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Use of interferon gamma release assay to assess latent tuberculosis infection among healthcare workers in Hong Kong

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KEY MESSAGES

1. Overall baseline interferon gamma release assay positivity was 20.7%.
2. The conversion to interferon gamma release assay positivity at 3 months was 8.85% in the exposed group and 4.54% in the non-exposed group using the conventional cut-off of 0.35 IU/mL.
3. When grey zone results (0.2I-0.7 IU/mL) were included, the proportion of non-specific conversions and reversions could be reduced.
4. Interferon gamma release assay can be an adjunct tool in contact investigation of latent tuberculosis infection in healthcare workers.

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Introduction

Tuberculosis (TB) is a highly infectious airborne disease. Healthcare workers are at increased risk of contracting infection because of exposure to a concentration of infectious patients in their work environment. Contact investigations are hampered by the lack of specific markers. The tuberculin skin test (TST) has been used to diagnose latent tuberculosis infection (LTBI) with variable success, as the majority of local residents have been inoculated with Bacillus Calmette-Guérin (BCG) vaccine at birth.[1]

In-vitro interferon gamma release assay (IGRA) including QuantiFERON-TB Gold In-Tube (QFT-GIT) can identify individuals infected with TB who have been vaccinated with BCG. It is non-invasive, with no 'booster' effect from repeated testing, and less painful compared with TST. Nonetheless, its applicability to daily use including contact investigation remains unclear, owing to the complex biological basis of IGRA.

Methods

This was a prospective cohort study. Healthcare workers from three acute hospitals with or without unprotected exposure to smear-positive TB patients were recruited between 1 January 2010 and 30 June 2011 and followed up until 30 June 2012 using QFT-GIT, as per the manufacturer's recommendations.[2] The two groups were matched for sex, age, rank, and department. Outcome measures included the baseline positive rate, the conversion and reversion over time, and the associated factors.

The number of years as a healthcare worker and the exposure incident including nature and duration were recorded. Blood samples were taken at baseline, 3 months, 6 months, and 12 months. Any participants with ambiguous QFT-GIT results or symptoms suggestive of active TB were encouraged to seek medical advice from microbiologists of the investigation team. They were then referred to respiratory physicians for further assessment using sputum AFB smear, culture, and chest radiography.

Results

A total of 159 exposed and 120 non-exposed healthcare workers aged 22 to 63 (mean, 39.2) years were recruited. The mean number of years as a healthcare worker was 11.48 (range, 0.1-43) years. The female-to-male ratio was 82.4:17.6; 59.5% of participants were nurses. Participants were recruited from non-admission medical wards (26.2%), medical admission wards (23.3%), orthopaedic wards (24.4%), surgical wards (13.3%), and others (12.9%). Baseline characteristics of the two groups were comparable. A total of 46 TB contact investigations were performed.

The baseline QFT-GIT positivity for the exposed and non-exposed groups was 19.5% and 20.8%, respectively (relative risk [RR]=0.96, 95% CI=0.74-1.25, P>0.05). It was associated with age ≥40 years (RR=1.62, 95% CI=1.23-2.11), and working

as a healthcare worker for ≥10 years (RR=1.44, 95% CI=1.15-1.79). Department or staff type was not associated with baseline positivity.

Regarding conversion and reversion over time, the AFB smear positivity of the index patients was as follows: AFB + 34.5%, ++ 12.8%, and +++ 52.7%. The mean number of hours of exposure was 27.08 (range, 8-220). Using a conventional cut-off of 0.35 IU/mL, 142 and 113 subjects from the exposed and non-exposed group had >1 specimen for assessment of conversion or reversion, respectively. For the respective groups, conversion at 3 months was 8.85% (10/113) and 4.54% (4/88) (RR=1.30, 95% CI=0.91-1.85), whereas conversion was detected in 14.2% (16/113) and 13.6% (12/88), and reversion occurred in 25% (7/28) and 29.2% (7/24). When a grey zone of 0.2 to 0.7 IU/mL was implemented, 133 and 106 participants in the respective groups were eligible for analysis: conversion at 3 months was 2.97% (3/101) and 1.03% (1/79), whereas conversion during the study period was 4.95% (5/101) and 3.79% (3/79), and reversion occurred in 13.6% (3/22) and 0% (0/13).

