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## Major Article

## A retrospective review of tuberculosis exposure among health care workers in a tertiary hospital



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## Key Words:

Tuberculosis  
Contact tracing

**Background:** We evaluated tuberculosis (TB) acquisition rate and risk factors among health care workers (HCWs) exposed to index TB patients.

**Methods:** We performed a retrospective cohort study on exposed HCWs from August 2016 to January 2018 at a tertiary hospital in Singapore. Demographic factors and TB exposure episodes per HCW were obtained. A modified Poisson regression model was used to identify factors associated with TB infection.

**Results:** A total of 32 TB exposure events occurred during the study period. A total of 881 HCWs with 1,536 exposure episodes were screened with QuantiFERON-TB Gold In-tube assay (QFT-GIT) at baseline and 8 weeks. A total of 129 (14.6%) HCWs had positive QFT-TB at baseline, whereas 22 (2.5%) HCWs had QFT-GIT conversion, with a latent TB infection (LTBI) rate of 1.14 cases per 100 exposure episodes per year. Foreign nationality, non-Chinese ethnicity, and age above 40 years were independently associated with baseline LTBI, whereas having >2 TB exposure episodes and working in internal medicine, medical subspecialties, and psychiatry wards were associated with QFT-GIT conversion.

**Discussion:** The QFT-GIT conversion rate among screened HCWs is low. Foreign HCWs with LTBI likely came from countries with higher TB transmission. Targeted prevention of repeated TB exposures can reduce QFT-GIT conversion.

**Conclusions:** The study results will guide TB contact tracing protocols in health care institutions.

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Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis*, which can result in severe morbidity and mortality. Singapore has a total population of about 5.6 million, of which a significant proportion (about 2.2 million) comprises permanent residents or foreigners working, staying, or staying as dependents in Singapore. A recent study found an overall 12.7% QuantiFERON-TB Gold In-tube assay (QFT-GIT, Qiagen, Germantown, MD) positivity rate among Singapore residents. The prevalence is higher with older age.<sup>1</sup>

Health care workers (HCWs) are at increased risk of occupational transmission of TB infection from patients.<sup>2–4</sup> A meta-analysis looking at the risk of TB infection among HCWs reported that the risk of latent TB infection (LTBI) and active TB were greater among HCWs, with an odds ratio of 2.27 and incidence rate ratio of 2.94,

respectively, compared with the general population.<sup>2</sup> In Singapore, baseline and periodic screening of HCWs for LTBI are not performed routinely. HCWs are only screened for TB infection if they have been identified to have significant exposure to index TB patients based on the contact tracing protocol.

To the best of our knowledge, no study has been done to evaluate the risk factors and rate of TB acquisition among HCWs in Singapore hospitals. As such, to better inform TB contact tracing policy, we evaluated the TB acquisition rate and demographic and occupational factors associated with baseline LTBI and QFT-GIT conversion among HCWs exposed to index TB patients at a tertiary hospital in Singapore.

## METHODS

## Settings

The study was carried out in a single institution in Singapore, which is a large 1,725-bedded tertiary hospital with over 70,000 patients

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admitted each year. It has 32 airborne infection isolation and 11 protective environment (which may double-up for airborne infection isolation patients) single-bedded rooms for the isolation of patients with airborne diseases, including those with suspected pulmonary TB. Apart from the isolation rooms, the rest of the hospital rooms are fully air-conditioned, and comprise single-bedded A class wards, 4-bedded B1 class wards, 6-bedded B2 class wards, 10-bedded C class wards, as well as single-bedded intensive care units (ICU), except 2 rooms with 2 beds in a surgical ICU, and operating theater (OT) rooms. At least 60% of the hospital rooms are 6 to 10-bedded wards. Out of 32 exposure events, 22 (68.8%) occurred in 4 to 6-bedded wards, 7 (21.9%) occurred in 10-bedded wards, 2 (6.3%) occurred in single-bedded OT rooms, and 1 (3.1%) occurred in a single-bedded ICU.

