
DATE: 24 May 2011

CONTEXT AND POLICY ISSUES

Tuberculosis (TB) is an infection caused by the Mycobacterium tuberculosis bacteria, and M. tuberculosis kills more people than any other infectious organism. It is estimated that there were 9.2 million new cases of TB in the world in 2006, and 1.7 million people died in 2006 as a result of TB. While over 80% of new cases of TB diagnosed in 2006 were in people from Africa, South-East Asia, and Western Pacific regions, approximately 1600 active cases were reported in Canada in 2009; this number has remained consistent for the previous seven years. Foreign-born individuals and Canadian-born Aboriginal individuals accounted for the majority of reported TB cases in 2009, 63% and 21%, respectively.

There are two types of TB: active TB, in which a person is generally symptomatic and infectious, and latent TB, where the M. tuberculosis infection is contained by host defenses, and the person is not considered infectious. Up to one-third of the world’s population is infected with latent TB, and the major concern with latent TB is that it has the potential to develop into active disease at any time. As a result, identification and treatment of individuals with latent TB is an important priority for reducing the incidence of TB.

Two types of testing are available to detect latent TB: the tuberculin skin test (TST) and interferon gamma release assay (IGRA) tests. The TST involves administration of tuberculin material under the skin of the forearm that contains a mixture of antigens shared by a number of mycobacteria. Subsequently, false-positives can occur in people who have been exposed to non-tuberculosis mycobacterium. False-positive reactions can also occur in people who have received the bacilli Calmette-Guerin (BCG) vaccination, a vaccination used to prevent tuberculosis. In addition, individuals who are immunocompromised or severely ill, such as people with HIV or active TB, can have false-negative results. Lastly, personnel without adequate training may misinterpret results of the TST. IGRA testing, therefore, was developed to improve on the shortcomings of the TST. It involves a blood test that measures T-cell release of interferon-gamma following exposure to M. tuberculosis antigens, and does not appear to react to other mycobacterium antigens, but IGRA testing is much more expensive than TST.

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Two IGRA tests are currently available in Canada: the QuantiFERON-TB Gold In-Tube (QFT-G-IT) (Cellestis Ltd., Carnegie, Australia), and the T-SPOT.TB assay (Oxford Immunotec, Oxford, U.K). This report will review the evidence on the clinical effectiveness of IGRA testing compared with TST testing for identifying TB, and discuss the evidence-based guidelines focused on testing to identify TB.

**RESEARCH QUESTIONS**

1. What is the comparative clinical effectiveness of interferon-gamma release assays (IGRA) testing versus tuberculosis skin test (TST) testing to identify tuberculosis?

2. What are the evidence-based guidelines regarding tuberculosis testing to identify tuberculosis?

**KEY MESSAGE**

The evidence suggests that IGRA testing appears to be more specific than TST testing for identification of latent TB in individuals who have received the BCG vaccination or who are immunocompromised. The guidelines recommend IGRAs as a confirmatory test for people with a positive TST, or in individuals who are immunocompromised with a negative TST if a false-negative test is suspected.

**METHODS**

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. For the first question, methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials. For the second question, methodological filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006, and April 18, 2011.

**SUMMARY OF FINDINGS**

The literature search identified one health technology assessment (HTA), eight systematic reviews and meta-analyses, and four guidelines and recommendations.

**Health technology assessments**

Dinnes et al. published an HTA in 2007 evaluating rapid diagnostic tests for the detection of tuberculosis infection, and one of the objectives of this HTA was to evaluate the use of interferon-gamma assays for detection of latent TB. The systematic review identified thirteen studies that included 4,035 children and adults evaluated in heterogeneous settings, including both high- and low-TB prevalence countries. The studies also differed in evaluation of exposure to TB, tests used to identify latent TB, and comorbidities of the study populations. The systematic review found that IGRA testing was less likely to have false-positive or false-negative results compared with TST for identifying latent TB in resource-rich, low-TB prevalence situations.
settings. No difference was found between TST and IGRA testing performance in high-TB prevalent countries. Although not statistically significant, IGRA tests were less likely to have false-positive results in people who received the BCG vaccination, and less likely to have false-negative results in individuals with HIV. The author were unable to identify literature that compared the cost-effectiveness between IGRA testing and TST testing, and the report did not include an economic evaluation.

A limitation of the HTA is the literature search was from 1975 until August 2003. More recent studies, therefore, were not included in the HTA. In addition, the results of the HTA were based on studies with small sample sizes (range: 49 to 1,045 individuals) and that were both clinically and statistically heterogeneous, thus, limiting the accuracy of pooled estimates.

