IGRAs in Children: Update and relevance to the region

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Advances in Tuberculosis: Australian and Regional Perspectives
14th-15th June 2013, Melbourne
IGRA

How do you use an IGRA in routine clinical practice in Australia?

How confident are you to base treatment decisions on the result of an IGRA?

Do you think they can have an impact on Global TB control?

What does the future hold?
Diagnosing Latent Tuberculosis Infection
The 100-year Upgrade

In many industrialized nations, tuberculosis case rates have declined significantly during the past decade, and elimination of tuberculosis is a realistic goal that hinges on treating latent tuberculosis infection (LTBI) to prevent development of disease. Whereas a vast array of molecular and immunologic tests is available to diagnose many infection diseases, detection Mycobacterium avium complex. QuantiFERON-TB test results correlate well with tuberculin skin test reactivity (1). However, because multiple M. tuberculosis antigens are used, some of which are shared with BCG, false-positive results will probably be obtained in BCG-vaccinated persons.

During the past decade, a major scientific advance has been the implementation of interferon-gamma release assays (IGRAs). These tests are based on measurement of interferon-gamma release by sensitized T cells in response to stimulation in vitro with M. tuberculosis-specific antigens.

Tuberculin skin test

PPD
Interferon Gamma Release Assays

Diagnosing Latent Tuberculosis Infection
The 100-year Upgrade

In many industrialized nations, tuberculosis case rates have declined significantly during the past decade, and elimination of tuberculosis is a realistic goal that hinges on treating latent tuberculosis infection (LTBI) to prevent development of disease. Whereas a vast array of molecular and immunologic tools is available to diagnose many infectious diseases, detection of Mycobacterium avium complex. QuantiFERON-TB test results correlate well with tuberculin skin test reactivity (1). However, because multiple M. tuberculosis antigens are used, some of which are shared with BCG, false-positive results will probably be obtained in BCG-vaccinated persons. During the past decade, a major scientific advance has
QuantiFERON-TB
QuantiFERON-TB Gold
QuantiFERON-TB Gold in tube

T-SPOT. TB

www.oxfordimmunotec.com
QuantiFERON®-TB Gold In Tube

3 ml blood

16-24 hour incubation

- CFP-10
- ESAT-6
- TB 7.7

Nil

Negative control

PHA

Positive control
QuantiFERON®-TB Gold In Tube

3 ml blood

16-24 hour incubation

IFN-γ

Nil

Negative control

CFP-10

ESAT-6

TB 7.7

Positive control

PHATB 7.7

ELISA
IGRA in children – a personal journey

- Excitement
- Indifference
- Disappointment

2005 - 2013
Early Detection of Perinatal Tuberculosis Using a Whole Blood Interferon-γ Release Assay

Tom Connell,¹ Naor Bar-Zeev,¹ and Nigel Curtis¹²

¹Infectious Diseases Unit, Department of General Medicine, and ²Department of Paediatrics, University of Melbourne, Royal Children’s Hospital Melbourne, Parkville, Australia

13 week old
- Poor weight gain, cough, abnormal CXR
- TST negative/IGRA+
- TB culture positive

18 day old
- 24 hour history of vomiting and lethargy
- CXR-disseminated TB
- TST negative/IGRA+
QuantiFERON-TB Gold: state of the art for the diagnosis of tuberculosis infection?

Tom G Connell*, Molebogeng X Rangaka, Nigel Curtis and Robert J Wilkinson

Tuberculosis (TB) remains a major threat to global health. The recently launched Global Plan to Stop Tuberculosis 2006-2015 highlights the need for accurate, simple and low-cost diagnostic tests for the detection of TB infection. For the first time in decades, new diagnostic tools have emerged that may facilitate this goal. The discovery of Mycobacterium tuberculosis-specific immunodominant antigens has led to the development of interferon-γ-release assays that have been shown to have high sensitivity and specificity for TB disease. This review focuses on the QuantiFERON-TB Gold test and addresses the potential strengths and limitations of the current assays, summarizes the available evidence for their use and identifies areas of future research and development. Although representing an advance in TB diagnostics, with the potential to have a significant impact on global TB control, many issues remain unanswered. The cost of the tests and laboratory requirements may limit their use in developing countries. Most importantly, additional studies are needed in TB-endemic regions, particularly in high-risk persons such as children and individuals who are also co-infected with HIV.

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Circa 2006

QFT correlates better with defined MTB exposure than TST in adults

Majority of studies in low TB prevalence settings

Limited data in children

No data on the positive predictive value of IGRA

Discordant results between TST and IGRA remain largely unexplained
How to evaluate IGRA in children?