### Study design

This is a retrospective cohort study to evaluate the association between demographic/occupational exposure factors and TB infection among all HCWs exposed to patients with pulmonary TB at a tertiary hospital in Singapore from August 2016 to January 2018. This study duration was selected because of the completeness of the TB exposure data over this time period during our review.

### Management of suspected TB cases

Patients with symptoms or signs of pulmonary TB would be investigated and isolated, if necessary, to prevent transmission of TB. Although there is guided policy to determine patients for isolation, the decision to isolate is still based on the clinical assessment of the treating physician. This often includes patients (both immunocompetent and immunocompromised) with chronic respiratory and/or constitutional symptoms such as prolonged cough and loss of weight, or those with chest radiographic findings suspicious of active pulmonary TB. Patients with positive sputum acid-fast bacilli (AFB) smear will certainly be isolated with airborne infection precautions. Patients with pulmonary TB will be deisolated if he or she is on effective treatment for at least 14 days and is clinically improving, or he or she has 3 consecutively negative sputum AFB smears.

### Current TB contact tracing protocol

In this hospital, the TB contact tracing protocol defines a contact as someone who (1) had an exposure to an index TB case while performing high-risk procedures without wearing appropriate personal protective equipment, that is an N95 mask, and/or (2) had an exposure to an index case without use of an N95 mask, for example exposure to index case in the same location with shared air supply for >8 hours (accumulated total of 8 hours exposure). A location refers to either the ward or any other areas, for example clinic, endoscopy center, office that shares the same air supply, and the size of each ward that ranges from 470–2,430 m<sup>2</sup>. An index case is defined as a patient with active pulmonary TB and whose sputum is tested positive for AFB.

Contacts are screened at the hospital's staff clinic using QFT-GIT, except for those with previously documented positive QFT-GIT result or with a history of active TB disease. QFT-GIT is performed twice: first within 2 weeks after exposure to an index TB patient (T0), and the second test at 8–10 weeks postexposure (T1) on all exposed HCWs who had a negative QFT-GIT result at T0.

### Demographic and occupational exposure factors

Demographic information such as age, sex, ethnicity, nationality, and occupation were obtained from all HCWs exposed to index TB cases. The number of TB exposure episodes per HCW was also

obtained. A review of clinical notes from the hospital's staff clinic revealed that certain TB exposure details, such as cumulative exposure time and proximity of contact as well as comorbidities of the HCWs, were not clearly and consistently documented. As such, we were unable to include the TB exposure details as well as comorbidities of the HCWs in our analysis. In terms of clinical disciplines of HCWs, 451 (51.2%) of the exposed HCWs were from the internal medicine working at 4–6 as well as 10-bedded wards, whereas 101 (11.5%) of them are from surgical disciplines working in the single-bedded OT, with the remaining 329 (37.3%) from other medical subspecialties and psychiatry department working at 4 to 6-bedded wards. A total of 22 (68.8%) of the 32 TB exposures occurred in 4 to 6-bedded wards under internal medicine or other medical subspecialties, 7 (21.9%) TB exposures occurred in 10-bedded wards under internal medicine discipline, whereas 3 (9.4%) TB exposures occurred in single-bedded ICU or OT rooms under surgical disciplines.

### Outcome assessment

Cases: QFT-GIT conversion postexposure is defined as HCWs with negative QFT-GIT at T0 but positive QFT-GIT (defined as TB antigen response  $\geq 0.35$  IU/mL above negative control) at T1. Baseline LTBI is defined as an asymptomatic HCW with positive TB QFT at T0.

Control group: HCWs with negative QFT-GIT at T0 and T1 belong to the control group of exposed HCWs who were uninfected.

### Statistical analysis

Baseline prevalence of LTBI among HCWs screened was calculated using the number of QFT-GIT positive at T0 (numerator) over the total number of exposed HCWs who received the tests at T0 (denominator), multiplied by 100.

The QFT-GIT conversion rate postexposure was calculated by dividing the number of QFT-GIT conversions among exposed HCWs (numerator) by the total number of exposure episodes in which the HCWs received the tests at T1 (denominator), multiplied by 100 and divided by the total study duration of 1.5 years, between August 2016 and January 2018, from which the information of the exposed HCWs was obtained. This would allow us to obtain the rate of QFT-GIT conversion postexposure per 100 exposure episodes per year.