Systematic reviews and meta-analyses

The study characteristics of the systematic reviews and meta-analyses comparing TST testing to IGRA testing are listed in Table 1. The systematic reviews identified were heterogeneous in the populations examined, tests used to identify TB, search strategies, and study objectives. For example, Cattamanchi and colleagues evaluated IGRAs in people with HIV only, and Zwerling et al. examined use of IGRAs for TB screening in healthcare workers. Although heterogeneous, the other systematic reviews included in this report overlapped considerably in studies identified and included. No systematic review specifically compared IGRA testing to TST testing in the Aboriginal population.

Table 2 lists the critical appraisal, study results, conclusions, and limitations of each of the systematic reviews and meta-analyses. Critical appraisal of the systematic reviews was performed using the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) proposal for reporting. MOOSE was chosen as the proposal for critical appraisal because the systematic reviews in this report included only observational studies. Each systematic review suffered from similar limitations, including heterogeneity associated with pooled estimates, small sample sizes of included studies, and lack of a gold standard for identification of latent TB to act as a comparator for calculating sensitivity and specificity of tests. Only one systematic review assessed the possibility for publication bias with funnel plots, and a number of reviews excluded non-English language studies and conducted limited literature reviews.

The conclusions of each systematic review for latent TB differed. Cattamanchi et al. reported finding little difference between TST testing and IGRA testing for identifying TB in HIV-infected individuals, and included studies from a number of high- and low-TB incidence countries, including Tanzania, Chile, Cambodia, Mexico, Uganda, and India for high-incidence countries, and Austria, Denmark, Italy, Spain, and the United States for low-incidence countries. Sample sizes ranged from 19 to 822 individuals.

Diel et al. conducted two systematic reviews, one evaluating TST testing compared with IGRAs for diagnosis of latent TB, and the second evaluating IGRAs and TST testing among definitely confirmed seven participants and as large as 830 participants, whereas the systematic review among active TB cases ranged from 19 subjects to 3,678 subjects. Studies were conducted in a number of countries, including South Africa, Austria, Germany, the United Kingdom, The Netherlands, Vietnam, Turkey, and Switzerland for the latent TB systematic review, and Korea, Germany, Italy, Japan, South Africa, Greece, and India for the active TB systematic review. Prevalence of BCG vaccination ranged from 4.1% to 92.8% in the latent TB systematic review.
and was not reported in the active TB systematic review. When evaluating studies identifying latent TB, it was found that a positive TST result was significantly correlated with a history of BCG vaccination, whereas no correlation was found for BCG-vaccinated individuals who received IGRA testing. In those with confirmed active TB, IGRA were found to be more sensitive for identifying TB relative to TST testing.

In studies evaluating identification of active TB, IGRA testing was found to be more sensitive than TST for identifying active TB, but TST testing was found to be more specific (0.75) than the T-SPOT.TB test (0.59), and comparable to the QFT-G-IT test (0.80), for identification of active TB. This systematic review involved studies from South Africa, Italy, Germany, and Korea. Sample sizes varied across the studies, with a median (inter-quartile range) of 20 individuals per study, and 53.8% (standard deviation: 25.3%) were immunized with the BCG vaccination.

Zwerling et al. found inconsistent evidence for using IGRA testing for screening for latent TB in healthcare workers. The systematic review population included studies from both high- and low-TB incidence countries, including India, Russia, Vietnam, Japan, United States, Denmark, Germany, Australia, Spain, and the United Kingdom. Samples sizes of the included studies ranged from 12 individuals to 1,313 individuals. BCG vaccination prevalence was not measured in three studies, and was as low as 7% and as high as 100%. Contrary to other systematic reviews, no difference was found between likelihood of a positive TST test compared to a positive IGRA test in people with a history of BCG vaccination.

Chang et al. conducted a systematic review evaluating IGRA testing compared to TST testing for identification of latent TB. Studies from Denmark, Italy, Japan, Turkey, Brazil, South Korea, Taiwan, China, and Zambia were included in the review. Sample sizes ranged from 20 individuals to 331 individuals. They found that the sensitivity and specificity of IGRA testing was higher than TST testing, particularly in predominantly BCG-vaccinated populations.

Pai et al. also found that IGRA tests had better specificity in populations with a high prevalence of BCG-vaccination compared to TST testing, whereas TST testing had a similar specificity to IGRA testing in populations with a low prevalence of BCG vaccination. This systematic review involved studies from Japan, Italy, South Korea, Denmark, United States, Germany, and Gambia. Sample sizes ranged from 34 to 544 people, and 0% to 100% of individuals were BCG-vaccinated in the included studies.

