<sup>4</sup>. Nosocomial TB transmission is thus no longer dependent solely on the TB burden of one 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, approximately 10% of immunocompetent individuals with LTBI will develop active TB, of whom 5% will develop active disease in the first two years, and the next 5% at some point in their lifetime<sup>5</sup>. 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 U.S., the TB incidence rate in non-U.S.-born HCWs was 10-fold higher than their U.S.-born counterparts<sup>6</sup>. While universal screening for LTBI is recommended by the U.S. Centers for Disease Control and Prevention<sup>7</sup>, intensified screening of HCWs from high TB-burden countries has also been proposed<sup>6</sup>.

Singapore has an intermediate TB incidence of 35-45 cases/100,000 population among Singapore residents<sup>8</sup>, but a considerable number of HCWs are at higher risk. For instance, almost a quarter of nurses in Singapore originate from high TB-burden countries

like the Philippines which has a TB incidence of 288/100,000 population<sup>9,10</sup>. At present, LTBI screening for HCWs is neither mandated nor routinely practiced. Migrant workers in Singapore for more than six months including HCWs, are only required to undergo a one-time chest x-ray to screen for active TB<sup>11</sup>.

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 eight exposed pediatric patients had LTBI, and this large-scale exposure resulted in a significant cost (more than US\$100,000 in direct costs<sup>12</sup>). 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 Figure 1), was designed to simulate various screening strategies and health outcomes among a hypothetical cohort of 30-year old newly hired HCWs over three years, the approximate length for one budgetary cycle. Several assumptions, based on published literature or expert opinion, were used to simplify model construction.

Newly hired HCWs were categorized as “Singaporean” or “International” (with a higher likelihood of having LTBI as majority 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 more than 1 area concomitantly). High-risk areas were classified to be emergency medicine, radiology, respiratory, general medicine, hematology-oncology, microbiology and pathology laboratories, medical intensive care and transplant units, based on likelihood of encountering unrecognized pulmonary TB, performing aerosol-generating procedures, or encountering infectious specimens<sup>13–15</sup>.

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

### **Screening strategies**

Based on discussion with hospital stakeholders including 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 three years. Partial adherence to screening among existing staff is assumed.

- (4) “New international + annual high risk”: Newly hired international staff undergo mandatory LTBI screening, while 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, while 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, while 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 while 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, as 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 (CEA)**

A cost effectiveness analysis (CEA) of seven 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, while 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 hospital finance. As the majority of newly hired international HCWs come from regional high burden TB countries (e.g. China and the Philippines), estimates for the prevalence of LTBI and active TB were based on these countries. In addition, the quality-adjusted life years attributed to an individual with LTBI were assumed to be the same as that of a TB-free individual<sup>16</sup>. Costs were adjusted to 2016 Singapore dollars and converted to 2016 U.S. dollars (US\$1=S\$1.3815)<sup>17</sup>. 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 estimated clinical effectiveness by comparing the number of active TB cases 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 (i.e. the difference in total discounted costs over the difference in discounted QALYs), relative to the benchmark of “No screening”. To determine whether an intervention is cost-effective, we compared the cost per QALY gained from each strategy to a locally-appropriate willingness-to-pay threshold of US\$50,000/QALY, based on WHO-CHOICE guidelines<sup>18</sup>.

Interventions below this threshold represent an efficient allocation of healthcare resources. TreeAge Pro Healthcare (Treeage Pro Healthcare. Inc. Williamstown, MA: TreeAge Software; 2017) was used to conduct the cost-effectiveness analysis.

### **Budget impact analysis (BIA)**

An intervention can be cost-effective but still unaffordable if the total cost required exceeds available resources. Alongside the CEA, we therefore 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 (e.g. 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 in order to assess the actual dollar impact expected at each time point<sup>19</sup>. The BIA was performed using Microsoft Excel (Microsoft Corporation, Redmond, Washington; 2016).

### **Sensitivity analysis**

As 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 1000 runs and calculating the realized ICER for each strategy in each one. A gamma distribution was assumed for the cost parameters while beta 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<sup>20</sup>. PSA results were presented as a cost-effectiveness acceptability curve (CEAC), showing 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).

This study was exempted from full ethics review by the National Healthcare Group Domain Specific Review Board (Reference no.: 2016/01000).

## **RESULTS**

In the “No-screening” benchmark, our model predicted approximately 19 cases of active TB over three years among the HCWs, close to the 21 cases that were extrapolated from the recorded seven cases in our hospital in 2015.