Bivariate analysis was performed to investigate the association between demographic factors and baseline LTBI, as well as the association between demographic/occupational exposure factors and QFT-GIT conversion postexposure.

Independent factors associated with baseline LTBI and QFT-GIT conversion were obtained using the modified Poisson regression model adjusting for potential confounding factors including age, ethnicity, nationality, sex, and occupation. STATA 14.0 (Stata Corp, College Station, TX) was used for statistical analysis.

### Data approval process

Access to the clinical pseudonymized medical information was approved by hospital management as part of the operational evaluation of its current TB contact tracing protocol. A third-party information technology vendor performed pseudonymization before the data were released for analysis. No patient identifiers were provided or used in this study.

## RESULTS

### Descriptive statistics

From August 2016 to January 2018, there were 32 TB exposure events. The average number of exposed HCWs involved in each

**Table 1**  
Demographic characteristics of HCWs exposed to TB in a tertiary hospital

Variables		Control (n(%))	TB infected (n(%))	Overall sample (n(%))
Number of study participants		730 (82.9%)	151 (17.1%)	881 (100%)
Nationality	Singaporean	444 (60.8%)	62 (41.1%)	506 (57.4%)
	Foreigners	286 (39.2%)	89 (58.9%)	375 (42.6%)
Sex	Female	619 (84.8%)	129 (85.4%)	748 (84.9%)
	Male	111 (15.2%)	22 (14.6%)	133 (15.1%)
Ethnic group	Chinese	306 (41.9%)	29 (19.2%)	335 (38.0%)
	Indian	97 (13.3%)	19 (12.6%)	116 (13.2%)
	Malay	178 (24.4%)	24 (15.9%)	202 (22.9%)
	Others	149 (20.4%)	79 (52.3%)	228 (25.9%)
Age group	<40	617 (84.5%)	89 (58.9%)	706 (80.1%)
	≥40	113 (15.5%)	62 (41.1%)	175 (19.9%)
Number of TB exposure episodes	1	478 (65.5%)	70 (46.4%)	548 (62.2%)
	2	97 (13.3%)	33 (21.8%)	130 (14.8%)
	3	77 (10.6%)	24 (15.9%)	101 (11.5%)
	4	68 (9.3%)	21 (13.9%)	89 (10.1%)
	5	6 (0.8%)	3 (2.0%)	9 (1.0%)
	6	4 (0.5%)	0 (0.0%)	4 (0.4%)
Occupation	Nurses/nursing students	560 (77.5%)	121 (80.1%)	681 (77.3%)
	Doctors/medical students	15 (2.1%)	1 (0.7%)	16 (1.8%)
	Allied health/allied health students	101 (14.0%)	25 (16.6%)	126 (14.3%)
	Ancillary HCWs	46 (6.4%)	4 (2.6%)	50 (5.7%)
	Unknown			8 (0.9%)
Clinical discipline	Surgery	93 (12.7%)	8 (5.3%)	101 (11.5%)
	Other medical subspecialties and psychiatry	274 (37.5%)	55 (36.4%)	329 (37.3%)
	Internal medicine	363 (49.7%)	88 (58.3%)	451 (51.2%)

HCWs, health care workers; TB, tuberculosis.

exposure event was 50.1 (SD, 44.2; range, 1–179). Overall, 947 HCWs were identified from our contact tracing protocol with 1,604 TB exposure episodes. Out of the 947 HCWs, 66 did not undergo any QFT-GIT blood tests. Therefore, only 881 HCWs with 1,536 exposure episodes were included in our study. Out of those who had undergone the QFT-GIT blood test, 129 (14.6%) were found to have positive QFT-GIT result at baseline, whereas 22 (2.5%) experienced QFT-GIT conversion. Excluding those with positive QFT-GIT results at baseline, only 752 HCWs with 1,281 exposure episodes underwent the second QFT-GIT at T1. Ten (1.3%), 7 (2.6%), 2 (1.2%), and 3 (3.7%) of exposed HCWs experienced TB seroconversion after the first, second, third, and fourth exposure, respectively. The overall rate of QFT-GIT conversion was calculated to be 1.14 cases per 100 exposure episodes per year. The rate of QFT-GIT conversion is calculated by using 22 QFT-GIT conversion divided by 1,281, multiplied by 100 and divided by the study duration of 1.5 years (study duration) to obtain 1.14 cases per 100 exposure episodes per year.