A systematic review by Menzies et al. included studies from both high-TB and low-TB incidence countries, including Gambia, Nigeria, India, Korea, United Kingdom, United States, Italy, Switzerland, and Denmark. Sample sizes of the included studies ranged from 45 to 735 individuals. Prevalence of BCG vaccination varied between studies as well, from 0% to 100% of people studied. The authors found that neither the TST or IGRA tests had the ability to distinguish between latent and active TB. TST specificity was comparable to IGRA testing in populations without BCG-vaccination (0.98 versus. 0.97 for the QuantiFERON test and 0.92 for the T-SPOT.TB test), but was significantly lower than QuantiFERON testing in BCG-vaccinated populations (0.56 versus 0.96, respectively). It is important to note that some of the studies evaluating TST testing used a subtherapeutic dose of tuberculin, so the results may be different in studies using therapeutic doses of tuberculin. Lastly, this review was published in 2007, therefore more recently published systematic reviews are more current.
Guidelines and recommendations

A number of guidelines and consensus statements exist for identifying TB. Each guideline stated that IGRA testing and TST testing should not be used to diagnose active TB, and these tests should be focused on the diagnosis of latent TB in different populations. A summary of the recommendations from each guideline, as well as the critical appraisal of the guidelines, is listed in Table 3. The Appraisal of Guidelines for Research & Evaluation II (AGREE-II) instrument was used to critically appraise the currently available guidelines for identifying TB.

The majority of guidelines recommend a two-step approach for evaluating a patient for latent TB: start with a TST test, and then an IGRA test to improve either sensitivity or specificity. The guidelines from the Centers for Disease Control and Prevention were the exception, stating that either a TST test or IGRA test can be used to screen for latent TB in situations where other guidelines recommended the two-step approach. The guidelines were also consistent in children under five years old should only receive TST testing to screen for latent TB.

Limitations

The primary limitation of comparing IGRA testing with TST testing for identifying latent TB is the heterogeneity of the evidence currently available, as demonstrated by the systematic reviews included in this report. The pooled results of each systematic review must be interpreted with caution due to heterogeneity in populations and tests studied, study design, time frame, and comparison used to validate a diagnosis of TB. In addition, the majority of studies included in the systematic reviews were cross-sectional and of low methodological quality. Lastly, some of the systematic reviews used narrow search strategies to identify relevant articles.

While the systematic reviews included studies from low-TB incidence countries such as the United States and the United Kingdom, very few included studies were from Canada. Subsequently, the results must be interpreted with caution as they may or may not be generalizable to the Canadian population. In addition, while Canadian-born Aboriginals accounted for 21% of the TB cases in Canada in 2009, no information was found specifically evaluating IGRA and TST testing in this population. As a result, it is unclear whether the results of the included systematic reviews and guidelines apply to the Aboriginal population in Canada.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The comparative clinical effectiveness of IGRA testing in comparison with TST testing for identification of TB

Based on systematic reviews and meta-analyses that compared the effectiveness of IGRA testing to TST testing for identifying TB, IGRA testing does not appear to offer benefit in terms of screening individuals exposed to someone with active TB, without a risk for false-positive or false-negative test results. IGRA testing may offer clinical benefits in people who have been previously vaccinated with the BCG vaccination, as false-positive results are less likely to occur with the IGRA testing compared with TST testing. IGRA testing may also be more useful in immunocompromised patients who are at risk of a false-negative result on a TST test.
Evidence-based guidelines regarding TB testing to identify TB

The currently available guidelines consistently state that IGRA testing should not be used to identify active TB. The majority of evidence-based guidelines recommend a two-step approach when screening a patient for latent TB: a TST test initially, followed by an IGRA test to improve either sensitivity or specificity based on the result of the TST test and the population being evaluated.

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REFERENCES:


**APPENDIX 1: Study Characteristics of Systematic Reviews and Meta-analyses Comparing IGRA Testing with TST Testing**

<table>
<thead>
<tr>
<th>Author, Publication Year, Country of Study</th>
<th>Primary Objective</th>
<th>Search Strategy</th>
<th>Study Population</th>
<th>Study Criteria</th>
<th>Studies Selected</th>
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<tbody>
<tr>
<td>Cattamanchi et al, 2011, USA(^8)</td>
<td>To determine if the available data support the use of IGRA to improve the identification of HIV-infected individuals who could benefit from isoniazid preventive therapy. (p.231)(^8)</td>
<td>PubMed, Embase, BIOSIS, and Web of Science until May 2010. Reviewed bibliographies of reviews and guidelines, screened citations of all included studies, contacted experts and IGRA manufacturers to identify additional unpublished or ongoing studies. All languages eligible.</td>
<td>HIV-infected individuals</td>
<td>Studies that evaluated QFT-G-IT or T-SPOT.TB, with at least 10 HIV-infected individuals. The reference test was the TST test.</td>
<td>37 studies were identified that included 5,736 individuals with HIV. 19 evaluated QFT-GIT and 19 evaluated T-SPOT.TB. 22 studies were in low-income countries.</td>
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<tr>
<td>Diel et al, 2011, Germany(^9)</td>
<td>The diagnostic specificity of IGRA relative to the TST, the IGRA’s negative (NPV) and positive (PPV)</td>
<td>Medline, Embase, Cochrane Central Register of Controlled Trials until November 15, 2009. English language</td>
<td>No restrictions made based on study participants.</td>
<td>Studies that evaluated the QFT-G-IT or the T-SPOT.TB test compared to TST (reference) for diagnosis of latent TB.</td>
<td>60 studies included: 4 evaluated specificity, 18 evaluated NPV, 34 evaluated PPV, and 34 evaluated exposure of patients to TB and IGRA and TST test results</td>
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<td>Sester et al, 2011, Germany&lt;sup&gt;10&lt;/sup&gt;</td>
<td>To evaluate the performance of TST and commercial IGRA from blood and compartment other than blood for the diagnosis of active TB.</td>
<td>PubMed, Embase, Cochrane Central Register of Controlled Trials, from January 2001 until November 2009. English language only. Unpublished sources of data not included. No restrictions based on study design or data collection.</td>
<td>Studies that reported the assessment of IGRA in people with a clinical suspicion of active TB, performed in blood or other biological fluid.</td>
<td>Studies evaluating QFT-G-IT or the T-SPOT.TB test compared to TST (reference).</td>
<td>27 studies included: 18 evaluated tests in blood, 9 evaluated tests in extrasanguinous fluids (5 bronchoalveolar lavage fluid, 3 pleural fluids, one ascites).</td>
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<td>Zwerling et al, 2011, Canada(^{11})</td>
<td>Systematically to review all studies using IGRA to test healthcare workers, including cross-sectional, longitudinal and serial testing studies, to summarize their performance characteristics.(^{(p.1)})(^{11})</td>
<td>Pubmed, Embase, Biosis, and Web of Science until April 30, 2010 (updated again on October 1, 2010). Reviewed bibliographies of previous reviews and guidelines on IRGAs, conference proceedings, abstracts, and screened citations of relevant original articles. Any language could be included.</td>
<td>Healthcare workers</td>
<td>Studies that used a commercial IGRA assay: QuantiFERON-TB Gold/QFT-GIT, T-SPOT.TB, for TB screening in healthcare workers in any setting. Cross-sectional, longitudinal, and serial testing designs included. Had to have more than 10 participants. TST was the reference test.</td>
<td>50 studies, of which 44 reported a main outcome. 11,963 healthcare workers evaluated across the 44 studies. 34 studies were cross-sectional.</td>
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<tr>
<td>Chang et al, 2010, China(^{12})</td>
<td>To clarify the clinical roles of IGRA in latent TB and TB disease by focusing</td>
<td>Medline, Embase until July 11, 2009. English language</td>
<td>Adults only.</td>
<td>Studies evaluating QuantiFERON-TB Gold (QFT-G)/QFT-G-IT or the T-SPOT.TB</td>
<td>35 studies included. Majority of study participants were BCG-vaccinated.</td>
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<td>Diel et al, 2010, Germany (p.272)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>To investigate the sensitivity and specificity of T-SPOT.TB and QFT-IT among definitely confirmed TB cases.</td>
<td>Medline, Embase, and Cochrane Register of Controlled Trials, until July 15, 2009. No language restrictions.</td>
<td>Identified active TB only. Individuals could not have received TB treatment for ≥2 weeks.</td>
<td>Studies that evaluated QFT-GIT or T-SPOT.TB, with active TB confirmed by culture and/or polymerase chain reaction and/or histologic examination for assessment of sensitivity. All studies had to compare 2 or more tests. TST was the reference test.</td>
<td>124 studies included. 40 evaluated sensitivity, 7 evaluated specificity of IGRAs, 116 were indeterminate. 45 studies evaluated immunosuppressed individuals. 17 studies evaluated children.</td>
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<td>Pai et al, 2008, Canada (p.134)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>To incorporate newly reported evidence</td>
<td>PubMed until March 31, 2008. English</td>
<td>Studies that did not include only immunocompromised</td>
<td>Studies evaluating QuantiFERON-TB Gold (QFT-G)/QFT-G-IT or</td>
<td>38 studies included. 15 evaluated QFT-G/QFT-G-IT and 9 evaluated T-SPOT.TB. All</td>
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| Menzies et al, 2007, Canada 

Do new ex-vivo interferon-gamma release assays (IGRAs) detect latent tuberculosis (TB) more accurately than tuberculin skin tests (TSTs)?  

(p.341)

| from 20 studies into an updated meta-analysis on the sensitivity and specificity of IGRAs.  