Table 3 shows 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 less than US\$50,000/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). Annual universal screening for all employees (“New + annual universal”) was 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 two 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 three 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” (Figure 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/QALY, our findings about cost-effectiveness are robust (i.e. our conclusions remained unchanged across a realistic range of possible parameters). One-way sensitivity analysis on the BIA results (Supplemental material Figure 2) 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 (Figure 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 in HCWs need to consider trade-offs between the additional number of active TB cases prevented resources use 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<sup>9</sup>.

While 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 policymakers 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 three 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<sup>21</sup>, 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 tradeoff 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<sup>22</sup> particularly as whole-genome-sequencing has enabled more precise tracing of index cases in outbreak scenarios<sup>23</sup>. 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.

Decision makers should also consider wherever possible, 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 (i.e. screening for hepatitis B, verifying immunity to varicella and measles) while 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 was 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%<sup>16</sup>, and sensitivity ranges from 81% to 87%<sup>16,24</sup>. This could reduce the cost-effectiveness of screening, due to fewer positive tests and fewer HCWs treated for LTBI<sup>25</sup>. However, there is no existing LTBI test that meets 100% sensitivity and specificity while 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<sup>26</sup> 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<sup>21,25</sup>.

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## FIGURE LEGENDS

Figure 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

Figure 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.

## TABLES

Table 1. Description of screening strategies.

Strategy name	Year 1				Year 2 and 3	
	New staff		Existing staff		Existing staff	
	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	None

					assumed	
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: Partial adherence refers to adherence rate of screening as defined in Table 2.

Abbreviation: QFT-G = QuantiFERON-TB Gold In-Tube

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)			
<b>Workforce characteristics</b>			
Total number of HCWs eligible for screening	5000	4000-6000	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
<b>Annual probability</b>			
Prevalence of LTBI			
International	0.63	0.33-0.79	Menzies et al, 2007 <sup>27</sup>
Singaporean	0.24	0.04-0.46	Menzies et al, 2007 <sup>27</sup>
High-risk	0.30	0.225-0.375	Salpeter et al, 2004 <sup>28</sup>
Low-risk	0.04	0.03-0.05	Salpeter et al, 2004 <sup>28</sup>
Prevalence of active TB			
International	0.00089	0.00067-0.00395	WHO Global Tuberculosis Report <sup>29</sup>
Singaporean	0.00040	0.00035-0.00045	MOH, 2015 <sup>8</sup>
HCW from Year 2 onwards			



**Annual probability**

## Develop active TB

High-risk	0.0057	0.004275-0.007125	Salpeter, 2004 <sup>28</sup>
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Low-risk	0.0023	0.001725-0.004	Salpeter, 2004 <sup>28</sup>
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## Develop LTBI

High-risk	0.03	0.0225-0.0375	Salpeter, 2004 <sup>28</sup>
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Low-risk	0.003	0.00225-0.01	Salpeter, 2004 <sup>28</sup>
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LTBI not cured after INH treatment	0.35	0.07-0.5	del Campo et al, 2012 <sup>30</sup>
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INH treatment accepted by HCW	0.64	0.375-0.85	Pathak et al, 2016 <sup>31</sup>
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INH-induced hepatitis	0.003	0.001-0.02	del Campo et al, 2012 <sup>30</sup> ; Kowada et al, 2015 <sup>16</sup>
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Hepatitis resolved after INH treatment	0.95	0.80-0.99	Assumed based on del Campo et al, 2012 <sup>30</sup>
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Adherence with screening	0.80	0.40-1.00	Assumed
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**Cost, per person (USD)**

Screening program	4	2-8	NUH
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QFT-G	72	36-144	NUH
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6-month INH	72	36-144	NUH
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Treatment of INH-induced hepatitis	11,607	5,804-23,214	NUH
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Treatment of active TB	12,305	6,153-19,688	NUH
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Discount rate	3%	3%-5%	Assumed
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**QOL (QALY)**

During 6-month INH treatment	0.975	0.85-1.00	Dobler et al, 2015 <sup>32</sup>
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INH-induced hepatitis	0.667	0.4-0.8	Dobler et al, 2015 <sup>32</sup>
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During treatment of active TB	0.827	0.50-0.98	Dobler et al, 2015 <sup>32</sup>
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Discount rate	3%	1%-5%	Assumed
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Abbreviation: 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*	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*	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

\* Dominated

Abbreviation: HCW = Healthcare worker, ICER = Incremental cost effectiveness ratio, Incr. = Incremental, QALYs = Quality-adjusted life-years, TB = Tuberculosis