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## **Use of tuberculin skin test, chest radiograph and interferon-gamma release assay to select migrants for treatment of latent tuberculosis**

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# Use of tuberculin skin test, chest radiograph and interferon-gamma release assay to select migrants for treatment of latent tuberculosis

Michael G Flynn, Megan A Rees, Ayesha Saqib

## Abstract

Australian guidelines recommend the tuberculin skin test (TST) as the preferred test for latent tuberculosis infection (LTBI) with interferon-gamma release assay (IGRA) as a supplemental test to improve specificity. For many years the chest radiograph has been used to interpret a TST in the 5-9 mm range. The chest radiograph is known to predict subsequent reactivation of tuberculosis (TB). We report a retrospective database review of the Migrant Screening Clinic at Western Health Footscray Hospital during the period April 2010 to November 2011. Of 129 migrants under 35 years of age with TST 5-14 mm, IGRA was positive in 37 (28.7%). IGRA was positive in 7.7% of those with TST 5-9 mm and chest radiograph not suggestive of TB disease, 28.6% in those with TST 5-9 mm and chest radiograph that was suggestive of TB disease, and 39.5% in those with TST 10-14 mm ( $\chi^2$  trend=12.5,  $p=0.0004$ ). There were 21 (16%) of 129 persons who had a negative IGRA but both TST  $\geq 5$  mm and a chest radiograph suggestive of TB disease. These data support existing recommendations to use the chest radiograph when interpreting a TST of 5-9 mm and recommending treatment of LTBI.

Keywords: screening; migrants; tuberculin; IGRA; latent tuberculosis

## Introduction

The detection and prevention of active TB developing after migration is a priority in both Victorian state and Australian national TB control strategies.<sup>1,2</sup> Australian guidelines recommend the tuberculin skin test (TST) as the preferred test for latent TB infection (LTBI) with interferon-gamma release assay (IGRA) as a supplemental test to improve specificity.<sup>3</sup> A recent Victorian study of TB contact tracing found the most common reason for performing IGRA was to increase the specificity of a TST in the 10-14 mm range.<sup>4</sup>

Australian research shows the annual incidence rate of TB in refugees increases with TST reaction size up to 30 mm, but is unrelated to bacille Calmette-Guérin (BCG) scar status.<sup>5</sup> QuantiFERON-TB Gold is an interferon-gamma release assay (IGRA), which is known to be

more specific for TB than the TST.<sup>6</sup> While some studies have suggested IGRA may have a better predictive value than tuberculin,<sup>7-9</sup> others have not.<sup>10,11</sup> A recent review by the World Health Organization (WHO) found that in pooled estimates of the predictive utility of IGRA and TST, in head-to-head studies, the confidence intervals around risk ratio and incidence risk ratio for the TST and IGRA overlapped and were imprecise.<sup>12</sup> IGRA has been reported to have high negative predictive value in contact tracing studies,<sup>13-15</sup> as well as screening studies in asylum seekers.<sup>16</sup>

Under arrangements with the Department of Health and Human Services Victoria, the Migrant Screening Clinic (MSC) in the Department of Respiratory and Sleep Disorders Medicine at Footscray Hospital Western Health has provided post-migration screening for TB in Victoria since 1996. Migrants who have been found to have an abnormal chest radiograph at

the time of visa application are referred to the MSC by the Department of Immigration and Border Protection.<sup>17</sup> The MSC is a screening service, seeing each person once, and referring persons who need further assessment to other health services.<sup>18,19</sup> Persons with symptoms suggestive of TB, or with one or more chest radiographs suggestive of active TB, are defined as suspected active TB and referred to other specialist clinics. The Victorian Government TB program is advised of non-attendees with a chest radiograph suggestive of active TB; TB program nurses are asked to contact the person, and may make a home visit. Those without such features, but with a history of TB diagnosis, a positive TST or IGRA, or one or more chest radiographs thought likely to represent previous TB, are defined as inactive TB.