(p.177)

| language only. Citations of original articles, guidelines, and reviews searched. | patients. | the T-SPOT.TB test. Studies with less than 10 subjects were excluded, as were studies that included only immunocompromised populations. TST was the reference test. | studies were cross-sectional. |

| Medline from 1966 until October 31, 2006. English language only. Identified additional studies from reference lists and performed a hand search of the International Journal of Tuberculosis and Lung Disease 2002 – 2006. | No restrictions made based on study participants. Identified latent TB only. | Studies evaluating QuantiFERON or Elispot. TST was the reference test. | 58 studies included. 50 studies used cross-sectional designs; 8 used serial testing designs. |
### APPENDIX 2. Critical Appraisal, Study Results, Conclusions, and Limitations of Systematic Reviews Comparing IGRA Testing with TST Testing

<table>
<thead>
<tr>
<th>Author, Publication Year, Country of Study</th>
<th>Critical Appraisal using MOOSE(^9)</th>
<th>Study Results</th>
<th>Authors’ Conclusions</th>
<th>Limitations</th>
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| Cattamanchi et al, 2011, USA\(^8\)        | • No assessment of publication bias. | • Study results were inconsistent for head-to-head comparisons between IGRA and TST for sensitivity in culture-confirmed active tuberculosis in low- to middle-income countries and high-income countries.  
• T-SPOT.TB and TST results were concordant in 77% (95% CI: 67-88%) of cases in low- to middle-income studies, but there was significant heterogeneity between studies (p = 0.04).  
• In high-income studies, T-SPOT.TB and TST were concordant in 89% (95% CI: 81-89%) of cases (heterogeneity: p<0.001).  
• QFT-G-IT and TST results were concordant in 94% of cases (95% CI: 91-96%; heterogeneity p=0.17). | • Current evidence suggests that IGRA perform similarly to the tuberculin skin test at identifying HIV-infected individuals with latent tuberculosis infection. Given that both tests have modest predictive value and suboptimal sensitivity, the decision to use either test should be based on country guidelines and resource and logistic considerations. (p.230)\(^8\) | • Study results generalizable to people with HIV only.  
• Significant heterogeneity between studies limits conclusions that can be drawn from pooled estimates.  
• Study sample sizes were small.  
• Lack of a gold standard for identification of latent TB to act as the comparator for calculating sensitivity and specificity. |
<p>| Diel et al, 2011, Germany(^9)            | • No clear hypothesis stated. No inclusion | • Pooled specificity of the TST was 88.7% (95% CI: 84.6-92.0%). | In conclusion, the present systematic review and meta- | • Significant heterogeneity between studies limits conclusions |</p>
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<td>that can be drawn from pooled estimates.</td>
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<td>Lack of a gold standard for identification of latent TB to act as the comparator for calculating sensitivity and specificity.</td>
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<tr>
<td>Sester et al, 2011, Germany¹⁰</td>
<td>English language only with no justification of exclusion of non-English language studies. No assessment of publication bias but the authors suggested that the risk of publication bias is low due to the increasing</td>
<td>Pooled sensitivity of the TST was 0.65 (95% CI: 0.61-0.68), pooled specificity was 0.75 (95% CI: 0.72-0.78). Pooled sensitivity of the QFT-G-IT was 0.80 (95% CI: 0.75-0.84) and specificity was 0.79 (95% CI: 0.75-0.82). Pooled sensitivity of the T-SPOT.TB was 0.81 (95% CI: 0.78-0.84), specificity was 0.59 (95% CI: 0.56-0.62).</td>
<td>The sensitivity of both IGRAs for the diagnosis of active TB was higher than that of the TST. Overall sensitivities did not differ between the T-SPOT.TB and QFT-G-IT. In general, however, the diagnostic sensitivity of IGRAs is too low to support their use as a rule-out test for TB.(p.105)¹⁰</td>
<td>Significant heterogeneity between studies limits conclusions that can be drawn from pooled estimates.</td>
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### Study Results

- **Pooled specificity of the IGRAs was 99.4% (95% CI: 97.9–99.9%).**
- **TST positivity was significantly associated with BCG vaccination (OR 3.8 [95% CI: 1.0-13.9] to 24.7 [95% CI: 11.7-52.5]).**
- **No correlation found between IGRA positivity and BCG vaccination.**

### Limitations

- **Study sample sizes were small.**
- **Lack of a gold standard for identification of latent TB to act as the comparator for calculating sensitivity and specificity.**

### In conclusion

The current evidence brought forward in this systematic review and meta-analysis of the accuracy of the IGRAs for LTBI diagnosis confirm the concept that the IGRAs are a valid alternative to the TST. The superior specificity and the good NPV make them the first choice, especially in BCG-vaccinated subjects.(p.9)