The mean age of the exposed HCWs was 32.7 (SD, 9.95; range, 19–72 years). Among exposed HCWs, 84.9% of them were women, whereas 57.4% were Singaporeans. A total of 38.0% of all exposed HCWs were Chinese, 22.9% were Malays, 13.2% were Indians, and 25.9% were of other ethnicity. In terms of occupation, 77.3% of all exposed HCWs were nurses or nursing students, followed by 1.8% doctors, 14.3% allied health professionals or students, and 5.7% ancillary HCWs. Some 62.2% of all exposed HCWs had only 1 TB exposure, 14.8% had 2 TB exposures, and 23.0% had 3 or more TB exposures (Table 1).

#### Associations between demographic and occupational exposure factors and TB infection

Significant factors associated with baseline LTBI included foreign nationality (relative risk [RR], 1.93; 95% confidence interval [CI], 1.40–2.68), non-Chinese ethnicity (RR, 2.68; 95% CI, 1.76–4.09), and above 40 years of age (RR, 2.81; 95% CI, 2.07–3.83). Despite not reaching statistical significance, the crude risk ratio for baseline LTBI were higher for HCWs in internal medicine 4 to 6 and 10-bedded wards (1.99; 95% CI, 0.99–4.00) as well as those in other medical subspecialties

and psychiatric 4 to 6-bedded wards (RR, 1.92; 95% CI, 0.94–3.91) compared with those in surgical disciplines working in single-bedded OT rooms. After adjusting for age, ethnicity, nationality, sex, and occupation, non-Chinese ethnicity (adjusted RR, 2.16; 95% CI, 1.42–3.29), age above 40 years (adjusted RR, 2.60; 95% CI, 1.90–3.57), and foreign nationality (adjusted RR, 1.69; 95% CI, 1.24–2.31) remained independently associated with baseline LTBI (Table 2).

We also tested for multicollinearity between residency status and ethnicity. The Phi coefficient for association between nationality and ethnicity was 0.1636, whereas the variance inflation factors of nationality and ethnicity were 1.03 and 1.05, respectively, indicating little correlation between these variables in the regression model. As such, there was little collinearity between ethnicity and nationality.

Significant occupational exposure factors associated with QFT-GIT conversion were having >2 TB exposures (RR, 2.78; 95% CI, 1.22–6.35), working in the internal medicine 4 to 6 and 10-bedded wards (RR, 4.853584; 95% CI, 2.998281–7.856928), as well as working in medical subspecialties and psychiatric 4 to 6-bedded wards (RR, 2.774205; 95% CI, 1.138155–6.762005) (Table 3). After adjusting for age, ethnicity, nationality, sex, and occupation, the association between having >2 TB exposure episodes and QFT-GIT conversion was not statistically significant (adjusted RR, 2.24; 95% CI, 0.88–5.72), whereas working in internal medicine 4 to 6 and 10-bedded wards (adjusted RR, 3.772144; 95% CI, 1.867964–7.617423) as well as working in medical subspecialties and psychiatric 4 to 6-bedded wards (adjusted RR, 3.079876; 95% CI, 1.216970–7.794473) remained significantly associated with QFT-GIT conversion (Table 3). The crude and adjusted risk ratios calculated for exposed HCWs working in internal medicine, other medical specialties, and psychiatry compared with those working in surgical disciplines were significantly elevated, as there were no cases of QFT-GIT conversion among exposed surgical HCWs.