**TB disease**
- Sensitivity
  Children with culture confirmed TB
- Specificity
  Children in whom TB has been excluded/alternative diagnosis

**Latent TB infection**
- No gold standard
- Assessment of sensitivity/specificity problematic
- Compare results with TST and assess influence of different factors on test results
- Sensitivity
  Correlate test results with the degree of exposure
- Specificity
  Assess in populations with low prevalence of TB

Poor correlation between TST & QFT-G for latent TB

QFT-G negative in 26/37 (70%) patient with (TST-defined) LTBI

$\kappa = 0.38$ (95% CI 0.24-0.38)
False positive TST?
=> QFT-G/T.SPOT.TB higher specificity?

42% household TB contact
Median (range) TST induration 15 (12-22) mm
No effect of BCG on TST

The Likelihood of an Indeterminate Test Result from a Whole-Blood Interferon-γ Release Assay for the Diagnosis of Mycobacterium tuberculosis Infection in Children Correlates With Age and Immune Status

Thomas Haustein, MD,*†‡ Deborah A. Ridout, MSc,§ John C. Hartley, FRCPATH,*†‡ Urvashi Thaker, MSc,*†‡ Delane Shingadita, FRCPCH, MPH,†‡ Nigel J. Klein, PhD,¶ Vas Novelli, FRCP,* and Garth L. J. Dixon, PhD,*†‡

**TABLE 2.** Interactions Between Age, Immune Status, Sex, and Likelihood of an Indeterminate QFT-IT Result

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proportion With Indeterminate QFT-IT (%)</th>
<th>Univariate Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 yr</td>
<td>39/130 (30)</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>≤5 yr</td>
<td>44/101 (44)</td>
<td>1.92 (1.12, 3.30)</td>
<td>0.018</td>
</tr>
<tr>
<td>Immune status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not immunocompromised</td>
<td>44/175 (25)</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>59/93 (62)</td>
<td>5.94 (3.14, 11.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male†‡</td>
<td>51/138 (38)</td>
<td>0.77 (0.44, 1.35)</td>
<td>0.34</td>
</tr>
<tr>
<td>Female†‡</td>
<td>59/93 (62)</td>
<td>1</td>
<td>—</td>
</tr>
</tbody>
</table>

*P values from logistic regression.
†Information on sex was not available for 5 children.
‡NA indicates not applicable.

**TABLE 3.** Frequencies of Indeterminate QFT-IT Results by Age Group and Immune Status

<table>
<thead>
<tr>
<th>Age (Yr)</th>
<th>Indeterminate Results/Tests Performed (%)</th>
<th>Immunocompromised</th>
<th>Not Immunocompromised</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>2/5 (40)</td>
<td>10/25 (40)</td>
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</tr>
<tr>
<td>1–2</td>
<td>5/6 (83)</td>
<td>11/30 (37)</td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>6/8 (75)</td>
<td>11/34 (33)</td>
<td></td>
</tr>
<tr>
<td>6–8</td>
<td>11/18 (61)</td>
<td>6/28 (21)</td>
<td></td>
</tr>
<tr>
<td>10–13</td>
<td>9/14 (64)</td>
<td>3/41 (7)</td>
<td></td>
</tr>
<tr>
<td>14–17</td>
<td>6/8 (75)</td>
<td>3/20 (15)</td>
<td></td>
</tr>
</tbody>
</table>
**Hypotheses**

Age influences the magnitude of the positive control IFN-γ response in the QFT-G and QFT-GIT assays

A higher number of indeterminate assay results are seen in younger children

**Methods**

Results of positive control IFN-γ response in all QFT-G and QFT-GIT assays from children attending the RCH (2003-2008)

Positive control IFN-γ response correlated with age

Children stratified by age into three groups (0-5 yrs, 5-10 yrs, >10 yrs)
Results

Results of 875 assays from 783 children available for analysis
449 QFT-G and 429 QFT-GIT assays
Median age of children 9.1 yrs (range 25 days to 18 yrs)

118 (13%) assays indeterminate
89 (79%) failed positive control response
24 (21%) high negative (nil) control

Median age failed positive control younger
5.4 (0.24-12.0 vs. 9.4 (4.4-13.7) years, p<0.0001
Embracing Interferon-γ Release Assays for Diagnosis of Latent Tuberculosis Infection