Migrants are offered a TST if under 35 years of age and the chest radiograph is abnormal, or if under 35 years of age and a refugee,<sup>20</sup> or if under 35 years of age and born in one of the high burden countries whose migrants have the highest TB incidence in Victoria.<sup>21,22</sup> The age of 35 years was chosen because the frequency and severity of isoniazid associated hepatitis increase with age.<sup>23</sup> During the period under review (April 2010 to November 2011) chest radiographs were classified as described by Linh et al.<sup>24</sup> Migrants with a TST of 15 mm or greater were offered referral for treatment for LTBI. If the TST was in the range 5-14 mm, a QuantiFERON-TB Gold assay (Cellestis, Australia) was performed. The result was reported as positive, negative or indeterminate according to the manufacturer's guidelines. Those with a positive or indeterminate QuantiFERON-TB Gold were offered referral for consideration of treatment for LTBI.

We examine whether a comparison of TST and IGRA in our population supports the use of the chest radiograph to interpret TST.

## Methods

### Study population

In this observational study all persons under 35 years of age with TST and chest radiograph per-

formed in the MSC during the period April 2010 to November 2011 were identified from a search of the Migrant Screening database. The information extracted included the chest radiograph classification, the results of TST and IGRA, and whether the migrant was referred for follow-up.

TST was considered positive according to the criteria of the American Thoracic Society (ATS),<sup>25</sup> which are the criteria recommended in Victoria.<sup>1</sup> The ATS criteria are that a TST is positive at  $\geq 10$  mm, or at 5-9 mm if the chest radiograph demonstrates old fibrotic lesions thought to represent previous infection with TB. In this study, a TST of 5-9 mm was considered positive if the chest radiograph was classified as probable previous pulmonary TB disease (category 4a) or parenchymal infiltrate typical for TB (category 5a) as described by Linh et al.<sup>24</sup>

### Statistics

Proportion of those tested who were IGRA positive by TST category was examined using  $\chi^2$  for trend (Mantel extension, Epi Info v.6). Agreement between TST and IGRA was expressed as proportion in agreement, and corrected for chance agreement as Cohen's kappa statistic  $\kappa$  with 95% confidence interval (CI).<sup>26</sup>

### Ethics approval

The study was approved by the Melbourne Health Human Research Ethics Committee and Western Health Office for Research.

### Results

In the 19 months between April 2010 and November 2011, a total of 2,430 persons attended the MSC for an initial assessment. There were 509 migrants under the age of 35 years with chest radiograph and TST. Eight persons with TST in the 5-14 mm range did not have IGRA performed and were excluded from analysis. Three persons with indeterminate IGRA were also excluded from analysis. Demographics, BCG status and TST results of the remaining 498 persons are shown in Table 1. There was no

**Table 1. Demographics, BCG status and TST category**

<b>Number of migrants</b>	<b>498</b>
<b>Females</b>	45%
<b>Age (years)</b>	
Mean	26.5
Median	26
Range	16-34
<b>Country of Birth</b>	
India	36.5%
China	15.3%
Nepal	6.8%
Other	38.8%
Unknown	2.6%
Total	100.0%
<b>BCG scar</b>	
Present	46.8%
Absent	16.3%
Unknown	36.9%
Total	100.0%
<b>TST category (n)</b>	
0-4 mm	131
5-9 mm	53
10-14 mm	76
>=15 mm	238
Total	498

difference between mean TST in those with a BCG scar (15.4 mm) and those without a BCG scar (15.5 mm).

IGRA was performed in 129 migrants whose TST was in the range 5-14 mm. IGRA results after stratifying the TST 5-9 mm category by chest radiograph findings are shown in table 2. IGRA was positive in 7.7% of those with TST 5-9 mm and chest radiograph not suggestive of TB disease, 28.6% in those with TST 5-9 mm and chest radiograph that was suggestive of TB disease, and 39.5% in those with TST 10-14 mm ( $\chi^2$  trend=12.5,  $p=0.0004$ ). When TST of 10-14 mm is also stratified by chest radiograph findings, there is relatively little difference in the proportion positive by IGRA: 38.6% in those with a chest radiograph not suggestive of TB disease, 42.1% in those with a chest radiograph that was suggestive of TB disease (table 3,  $\chi^2$  trend=11.8,  $p=0.0006$ ).