Eight participants asked about their QFT-GIT results; two of them had sputum and chest radiographs examined and all were negative. No participant required consultation with a chest physician. One participant from the non-exposed group developed active TB. The three blood results were all >1 IU/ml. No participant from the exposed group had active TB.

Discussion

Conversion to positivity at 3 months was adequate to determine the infection status of contacts. The 3-month period is also the time frame required to exclude a false negative TST result following TB exposure.[3]

The overall baseline positivity rate was 20.7% using the conventional cut-off point. The exact significance of QFT-GIT positivity is not clearly understood. Although it is mostly implicated as diagnostic for LTBI, it can also represent a state of active TB infection, or even treated TB infection. QFT-GIT has consistently shown a higher specificity than TST, especially in BCG-vaccinated populations.

Conversion is generally interpreted as the acquisition of TB infection after a definitive history of TB exposure. False conversion can be due to

TABLE 1. Participant characteristics*

Characteristics	Overall (n=279)	Exposed (n=159)	Non-exposed (n=120)	P value (exposed vs non-exposed)
Age (years)	39.20±10.68 (63-22)	39.79±10.64 (58-22)	38.41±10.73 (63-22)	>0.05
No. of years as a healthcare worker	11.48±9.12 (43-0.1)	11.43±9.10 (37-0.1)	11.56±9.19 (43-0.5)	>0.05
Age-group (years)				>0.05
<30	62 (22.7)	34 (21.8)	28 (23.9)	
30-39	93 (34.1)	48 (30.8)	45 (38.5)	
40-49	55 (20.1)	35 (22.4)	20 (17.1)	
≥50	63 (23.1)	39 (25.0)	24 (20.5)	
No. of years as a healthcare worker				>0.05
<10	122 (46.2)	70 (47.3)	52 (44.8)	
≥10	142 (53.8)	78 (52.7)	64 (55.2)	
Sex				>0.05
Female	230 (82.4)	134 (84.3)	96 (80.0)	
Male	49 (17.6)	25 (15.7)	24 (20.0)	
Ward/department				<0.05
Medical	73 (26.2)	42 (26.4)	31 (25.8)	
Medical admission	65 (23.3)	44 (27.7)	21 (17.5)	
Orthopaedics	68 (24.4)	15 (9.4)	53 (44.2)	
Surgical	37 (13.3)	33 (20.8)	4 (3.3)	
Others	36 (12.9)	25 (15.7)	11 (9.2)	
Staff type				>0.05
Nursing	166 (59.5)	95 (59.7)	71 (59.2)	
Allied health, supporting, and others	113 (40.5)	64 (40.3)	49 (40.8)	

* Data are presented as mean±SD (range) or No. (%) of participants

TABLE 2. QuantiFERON-TB Gold In-Tube (QFT-GIT) test results

QFT-GIT test	No. (%) of participants			Relative risk (95% CI)
	Overall (n=279)	Exposed (n=159)	Non-exposed (n=120)	
Baseline				0.96 (0.74-1.25)
Positive	56 (20.1)	31 (19.5)	25 (20.8)	
Negative or indeterminate*	223 (79.9)	128 (80.5)	95 (79.2)	
Conversion to positivity in the 2nd blood sample				1.30 (0.91-1.85)
Yes	14 (6.9)	10 (8.8)	4 (4.5)	
No	189 (93.1)	104 (91.2)	85 (95.5)	

* Three indeterminate results (one from exposed and two from non-exposed group)

TABLE 3. Association between participant characteristics, exposure details, and baseline positivity