#### Association between number of TB exposures and clinical discipline of HCW

A higher proportion of HCWs working in medical subspecialties, psychiatric, or internal medicine wards experienced >2 TB exposures compared with those in surgical disciplines. Among HCWs in surgical

**Table 2**  
Factors associated with baseline TB infection

Variables		Crude risk ratio (95% CI)	P value	Adjusted risk ratio (95% CI)*	P value
Nationality	Singaporean	1	<.001	1	.001
	Foreigner	1.93 (1.40–2.68)		1.69 (1.24–2.31)	
Ethnicity	Chinese	1	<.001	1	<.001
	Non-Chinese	2.68 (1.76–4.09)		2.16 (1.42–3.29)	
Age	<40 years old	1	<.001	1	<.001
	>40 years old	2.81 (2.07–3.83)		2.60 (1.90–3.57)	
Clinical discipline	Surgery	1		1	
	Other medical subspecialties and psychiatry	1.92 (0.94–3.91)	0.073	1.40 (0.68–2.91)	.365
	Internal medicine	1.99 (0.99–4.00)	0.054	1.64 (0.78–3.42)	.190

CI, confidence interval; TB, tuberculosis.

\*Adjusted for age, ethnicity, nationality, sex, and occupation.

**Table 3**  
Factors associated with postexposure latent TB infection

Variables		Crude risk ratio (95% CI)	P value	Adjusted risk ratio (95% CI)*	P value
Number of TB exposure episodes	0–2	1	.012	1	.091
	>2	2.78 (1.22–6.35)		2.24 (0.88–5.72)	
Clinical discipline	Surgery	1		1	
	Other medical subspecialties and psychiatry	2774205 (1138155–6762005)	<.05	3079876 (1216970–7794473)	<.05
	Internal medicine	4853584 (2998281–7856928)	<.05	3772144 (1867964–7617423)	<.05

CI, confidence interval; TB, tuberculosis.

\*Adjusted for age, ethnicity, nationality, sex, and occupation.

disciplines, none experienced >2 TB exposures compared with 37 (11.3%) in medical subspecialties and psychiatry wards, and 166 (36.8%) in internal medicine wards experiencing >2 TB exposures.

## DISCUSSION

Our study found that the baseline prevalence of LTBI among HCWs screened for TB exposure was 14.6%, which was slightly higher than the prevalence of LTBI in our local resident population, which was reported to be 12.7%.<sup>1</sup> Previous studies have demonstrated that the overall prevalence of LTBI among HCWs was 37%,<sup>2</sup> ranging from 7.2%–14.9% in low-burden countries<sup>5,6</sup> to 47% in high-burden countries.<sup>7</sup> A review article by Menzies et al<sup>4</sup> reported that the median prevalence of LTBI was 63% (33%–79%) among HCWs in low- to middle-income countries, and 24% (4%–46%) among HCWs in high-income countries. Therefore, the baseline prevalence of LTBI among HCWs in our study reflects that in low-burden high-income countries. However, our study only obtained baseline LTBI prevalence among HCWs screened for TB exposure, which may not be representative of all the HCWs in the hospital. In addition, the prevalence of baseline LTBI in our study was obtained by calculating the proportion of HCWs with positive QFT-GIT at T0 for each exposure event, which will be an underestimation as it excludes those who had TB infection in the past and were not screened with QFT-GIT at baseline.

Age above 40 years, non-Chinese ethnicity, and foreign nationality were associated with baseline LTBI both in the bivariate analysis as well as in the multivariable analysis after adjusting for age, ethnicity, nationality, sex, and occupation. This could be due to foreign HCWs coming from countries with a higher prevalence of TB transmission. Although the incidence of TB in Singapore was 300 cases per 100,000 population in 1960, the incidence rate has declined to 47 per 100,000 by 2017, owing to an active TB control program. This rate is much lower than that of neighboring countries, including the Philippines, which has a TB incidence rate of 554 cases per 100,000 population.<sup>8</sup> As such, foreign HCWs and HCWs of non-Chinese ethnicity above 40 years of age may be at increased risk of baseline LTBI unrelated to occupational TB exposure at work. TB screening of all exposed HCWs at baseline is therefore important to distinguish between baseline LTBI unrelated to work and work-related QFT-GIT conversion

postexposure. HCWs with recent occupationally acquired LTBI are at higher risk of TB activation within the first 2 years.