When TST was considered positive at  $\geq 10$  mm, the proportion in agreement with IGRA was 59% (95%CI 50-67), Cohen's kappa statistic  $\kappa = 0.24$  (0.08-0.39). When TST was also considered positive at 5-9 mm if the chest radiograph showed probable previous pulmonary TB disease (category 4a) or parenchymal

**Table 2. Proportion IGRA positive by TST category, stratified by chest radiograph for TST 5-9 mm, as recommended by ATS.**

TST Category	n	IGRA negative n	IGRA positive n	IGRA positive (row %)
5-9 mm without radiographic disease	39	36	3	7.7*
5-9 mm with radiographic disease	14	10	4	28.6*
10-14 mm	76	46	30	39.5*
Total	129	92	37	28.7

\*  $\chi^2$  trend=12.5,  $p=0.0004$

**Table 3. Proportion IGRA positive by TST category, stratified by chest radiograph for both TST 5-9 and 10-14 mm categories.**

TST Category	n	IGRA negative n	IGRA positive n	IGRA positive (row %)
5-9 mm without radiographic disease	39	36	3	7.7*
5-9 mm with radiographic disease	14	10	4	28.6*
10-14 mm without radiographic disease	57	35	22	38.6*
10-14 mm with radiographic disease	19	11	8	42.1*
Total	129	92	37	28.7

\*  $\chi^2$  trend=11.8,  $p=0.0006$

**Table 4. Agreement between TST and IGRA for different criteria of positive TST**

	TST positive if $\geq 10$ mm		TST positive if $\geq 10$ mm, or if 5-9 mm and radiographic disease	
	n	%	n	%
TST negative - IGRA negative	46	35.7	36	27.9
TST negative - IGRA positive	7	5.4	3	2.3
TST positive - IGRA negative	46	35.7	56	43.4
TST positive - IGRA positive	30	23.3	34	26.4
Total	129	100	129	100

infiltrate typical for TB (category 5a), proportion in agreement was 54% (46-63),  $\kappa = 0.22$  (0.07-0.36). In comparison to a 10 mm cut-off, use of the ATS criteria resulted in 14 persons changing from TST negative to positive, 10 of whom were IGRA negative and 4 of whom were IGRA positive (table 4).

Using the ATS criteria there were 328 persons with positive TST, comprising 14 with TST 5-9 mm plus fibrotic lesions on chest radiograph, 76 with TST 10-14 mm and 238 with TST  $\geq 15$  mm. If supplemental IGRA is used to interpret TST in the 5-14 mm range there were 275 persons with LTBI, comprising 37 with TST 5-14 mm plus positive IGRA, and 238 with TST  $\geq 15$  mm in whom IGRA was not performed. Of those 275 persons 264 (96%) were referred for follow-up. There were 21 (16%) of 129 persons who had a negative IGRA but both TST  $\geq 5$  mm and a chest radiograph considered consistent with fibrotic TB disease, of whom 6 (29%) were referred for follow-up.

## Discussion

In this study of migrants with a TST of 5-14 mm the presence of a chest radiograph suggestive of TB disease made a positive IGRA more likely, probably because the combination of TST and suggestive chest radiograph is more specific for LTBI than a positive TST with normal radiograph. Our data show that a chest radiographic finding of TB disease has a large effect on the chance of a positive IGRA when TST is 5-9 mm (28.6% versus 7.7%), but little effect when TST is 10-14 mm (42.1 versus 38.6%). Although proportion in agreement was not improved when TST was considered positive in the presence of

radiographic TB disease, the  $\chi^2$  for trend analysis is highly significant and supports the ATS recommendation to use the chest radiograph when interpreting a TST of 5-9 mm.<sup>25</sup> Given that a chest radiograph suggestive of previous TB is known to predict subsequent active TB,<sup>24</sup> we believe that the chest radiograph should remain important to interpreting the TST, and in considering whether to recommend treatment of LTBI.