Variables	No. (%) of participants		P value (positive vs negative/ indeterminate)	Relative risk (95% CI)
	Baseline positive (n=56)	Baseline negative/ indeterminate (n=223)		
Exposure			>0.05	0.96 (0.74-1.25)
Non-exposed (reference)	25 (20.8)	95 (79.2)		
Exposed	31 (19.5)	128 (80.5)		
AFB result of the index patient			>0.05	-
Non-exposed	25 (20.8)	95 (79.2)		
+	7 (13.7)	44 (86.3)		
++	4 (21.1)	15 (78.9)		
+++	17 (21.8)	61 (78.2)		
Age (years)			<0.05	1.62 (1.23-2.11)
<40 (reference)	20 (12.9)	135 (87.1)		
≥40	33 (28.0)	85 (72.0)		
No. of years as healthcare worker			<0.05	1.44 (1.15-1.79)
<10 (reference)	15 (12.3)	107 (87.7)		
≥10	37 (26.1)	105 (73.9)		
Sex			>0.05	0.78 (0.39-1.56)
Female (reference)	48 (20.9)	182 (79.1)		
Male	8 (16.3)	41 (83.7)		
Ward/department			>0.05	-
Medical	14 (19.2)	59 (80.8)		
Medical admission	13 (20.0)	52 (80.0)		
Orthopaedics	13 (19.1)	55 (80.9)		
Surgical	6 (16.2)	31 (83.8)		
Others	10 (27.8)	26 (72.2)		
Staff type			>0.05	1.07 (0.76-1.51)
Nursing (reference)	32 (19.3)	134 (80.7)		
Allied Health, supporting and others	24 (21.2)	89 (78.8)		

concomitant illness, non-specific boosting, and fluctuation of IFN-gamma responses, as well as laboratory factors. When analysing risk factors for conversion at 3 months for the exposed group, age ≥40 was a significant risk (RR=1.96, 95% CI=1.30-2.96), raising the possibility of an immune-boosting phenomenon. No relationship between conversion and TB disease was identified; thus longer follow-

up is required. Reversion may be due to a 'false positive' in the first specimen, or spontaneous immune clearing of the infection with TB treatment. 'Wobbling phenomenon' may be due to one or more factors mentioned above. In one longitudinal study, contacts with precisely defined exposure in point-source outbreaks were monitored serially. Subjects who had transiently positive IGRA results were identified; there was a possibility that some contacts may have acquired, and spontaneously cleared, a transient *M tuberculosis* infection.[4] Nonetheless, an immune-boosting phenomenon is a more likely explanation. In the present study, transient change of positivity/negativity was noted in 16 participants.

Non-specific conversion and reversion is a cause of concern, as this might precipitate unnecessary LTBI treatment. Participants with results close to the cut-off value of 0.35 IU/mL tended to have more non-specific conversions and reversions. A high positive result of >1.0 IU/mL tended to remain positive. For this reason, a grey zone of 0.2-0.7 IU/mL is proposed. Results outside this zone are presumed to be true negatives or positives. In the present study, the use of a grey zone significantly reduced the number of conversions and reversions. Whether this reduction represents a true improvement in detection of true conversion and reversion has yet to be confirmed. In addition, the current FDA-approved package insert and management guidelines do not provide advice on interpretation of results in the grey zone.[5]

As the high positive result of >1.0 IU/mL tends to remain positive, quantitative measurements for IGRAs should be reported.[3] This may be highly relevant as the only participant that developed active TB disease had high values (>1 IU/mL). Nonetheless, there are no interpretive guidelines for the quantitative levels. The following approach to interpretation has been recommended: (1) quantitative results should not be used for prognostic or therapeutic monitoring purposes at this time, and (2) if the quantitative results are close to cut-off values, reversion or conversion is more likely upon re-testing.[5]

The most appropriate contact investigation procedure in Hong Kong hospitals remains controversial. In our study, the baseline LTBI rate was quantified as 20.7%. For IGRA, the exposed group had a tendency to convert at 3 months, regardless of the cut-off value, indicating an association between TB exposure and conversion. Despite the large cohort, none of the exposure events reached the threshold of AFB +++ with exposure ≥120 hours arbitrarily set by the infection control team of the Queen Elizabeth Hospital. Repeated immune boosting might be a significant cause of QFT-GIT positivity, as evidenced by the association of baseline positivity with age ≥40 years and working as a healthcare worker for ≥10 years, as well as more conversion with age ≥40 years. No clear association between QFT-GIT positivity and active TB disease was found, possibly owing to the short follow-up duration of one year.

Further studies to include longer term serial monitoring, other TB exposure events, and the prognostic implication of IGRA in the development of active TB disease are warranted.

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