Our findings on risk factors for baseline LTBI were similar to previous studies, which demonstrated that increased age<sup>9,10</sup> and foreign origin<sup>11</sup> were risk factors for baseline LTBI among HCWs. Other factors associated with baseline LTBI reported in previous studies include working as a nurse<sup>12,13</sup> or physician,<sup>5</sup> being a man, and having diabetes mellitus.<sup>14</sup> Our study, however, did not find any statistically significant association between occupational groups/sex and baseline LTBI.

Out of all the HCWs screened for LTBI, only 2.5% of them experienced QFT-GIT conversion, with an incidence rate of 1.14 cases per 100 exposure episodes per year. In comparison, TB contact tracing investigations in the United States found 23% with LTBI and 1% with active TB disease. This could be because of an overly cautious TB contact tracing protocol, which identifies someone as a TB contact if he or she has been exposed to an index TB case at the same location with shared air supply for >8 hours cumulatively. Moreover, the area dimensions of the locations covered for screening of potential TB contacts may have been too broad, involving those who may not have had close contact with the index TB patient. The TB contact tracing protocol also does not take into account the characteristics of the index patient, susceptibility and vulnerability of contacts, and circumstances of exposure, which have been used to assign priorities for contact investigations by the US Centers for Disease Control and Prevention.<sup>15</sup> This “stone in the pond” risk stratified approach to TB contact tracing has also been used in a tertiary care hospital in Singapore. As such, further studies are needed to better refine our contact tracing protocol through risk stratification based on exposure settings, as well as characteristics of the index patient and contacts.<sup>16</sup>

The number of TB exposure episodes per HCW was associated with QFT-GIT conversion in the bivariate analysis. HCWs with 3 or more TB exposure episodes were 2–3 times as likely to develop LTBI compared with those with only 1 or 2 exposure episodes. This finding is supported by Menzies et al<sup>4</sup> who reported that the occurrence of TB infection among HCWs was associated with the likelihood of TB exposure, as estimated by the annual number of TB admissions as well as the presence or absence of adequate TB infection control measures. In other words, the higher the likelihood of TB exposure and/or the poorer the infection control measures, the higher the risk of TB acquisition among exposed HCWs. HCWs in medical subspecialties, psychiatric, and

internal medicine wards were more likely to experience >2 TB exposures compared with those working in surgical disciplines OT rooms. As such, our study also reported that HCWs in medical subspecialties and psychiatric 4 to 6-bedded wards as well as internal medicine 4-6 and 10-bedded wards were more likely to develop LTBI compared with those in surgical disciplines OT rooms. On a separate note, although a study done in Italy reported that older age was associated with postexposure LTBI,<sup>17</sup> our study did not find any statistically significant association between old age and postexposure LTBI.

As such, measures should be taken to reduce TB exposure among HCWs by having a high index of suspicion and early diagnosis of pulmonary TB cases, as well as educating HCWs on the strict compliance to the donning of appropriate personal protective equipment during patient care. These measures should also be targeted toward HCWs in clinical disciplines more likely to be exposed to repeated TB exposures and at risk of developing LTBI such as internal medicine, medical subspecialties, and psychiatry with multibedded wards. Although HCWs in Singapore still routinely diagnose TB in patients, there could be delays in diagnosis and isolation. The delay in diagnosis could be due to (1) patients with negative AFB sputum smear but culture-positive pulmonary TB<sup>18</sup>; (2) pulmonary TB patients but atypical chest radiographic findings<sup>19</sup>; (3) difficulties in obtaining sputum specimen of sufficient quality for AFB smear<sup>20</sup>; (4) low awareness of TB among HCWs owing to decline in TB rates among local population following stricter TB infection control measures implemented since 1997<sup>21</sup>; and (5) diverse manifestations of TB masquerading as other diseases.<sup>22</sup> A systemic review found that mean health care system delay in diagnosis of TB in both inpatient and outpatient settings was 28.4 days in low-middle income countries and 21.5 days in high-income countries.<sup>23</sup> Delays in isolation could be because of (1) resistance to isolation among patients and family members because of inconveniences and social isolation<sup>24</sup>, and (2) shortage of dedicated negative-pressure single-bedded rooms, which was exacerbated by a need to reserve standby single-bedded isolation rooms for emerging infectious diseases like avian influenza A and Middle East respiratory syndrome coronavirus.<sup>25</sup>