A direct measurement tool for LTBI in humans is currently unavailable.<sup>12</sup> The presence of mycobacteria capable of causing reactivation TB cannot be directly detected by current methods such as bacterial culture, amplification of genomic material or detection of expressed proteins. Instead, evidence of their presence must be deduced from a specific immune response (TST, IGRA), or observing historical targeted inflammatory responses such as chest radiograph abnormalities, or by observation over time until reactivation disease occurs. This epidemiological information has been combined to determine estimates of TB reactivation in individuals.<sup>27</sup> Incorporating the chest radiograph in the assessment of likelihood of TB reactivation is particularly pertinent in patients who may have an attenuated immune response.<sup>28</sup>

Criteria for the diagnosis of LTBI in migrants from high incidence countries vary. In 1999, the ATS recommended targeted testing of persons at high risk for developing TB, and that a TST was positive at 10 mm or more in recent immigrants from high prevalence countries, or at 5 mm or more in persons with a chest radiograph demonstrating fibrotic lesions thought to represent previous TB disease.<sup>25</sup> We do not use BCG

status in the interpretation of TST because the ATS recommendation is that a positive TST in BCG-vaccinated persons indicates TB infection when the person tested is at increased risk for recent infection;<sup>25</sup> and because a cohort study of Australian refugees found the incidence of active TB increased with the size of the TST, but that BCG status was not significant in multivariate analysis.<sup>5</sup> In 2006, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) recommended treatment for LTBI for people aged 35 or younger with a positive TST (6 mm or greater if no previous BCG, or 15 mm with previous BCG), *and* a positive interferon-gamma test (if this test was available).<sup>29</sup> In 2010, the United States' Centers for Disease Control and Prevention recommended that an IGRA may be used in place of (but not in addition to) a TST in all situations.<sup>30</sup> In 2011 the NICE guideline was revised to recommend initial IGRA, or initial TST with IGRA if TST 6 mm or greater.<sup>31</sup> In 2012, the National TB Advisory Committee Australia (NTAC) recommended TST and supplemental IGRA assessment for people with a positive TST.<sup>3</sup> Although the NTAC guideline does not directly cite the ATS guidelines on reading the TST, it does cite Lee and Holzman,<sup>32</sup> who do recommend the ATS criteria. In 2015 the WHO recommended that either TST or IGRA can be used to test for LTBI in high income and upper middle income countries with estimated TB incidence less than 100 per 100,000.<sup>12</sup> The WHO guidelines note that chest radiography can be used in the algorithm to detect LTBI where screening is also directed towards active case finding. In 2016, the NICE guideline was revised again, and recommended initial TST, offer treatment if TST 5 mm or larger, and only offer IGRA if TST is unavailable.<sup>33</sup> The 2016 NICE guidelines do not use the chest radiograph to interpret the TST. Also in 2016, the Australasian Society for Infectious Diseases (ASID) recommended using TST or IGRA to screen for LTBI; and that TST is positive at 10mm in those from refugee-like backgrounds, or 5 mm in the setting of severe malnutrition, HIV infection, immuno-suppression, or in children who are recent contacts of active TB cases.<sup>20</sup> While the ASID recommendations note the importance of chest radiograph

in the detection of active TB, they do not mention incorporation of chest radiograph findings in the interpretation of TST. Whilst there are robust historical data to support the role of chest radiograph in predicting later reactivation of TB, it requires specialized skills to do so.<sup>24</sup>

Many studies have compared TST with IGRA.<sup>30</sup> Nienhaus et al.<sup>34</sup> found agreement between QuantiFERON-TB Gold and TST was best with a TST diameter of at least 15 mm as cut-off point (89.8%); but the kappa value was best with at least 10 mm as cut-off point for the TST (0.37). Although TST, IGRA and chest radiograph have all been studied in the detection of latent TB,<sup>35</sup> we are unaware of any studies comparing TST and IGRA using the ATS recommendation that TST be considered positive at 5-9 mm if the chest radiograph suggests previous TB disease.<sup>25</sup>

The purpose of the Australian Government's health requirement for immigrants is to protect the Australian community from public health and safety risks, particularly active TB.<sup>36</sup> If active TB is found, Australian migration law does not allow a visa to be granted until the person has undergone treatment and been declared free of active TB.<sup>37</sup> Applicants aged 11 years or older must undergo a chest radiograph,<sup>37</sup> which is available when interpreting the TST.

## Conclusion

In migrants with a TST of 5-9 mm the presence of a chest radiograph suggestive of previous TB disease makes it more likely that IGRA will be positive. The chest radiograph is known to predict risk of subsequent active TB, and is recommended in the reading of the TST. Therefore the chest radiograph remains an important factor in considering whether to recommend treatment of LTBI.

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