Deborah A. Lewinsohn, MD

Although results vary IGRA show promise for diagnosing LTBI in children

Correlate well or better with results of TST with defined exposure

In non-endemic areas much more specific than TST(false + due to BCG)

Children are at much higher risk of progression to disease compared to adults so we should embrace every new test

Recommendations to expand their use not curtailed by negative data but lack of data to support their implementation into guidelines
Interferon Gamma Release Assays in the Evaluation of Children With Possible *Mycobacterium tuberculosis* Infection

*A View to Caution*

*Dwight A. Powell, MD*†

High incidence of indeterminate IGRA results in children

How to manage children with TST >15 mm with negative IGRA

Not all due to prior BCG immunisation

How reliable is an IGRA in detecting remote vs. recent infection
### T-SPOT TB Sensitivity

<table>
<thead>
<tr>
<th>Country</th>
<th>Sensitivity</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-income countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bamford, 2009, UK</td>
<td>50 (40–60)</td>
<td>11.63</td>
</tr>
<tr>
<td>Bergamini, 2009, Italy</td>
<td>100 (59–100)</td>
<td>10.54</td>
</tr>
<tr>
<td>Connell, 2008, Australia</td>
<td>100 (66–100)</td>
<td>10.99</td>
</tr>
<tr>
<td>Detjen, 2007, Spain</td>
<td>93 (77–99)</td>
<td>11.56</td>
</tr>
<tr>
<td>Dominguez, 2007, Spain</td>
<td>86 (42–100)</td>
<td>9.38</td>
</tr>
<tr>
<td>Kampmann, 2009, UK</td>
<td>54 (41–68)</td>
<td>11.35</td>
</tr>
<tr>
<td>Subtotal (I² = 90.9%, P = 0.000)</td>
<td>86 (67–100)</td>
<td>65.45</td>
</tr>
<tr>
<td>Low- and middle-income countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hansted, 2008, Lithuania</td>
<td>100 (85–100)</td>
<td>11.84</td>
</tr>
<tr>
<td>Nicol, 2009, South Africa</td>
<td>40 (27–53)</td>
<td>11.39</td>
</tr>
<tr>
<td>Warier, 2009, India</td>
<td>42 (28–56)</td>
<td>11.32</td>
</tr>
<tr>
<td>Subtotal (I² = 97.9%, P = 0.000)</td>
<td>77 (23–100)</td>
<td>34.55</td>
</tr>
<tr>
<td>Overall (I² = 94.6%, P = 0.000)</td>
<td>84 (63–100)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
TST

High-income countries
Chun, 2008, Korea
Specificity
99 (92–100)
Weight
17.8

QFT

High-income countries
Detjen, 2007, Germany
Specificity
100 (84–100)
Weight
28.2
Kampmann, 2009, UK
Specificity
88 (69–97)
Weight
15.6

Subtotal ($I^2 = 51.1\%, P = 0.153$)
Specificity
95 (84–100)
Weight
43.8

Low- and middle-income countries
Nicol, 2009, South Africa
Specificity
84 (71–93)
Weight
21.4
Warier, 2009, India
Specificity
98 (89–100)
Weight
34.9