To reduce likelihood of TB exposure and decrease the risk of TB infection among HCWs, measures should be taken to minimize unnecessary delay in diagnosis and isolation of patients with pulmonary TB. This could be achieved by (1) developing and implementing clear clinical guidelines on the diagnostic pathway and isolation protocols for patients with suspected TB; (2) encouraging same-day sputum AFB smear microscopy for all patients with suspected pulmonary TB, which is faster and as effective as standard AFB smear microscopy over 2 separate days<sup>26</sup>; (3) increase availability of sputum induction facilities to improve diagnostic yield in patients with suspected TB<sup>27</sup>; (4) increase supply of single-bedded isolation rooms; and (5) raise awareness of TB among HCWs.

The main limitations of our study were the nonavailability of certain TB exposure details, which could affect the likelihood of an HCW's acquisition of LTBI such as cumulative exposure time and proximity of contact. Furthermore, there could be nonresponse bias from 66 exposed HCWs who defaulted all their QFT-GIT blood test as well as missing data from HCWs who may have missed some of their QFT-GIT blood test appointments. Despite having missing information on the 66 exposed HCWs, we were not aware of any exposed HCWs who developed active TB during and 3 months after the study period. Also, given that Singapore is endemic for TB with an incidence rate of 47 per 100,000 in 2017, HCWs who experienced QFT-GIT conversion may have contracted TB outside of the health care setting and not attributable to his or her exposure to TB patients in the hospital. Further studies may be needed to identify other occupational exposure risk factors associated with TB infection, such as cumulative duration of exposure and geospatial mapping of HCWs' contact with TB index cases. To aid in this endeavor, physicians caring for exposed HCWs should complete a standardized TB exposure form to better document pertinent details

of the TB exposure episode. Future studies should also include a cost-effectiveness analysis of the TB contact investigation protocols to better inform TB contact tracing policies.

## CONCLUSIONS

Only 2.5% of all HCWs screened had QFT-GIT conversion postexposure. This is very low considering the complexity and cost of contact tracing. Although our study identified certain demographic risk factors such as foreign nationality, non-Chinese ethnicity, and above 40 years of age to be independently associated with baseline LTBI unrelated to TB exposures at work, further studies are needed to identify occupational exposure risk factors to develop a risk-stratified TB contact investigation protocol, which is likely to be more cost-effective. Moreover, as repeated TB exposures are associated with QFT-GIT conversion, measures should be taken to reduce TB exposure among HCWs in high-risk wards.