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<thead>
<tr>
<th>Author, Publication Year, Country of Study</th>
<th>Critical Appraisal using MOOSE</th>
<th>Study Results</th>
<th>Authors’ Conclusions</th>
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<tr>
<td>Zwerling et al, 2011, Canada¹¹</td>
<td>- No assessment of publication bias.</td>
<td>- 25 studies compared IGRA to TST, and all but one reported a lower prevalence of positive IGRA than positive TST, with a statistically significant difference found in 17 of these studies (individuals study results not reported). - The difference in prevalence was significant in low- to moderate-TB incidence settings, but not in high-TB incidence settings. - Studies with a higher proportion of people who were BCG-vaccinated did not demonstrate a higher positive TST prevalence or a larger difference between positive TST and positive IGRA compared to studies with a low proportion of people who were BCG-vaccinated.</td>
<td>Analysis shows that the IGRAs have limited accuracy in diagnosing active TB. (p.110)¹⁰</td>
<td>- Results only generalizable to screening of healthcare workers for latent TB. - Did not perform a meta-analysis due to heterogeneity.</td>
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<tr>
<td>Diel et al, 2010,</td>
<td>- No clear</td>
<td>- Pooled sensitivity of Our metaanalysis</td>
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<td>Author, Publication Year, Country of Study</td>
<td>Critical Appraisal using MOOSE&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Study Results</td>
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| **Germany<sup>12</sup>**               | description of problem or hypothesis.          | T-SPOT.TB (90.1%) was greater than pooled sensitivity for TST (68.3%).  
• Pooled sensitivity for QFT-IT (83.1%) was greater than TST (62.3%), p< 0.001 for both comparisons. | of the existing literature has produced results showing that IGRAs are superior to the TST for detecting confirmed active TB disease, irrespective of the degree of economic resources of the particular setting. (p.963)<sup>12</sup> | heterogeneity between studies limits conclusions that can be drawn from pooled estimates.  
• Study sample sizes were small.  
• Lack of a gold standard for identification of latent TB to act as the comparator for calculating sensitivity and specificity. |
| **Chang et al, 2010, China<sup>13</sup>** | No clear hypothesis stated.  
• No inclusion of unpublishe d sources of data. English language only with no justification of exclusion of non-English language studies. | Mean sensitivity of TST ranged from 64% (95% CI: 52-75%) to 75% (63-86%) and specificity ranged from 43% (95% CI: 16-69%) to 71% (95% CI: 58-85%) in a population predominantly BCG-vaccinated.  
• Sensitivity of QFT-G/QFT0G-IT ranged from 79% (95% CI: 72-84%) to 91% (95% CI: 85-94%); specificity ranged from 88% (95% CI: 78-94%) to 98% (95% CI: 97-99%).  
• Sensitivity of the T-SPOT.TB ranged from 74% (95% CI: 64-83%) to 92% (95% CI: 86-97%); specificity ranged from 40% (95% CI: 22-60%) to 87% (83-92%). | At a 90% certainty threshold, latent TB is best diagnosed by QFT-G/QFT-G-IT and excluded by T-SPOT.TB or QFT-G/QFT-G-IT; none can diagnose tuberculosis disease, whereas. T-SPOT.TB can exclude tuberculosis disease among middle-aged and older patients.(p.271)<sup>13</sup> | Study sample sizes were small.  
• Lack of a gold standard for identification of latent TB to act as the comparator for calculating sensitivity and specificity.  
• Method to evaluate heterogeneity (Moses-Shapiro-Littenberg method) may not have had statistical power to identify heterogeneity. |
<table>
<thead>
<tr>
<th>Author, Publication Year, Country of Study</th>
<th>Critical Appraisal using MOOSE\textsuperscript{19}</th>
<th>Study Results</th>
<th>Authors’ Conclusions</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Pai et al, 2008, Canada\textsuperscript{14}</td>
<td>No clear hypothesis stated. Only searched PubMed for eligible studies.</td>
<td>- Pooled sensitivity of TST was 0.77 (95% CI: 0.71-0.82); pooled specificity in non-BCG-vaccinated populations was 0.97 (95% CI: 0.95-0.99); pooled specificity in BCG-vaccinated populations was 0.59 (95% CI: 0.46-0.73). - Pooled sensitivity for QFT-G was 0.78 (95% CI: 0.73-0.82). - Pooled sensitivity for QFT-G-IT was 0.70 (95% CI: 0.63-0.78). - Pooled sensitivity for T-SPOT.TB was 0.90 (95% CI: 0.86-0.93). - Pooled specificity for both IGRAs in very low risk populations without BCG vaccination was 0.99 (95% CI: 0.98-1.00); specificity in BCG-vaccinated populations was 0.93 (95% CI: 0.86-1.00) to 0.96 (95% CI: 0.94-0.98). - All comparisons were significantly heterogeneous except IGRA pooled specificity in BCG-vaccinated populations (p=0.055).</td>
<td>The IGRAs, especially QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube, have excellent specificity that is unaffected by BCG vaccination. Tuberculin skin test specificity is high in non–BCG-vaccinated populations but low and variable in BCG-vaccinated populations. Sensitivity of IGRAs and TST is not consistent across tests and populations, but T-SPOT.TB appears to be more sensitive than both QuantiFERON tests and TST.\textsuperscript{(p.177)14}</td>
<td>- Study was published in 2008, therefore more recent publications were not included. - Significant heterogeneity between studies limits conclusions that can be drawn from pooled estimates. - Lack of a gold standard for identification of latent TB to act as the comparator for calculating sensitivity and specificity. - Studies had small sample sizes.</td>
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<td>Menzies et al, 2007, Canada\textsuperscript{15}</td>
<td>Only searched Medline for</td>
<td>No test distinguished active TB from latent TB. Sensitivity of TST</td>
<td>New IGRAs show considerable promise and have excellent</td>
<td>Significant heterogeneity between studies limits conclusions</td>
</tr>
<tr>
<td>Critical Appraisal using MOOSE(^9)</td>
<td>Study Results</td>
<td>Authors’ Conclusions</td>
<td>Limitations</td>
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<td>potential studies. English language only with no justification of exclusion of non-English language studies. No evaluation of publication bias.</td>
<td>was 0.71 (95% CI: 0.65 – 0.74) compared to 0.76 (95% CI: 0.70 – 0.83) for the QuantiFERON and 0.88 (95% CI: 0.81 – 0.95) for the Elispot or T-SPOT.TB.</td>
<td>specificity. Additional studies are needed to better define their performance in high-risk populations and in serial testing. Longitudinal studies are needed to define the predictive value of serial testing. (p.340)(^{15}) that can be drawn from pooled estimates.</td>
<td>Study sample sizes were small. Lack of a gold standard for identification of latent TB to act as the comparator for calculating sensitivity and specificity. Some studies used a dose of tuberculin for the TST that was 50% or less of the recommended dose, which impacts sensitivity of the TST. Study published in 2007, therefore more recent publications were not included.</td>
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<td>Study published in 2007, therefore more recent publications were not included.</td>
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**BCG**=Bacillus Calmette-Guérin; **IGRA**=interferon gamma release assay; **QFT-G**=QuantiFERON Gold; **QFT-G-IT**=QuantiFERON Gold In-Tube; **MOOSE**=Meta-analysis of observational studies in epidemiology; **TST**=tuberculin skin test; **TB**=tuberculosis
## APPENDIX 3: Description and Critical Appraisal of Guidelines Available for the Use of IGRA and TST Testing in TB