Subtotal ($I^2 = 79.4\%, P = 0.027$)
Specificity
93 (83–100)
Weight
56.2

Overall ($I^2 = 58.0\%, P = 0.067$)
Specificity
94 (87–100)
Weight
100
### Table 3
Concordance of tests for *M. tuberculosis* infection with dichotomized exposure to tuberculosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Author, year, reference</th>
<th>Exposed positive/total</th>
<th>Unexposed positive/total</th>
<th>OR*</th>
<th>Pooled effects OR (95% CI)</th>
<th>Fixed</th>
<th>Random</th>
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</thead>
<tbody>
<tr>
<td>TST 5 mm</td>
<td>Banchi, 200933</td>
<td>19/38</td>
<td>154/289</td>
<td>4.4</td>
<td>1.5 (1.03–2.1)</td>
<td>1.3</td>
<td>0.7–2.7</td>
</tr>
<tr>
<td></td>
<td>Chunj, 200855</td>
<td>26/42</td>
<td>16/29</td>
<td>1.3</td>
<td>1.3 (1.03–1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hansted, 200956†</td>
<td>33/45</td>
<td>36/52</td>
<td>1.2</td>
<td>1.2 (0.98–1.4)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Higuchi, 200957†</td>
<td>20/38</td>
<td>183/268</td>
<td>0.5</td>
<td>0.5 (0.34–0.83)</td>
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</tr>
<tr>
<td></td>
<td>Lucas, 201068</td>
<td>12/26</td>
<td>83/278</td>
<td>2.0</td>
<td>2.0 (1.5–2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mandalakas, 200869†</td>
<td>0/6</td>
<td>4/17</td>
<td>0.2</td>
<td>0.2 (0.1–0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stefan, 201088†</td>
<td>0/4</td>
<td>4/30</td>
<td>0.7</td>
<td>0.7 (0.2–2.2)</td>
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<tr>
<td>TST 10 mm</td>
<td>Banchi, 200933</td>
<td>16/38</td>
<td>31/289</td>
<td>6.0</td>
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<td>1.9</td>
<td>0.98–3.8</td>
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<tr>
<td></td>
<td>Chunj, 200855</td>
<td>14/42</td>
<td>7/29</td>
<td>1.6</td>
<td>1.6 (1.1–2.6)</td>
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<tr>
<td></td>
<td>Hansted, 200956†</td>
<td>27/45</td>
<td>34/52</td>
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<td>0.8 (0.5–1.3)</td>
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<td></td>
<td>Hesseling, 200854†</td>
<td>14/26</td>
<td>1/2</td>
<td>1.2</td>
<td>1.2 (0.8–1.7)</td>
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<td>13/38</td>
<td>77/268</td>
<td>1.3</td>
<td>1.3 (0.9–1.7)</td>
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<tr>
<td></td>
<td>Lighter, 200967‡</td>
<td>5/13</td>
<td>8/30</td>
<td>4.4</td>
<td>4.4 (2.4–8.4)</td>
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<td>8/26</td>
<td>48/278</td>
<td>2.1</td>
<td>2.1 (1.5–2.8)</td>
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<td>0/4</td>
<td>4/30</td>
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<td>TST 15 mm</td>
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<td>9/38</td>
<td>16/289</td>
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<td>1.7 (1.00–3.0)</td>
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<td>0.7–5.0</td>
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<td>2/52</td>
<td>0.5</td>
<td>0.5 (0.2–1.3)</td>
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<td>Lucas, 201068</td>
<td>4/26</td>
<td>18/278</td>
<td>2.6</td>
<td>2.6 (1.5–3.9)</td>
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<tr>
<td>QuantIFERON®-TB</td>
<td>Banchi, 200933</td>
<td>17/38</td>
<td>35/287</td>
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<td>Dominguez, 200745</td>
<td>28/64</td>
<td>16/61</td>
<td>3.0</td>
<td>3.0 (1.8–4.9)</td>
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<td>5.0</td>
<td>5.0 (3.0–9.0)</td>
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<td>3/265</td>
<td>6.9</td>
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<td>Lighter, 200967‡</td>
<td>8/13</td>
<td>0/30</td>
<td>94</td>
<td>94 (50–167)</td>
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<td>T-SPOT®.TB</td>
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<td>13/61</td>
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<td>1.5</td>
<td>1.5 (0.7–3.2)</td>
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<td></td>
</tr>
</tbody>
</table>

* In the calculation of ORs, a value of 0.5 was added to all cells if one cell had a 0 value.
† Indicates country classified as low-, low middle or upper middle-income country according to the World Bank.
‡ Three exposure groups defined by Lighter et al. However, results from the intermediate group were excluded from analysis, as their exposure was judged too heterogeneous.
OR = odds ratio; CI = confidence interval; TST = tuberculin skin test.
Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries

Policy Statement
3.2.2 Summary of results

The majority of IGRA studies in children had been performed in high-income countries and extrapolation to low- and middle-income settings with high background TB infection rates was not appropriate. However, based on available data, the results indicated that in low- and middle-income countries:

- IGRAs and the TST had very similar accuracy for diagnosis of LTBI and active TB in children;

- Major methodological inconsistencies between studies had a negative effect on the comparability of studies and results. A key constraint was the lack of appropriate reference standards for diagnosis of paediatric TB, limiting the interpretation of estimates of test accuracy in children other than those with definite TB;

- A clear advantage of IGRAs over TST in detecting LTBI in exposed or unexposed individuals or in a gradient of exposure was not detected;

- Lower sensitivity of both IGRAs and TST was found in study populations with >50% BCG coverage. The reasons were not clear; however, BCG coverage may capture populations from settings with a higher burden of TB, hence with different epidemiological background and underlying conditions that may impair test accuracy, such as co-infections with helminths and malnutrition;

- Both IGRAs and TST showed lower sensitivity in HIV-infected children in one study assessed;
Overall, the ability of TST and IGRAs were suboptimal to ‘rule out’ active TB. The main limitation for assessment of the specificity of the diagnostic assays among ‘no-TB’ groups was the small number of studies that described adequate methodology to exclude and diagnose active TB;

**Policy recommendation:** IGRAs should not replace the TST in low- and middle-income countries for the diagnosis of latent TB infection in children, nor for the diagnostic work-up of children (irrespective of HIV status) suspected of active TB in these settings (strong recommendation). It should also be noted that there may be additional harms associated with blood collection in children and that issues such as acceptability and cost had not been adequately addressed in any studies.

relevant implementation considerations.