## References

1. Yap P, Tan K, Lim W, Barkham T, Tan L, Chen M, et al. Prevalence of and risk factors associated with latent tuberculosis in Singapore: a cross-sectional survey. *Int J Infect Dis* 2018;72:55-62.
2. Uden L, Barber E, Ford N, Cooke GS. Risk of tuberculosis infection and disease for health care workers: an updated meta-analysis. *Open Forum Infect Dis* 2017;4:3.
3. Diel R, Seidler A, Nienhaus A, Rusch-Gerdes S, Niemann S. Occupational risk of tuberculosis transmission in a low incidence area. *Respir Res* 2005;6:35.
4. 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.
5. Schablon A, Beckmann G, Harling M, Diel R, Nienhaus A. Prevalence of latent tuberculosis infection among health care workers in a hospital for pulmonary diseases. *J Occup Med Toxicol* 2009;4:1.
6. Lamberti M, Muoio M, Arnesi A, Borrelli S, Di Lorenzo T, Garzillo E, et al. Prevalence of latent tuberculosis infection in healthcare workers at a hospital in Naples, Italy, a low-incidence country. *J Occup Med Toxicol* 2016;11:53.
7. Nasreen S, Shokoohi M, Malvankar-Mehta MS. Prevalence of latent tuberculosis among health care workers in high burden countries: a systematic review and meta-analysis. *PLoS One* 2016;11:e0164034.
8. World Health Organization. Tuberculosis country profiles. Available from: <http://www.who.int/tb/country/data/profiles/en/>. Accessed February 16, 2019.
9. Jo KW, Hong Y, Park JS, Bae IG, Eom JS, Lee SR, et al. Prevalence of latent tuberculosis infection among health care workers in South Korea: a multicenter study. *Tuberc Respir Dis* 2013;75:18-24.
10. Park JS. The prevalence and risk factors of latent tuberculosis infection among health care workers working in a tertiary hospital in South Korea. *Tuberc Respir Dis (Seoul)* 2018;81:274-80.
11. Ringshausen FC, Schlösser S, Nienhaus A, Schablon A, Schultze-Werninghaus G, Rohde G. In-hospital contact investigation among health care workers after exposure to smear-negative tuberculosis. *J Occup Med Toxicol* 2009;4:11.
12. Rafiza S, Rampal K, Tahir A. Prevalence and risk factors of latent tuberculosis infection among health care workers in Malaysia. *BMC Infect Dis* 2011;11:19.
13. Prado TND, Riley LW, Sanchez M, Fregona G, Nóbrega RLP, Possuelo LG, et al. Prevalence and risk factors for latent tuberculosis infection among primary health care workers in Brazil. *Cad Saúde Pública* 2017;33:e00154916.
14. Yeon J, Seong H, Hur H, Park Y, Kim Y, Park Y, et al. Prevalence and risk factors of latent tuberculosis among Korean healthcare workers using whole-blood interferon- $\gamma$  release assay. *Sci Rep* 2018;8:10113.
15. National Tuberculosis Controllers Association; Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. *MMWR Recomm Rep* 2005;54:1-47.
16. Bagdasarian N, Chan HC, Ang S, Isa MS, Chan SM, Fisher DA. 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;38:1509-11.
17. Muzzi A, Seminari E, Feletti T, Scudeller L, Marone P, Tinelli C, et al. Post-exposure rate of tuberculosis infection among health care workers measured with tuberculin skin test conversion after unprotected exposure to patients with pulmonary tuberculosis: 6-year experience in an Italian teaching hospital. *BMC Infect Dis* 2014;14:324.
18. Zhang ZX, Sng LH, Yong Y, Lin LM, Cheng YW, Seong NH, et al. Delays in diagnosis and treatment of pulmonary tuberculosis in AFB smear-negative patients with pneumonia. *Int J Tuberc Lung Dis* 2017;21:544-9.
19. Marciniuk D, McNab B, Martin W, Hoepfner V. Detection of pulmonary tuberculosis in patients with a normal chest radiograph. *Chest* 1999;115:445-52.
20. Kalimuddin S, Tan JM, Tan BH, Low JG. A retrospective review of a tertiary hospital's isolation and de-isolation policy for suspected pulmonary tuberculosis. *BMC Infect Dis* 2014;14:547.

21. Chee CB, Gan SH, Chua AP, Wang YT. TB control in Singapore: the high price of diagnostic delay. *Singapore Med J* 2012;53:505-7.
22. Teo SK. Tuberculosis—barriers to early diagnosis. *Singapore Med J* 2002;43:169.
23. Sreeramareddy CT, Panduru KV, Menten J, Van den Ende J. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. *BMC Infect Dis* 2009;9:91.
24. Haldar S, Filipkowski A, Mishra SR, Brown CS, Elera RG, Pollack AH, et al. “Scared to go to the hospital”: inpatient experiences with undesirable events. *AMIA Annu Symp Proc* 2017;2016:609-17.
25. Fang J. S'pore prepared for inevitable MERS case: PM. *Today Online*, 11 June 2015. Available from: <https://www.todayonline.com/singapore/singapore-prepared-mers-threat-pm-lee>. Accessed February 17, 2019.
26. Davis JL, Cattamanchi A, Cuevas LE, Hopewell PC, Steingart KR. Diagnostic accuracy of same-day microscopy versus standard microscopy for pulmonary tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2013;13:147-54.
27. Li LM, Bai LQ, Yang HL, Xiao CF, Tang RY, Chen YF, et al. Sputum induction to improve the diagnostic yield in patients with suspected pulmonary tuberculosis. *Int J Tuberc Lung Dis* 1999;3:1137-9.