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Critical Appraisal using the AGREE-II Instrument</th>
<th>Testing Recommendations</th>
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</thead>
</table>
| **Canadian Tuberculosis Committee**<sup>5</sup>     | Domain 1. Scope and purpose of the guideline was clearly outlined.  
Domain 2. Stakeholder involvement: members of the Canadian Tuberculosis Committee were listed in the document and covered a range of Canadian agencies.  
Domain 3. Rigour of development: The process of gathering and synthesizing evidence could have been reported more clearly. In addition, no formal grading of the quality of the evidence was applied.  
Domain 4. Clarity of Presentation: the recommendations within the guideline were presented clearly and the format was logical.  
Domain 5. Applicability: many stakeholder groups were involved when developing this guideline. Cost-effectiveness was also considered.  
Domain 6. Editorial independence: committee members disclosed their conflicts of interest. | A TST test should be used for diagnosing latent TB in:  
- adult and childhood contacts of a case of infectious tuberculosis, with no high risk factors for progression to active disease if infected;  
- contacts with an increased risk of progression to active disease if infected (can be used in combination with IGRA testing);  
- immunocompromised adults and children;  
- serial testing of healthcare workers, prison inmates and staff, and in employee screening programs;  
- population or community-based surveys examining prevalence of latent TB.  
IGRA testing should be used for diagnosing latent TB:  
- as a confirmatory test for a positive TST test;  
- in combination with a TST for contacts with a high risk of progression to active disease;  
- in immunocompromised individuals where a false-negative TST test is suspected.  
The above recommendations apply for targeted immigrant and traveler screening. |
| **Centers for Disease Control and Prevention (United States)**<sup>16</sup> | Domain 1. Scope and purpose of the guideline was clearly outlined.  
Domain 2. Stakeholder involvement: authors who prepared the document were listed, as well as the IGRA expert committee. The guidelines were | The guidelines state that both TST testing and IGRA testing should be used as aids in diagnosing *M. tuberculosis* infection. The selection of the test or combination of tests should be made based on the reasons for testing, the context in which the test will be administered, availability of tests, and cost effectiveness of tests. |
IGRA Testing versus Tuberculosis Skin Testing for Tuberculosis