- A third of studies were supported by manufacturers of IGRAs, mainly through donation of test kits.
IGRA are not sensitive enough to be used as ‘rule-out’ test for TB

A positive IGRA (and or TST in the right population) is suggestive of infection

Average number of indeterminate results for QFT in children is ~7%

Current IGRA cannot differentiate between active TB disease and LTBI

Sensitivity of IGRA is lower in middle and low-income countries

Neither TST nor IGRA have been shown to be superior for the detection of LTBI

Positive predictive value remains unknown but negative predictive value appears high
**ABSTRACT**

**Aims** To compare the QuantiFERON-TB GOLD In Tube test (QTF) and the tuberculin skin test (TST) in children.

**Methods** A prospective study was carried out in nine hospitals in Madrid, Spain. TST and QTF were performed in immigrants, tuberculosis (TB) contacts and patients with TB disease (TBD).

**Results** 459 children were included. Disagreement between the tests was more frequently observed among latent tuberculosis infection (LTBI) cases (54%; 38/70) than in non-infected or TBD cases (0.8%; 3/369) (p<0.01). There were more BCG-vaccinated children among LTBI cases with negative QTF (76%) than among LTBI cases with positive QTF (40%) (p<0.001). Agreement between tests in BCG-vaccinated children was lower than in non-vaccinated cases (p<0.05). Tests in TB exposed patients showed better agreement than in non-exposed children (p<0.05).

**Conclusions** Agreement of both tests was excellent in TBD cases, non-vaccinated children and non-infected patients. A significant number of QTF negative results were observed among LTBI cases, especially in BCG-vaccinated children. Agreement was better in exposed children.
What about Australia?

### Guidelines

**POSITION STATEMENT ON INTERFERON-\(\gamma\) RELEASE ASSAY IN THE DETECTION OF LATENT TUBERCULOSIS INFECTION**

National Tuberculosis Advisory Committee

June 2012

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Active TB</th>
<th>Recommendation</th>
<th>Contacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGRA (like TST) should only be used as an adjunctive test in addition to standard microbiological and radiological investigations.</td>
<td></td>
<td>IGRA does not replace TST for detection of LTBI in children and (like TST) cannot be used to exclude LTBI. IGRA may have additional value over TST in children that received BCG vaccination after the first year of life.</td>
<td></td>
</tr>
</tbody>
</table>
IGRA

How do you use an IGRA in routine clinical practice in Australia? I do both TST and IGRA and treat if one test in positive

How confident are you to base treatment decisions on the result of an IGRA? Not very. Newer assays may improve test performance (stage specific antigens). TB research group at RCH (NHMRC project)

Do you think they can have an impact on Global TB control? No

What does the future hold?
Thank you
Influence of BCG on TST?

**BCG < 12 months of age**

*Joncas et al 1975, Lifschitz et al 1965*
- 12 months post BCG, 0/354 infants had TST > 10 mm

*Sleiman et al 2007*
- No difference in TST induration between BCG immunised and BCG unimmunised children (n=4000)

**BCG > 12 months of age**

*Menzies et al 1992*
- BCG 2-5 yrs: 10-15% TST + up to 10-25 years post immunisation
- BCG 6-10yrs: 25% TST+

> Joncas et al 1975 CMAJ;113(2):127-8
> Lifschitz Pediatrics 1965;36(4):624-7
> Sleiman et al PIDJ 2007;26(2):134-8
> Farhat et al IJTLID 2006; 10(11):1192-204
> Wang et al Thorax 2002;57(9)804-9
### Influence of BCG on TST?

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#### Reviews
- Farhat et al 2006
  - Analysis of 24 studies > 240,000 children
  - Only 1% TST > 10 mm 10 years post BCG (if < 12m)
  - 42% TST+ (if BCG > 12m)
- Wang et al 2002
  - TST cut-off > 15 mm more likely due to MTB infection
Good agreement between TST and QFT ($\kappa = 0.7$)

Indeterminate 4%

Several limitations