<table>
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<td>coordinated with the American Academy of Pediatrics, the American Thoracic Society, the Infectious Disease Society of America, the Advisory Council for the Elimination of Tuberculosis, the Association of Public Health Laboratories, the Food and Drug Administration, the National Tuberculosis Controllers Association, Stop TB USA, the US Army, the US Air Force, and the Veterans Health Administration. Domain 3. Rigour of development: The process of gathering evidence was limited to a PubMed search for English language articles only. The expert committee provided written opinions as to how IGRAs should be used. Domain 4. Clarity of Presentation: the recommendations within the guideline were presented clearly. Domain 5. Applicability: many stakeholder groups were involved when developing this guideline. Domain 6. Editorial independence: conflicts of interest were not disclosed within the guidelines.</td>
<td>TST testing is preferred in children under 5 years of age. IGRA testing is preferred in the following situations: ▪ the test is being administered to a person with a low rate of returning to have a TST read; ▪ the person has previously received the BCG vaccination. Either a TST or IGRA test can be used: ▪ in people who have had recent contact with an individual with active or suspected active TB; ▪ for periodic screening of individuals with occupational exposure to TB. Both tests should may be used: ▪ when the initial test is negative and the risk for a poor outcome is increased; ▪ when the initial test is negative but clinical suspicion exists for TB; ▪ when additional evidence of TB diagnosis is required to encourage compliance.</td>
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<td>European Centre for Disease Prevention and Control</td>
<td>Domain 1. Scope and purpose of the guideline was outlined. Domain 2. Stakeholder involvement: members of the ad hoc scientific panel were from</td>
<td>The guidelines state that IGRA testing may be used as part of the overall assessment to identify individuals for preventive TB treatment. The simultaneous use of TST and IGRA testing should be used in people who are</td>
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<td>different countries in Europe. Domain 3. Rigour of development: It was stated that two systematic reviews and a meta-analysis were performed by the TB Network European Trials group, and were published in peer-reviewed journals. The process of gathering and synthesizing evidence could have been reported more clearly within the guidelines. Domain 4. Clarity of Presentation: the recommendations within the guideline were presented clearly and the format was logical. Domain 5. Applicability: many stakeholder groups were involved when developing this guideline. Cost-effectiveness was also considered. Domain 6. Editorial independence: committee members were reported to have a lack of conflict of interest.</td>
<td>IGRA testing should not be used in children under 5 years of age. There is no added value in using IGRA testing to diagnose latent TB in high-TB incidence countries. IGRA testing should be used with a two-step approach (following TST in TST-positive subjects) in low-TB incidence countries. IGRA testing has a clear advantage in diagnosing latent TB relative to TST testing in those who have received the BCG vaccination. The two-stepped approach (TST first and an IGRA test if the TST test is positive) may be useful in screening of healthcare workers, particularly those with the BCG vaccination.</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence (NICE)</td>
<td>Domain 1. Scope and purpose of the guideline was clearly outlined. Domain 2. Stakeholder involvement was not clearly provided, but information was available upon request regarding the stakeholders. Domain 3. Rigour of development: The process of gathering and synthesizing evidence could have been</td>
<td>A TST should be used for diagnosing latent TB in: - household and non-household contacts of all people with active TB (5 years of age and older); - children 2 to 15 years of age who are new entrants from a high-TB incidence country; - new healthcare workers who will be in contact with patients or clinical materials, if they are not new entrants from a high-TB incidence country and have not had a BCG vaccination.</td>
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<tr>
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<td>Critical Appraisal using the AGREE-II Instrument</td>
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|           | improved, as one person conducted a literature search and synthesized the evidence to inform the guidelines committee. Domain 4. Clarity of Presentation: the guideline was presented very clearly and the format was logical. Domain 5. Applicability: many stakeholder groups were considered when developing this guideline, as well as available cost-effectiveness information available in the literature. Domain 6. Editorial independence was unclear for this guideline in terms of personal biases that may have impacted recommendations. | IGRA testing should be used for diagnosing latent TB in:  
- those with positive TST results or people in which TST may be less reliable (e.g. BCG-vaccinated people);  
- new entrants from a high-TB incidence country who are 16 to 35 years of age (can also use a dual strategy);  
- children in contact with a person with sputum-smear-positive disease with a negative TST test, an IGRA test and repeat TST should be conducted 6 weeks after the initial TST test;  
- healthcare workers who are new entrants from high-TB incidence countries or who have had contact with patients in settings with a high prevalence of TB;  
- people with HIV and CD4 count of < 200cells/mm³, IGRA testing should be administered concurrently with a TST test;  
- people with HIV with CD4 counts of 200-500cells/mm³, or other immunocompromised patients, an IGRA test can be used alone or in combination with a TST test;  
- hard-to-reach groups. |

AGREE-II=Appraisal of guidelines for research & evaluation II; IGRA=interferon gamma release assay; TST=tuberculin skin test; TB=tuberculosis
APPENDIX 4: Additional Guidelines and Supplementary Information


