IGRAs
Utility in high and low burden settings
NDWG meeting, Lille, 2011

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Conflict of interest: Cellestis and OI have provided
in-kind co-funding for several studies that I have undertaken
‘How on earth do you keep up- there’s an IGRA paper published every minute………?’
A PhD student

**SRs and meta-analyses**

WHO commissioned several SR and MA’s on IGRA (Pai and Menzies; McGill)………11th STAG meeting (2010)….WHO policy (2011)
Europe- ECDC tender and TB-NET (Lange and Sester, TB-NET)
Overview

- What is an IGRA measuring, what is the reproducibility, and what have we learnt from serial testing?
- The life cycle of MTB
- What is the TST measuring?
- How do we evaluate IGRA’s?
- What are PPV and NPV of IGRA’s for active TB?
- In low burden countries (specificity, cost effectiveness, testing strategies, risk stratification, IMID)
- In high burden countries (active TB, extrapulmonary TB, children, and research focus)
- Summary
Dheda K, Respirology, 2010
IGRAs highly dynamic tests with high reversion rates

- Longitudinal data: suggest many IGRA test results are transient

N = 14 TST-ve IGRA+ve students

Ewer et al, AJRCCM, 2006

- Of 134 contacts, 54 (40.2%) underwent 3-mo ELISPOT reversion
  [less likely in those with a positive recruitment TST (OR 0.3, 95% CI 0.1–0.8, p= 0.014)].


Perry S, Clin Vaccine Imm, 2008

High week-to-week variability
Innate immunity
No detectable T cell priming (IGRA neg., TST neg.)

Close contacts inhale M.tb

Adaptive immunity
Evidence of T cell priming (IGRA pos., TST pos.)

~ 50% or more of exposed persons have no immuno
diagnostic evidence of M.tb sensitisation and may
remain uninfected through sterilizing immunity#

Evidence of T cell priming (IGRA pos., TST pos.)

1. Close contacts inhale M.tb

2. ~50% or more of exposed persons have no immuno
diagnostic evidence of M.tb sensitisation and may
remain uninfected through sterilizing immunity#

3. The remainder of exposed persons have
conversion of TST or IGRA and a
proportion have presumed infection**

4. LTBI**

5. Clinically detectable active or subclinical
disease

6. Reversion of TST or IGRA
(Acute or chronic resolving
infection)

7. Reinfection

In ~ 95 % containment

~ 5 %

~ 2 to 5 %

Schwander and Dheda, AJRCCM, 2011
Both IGRA formats are discordant
Need phlebotomist (15% of children cannot be bled)
Indeterminate rates are significant
Farrara G, Lancet, 2006
Of 503 adults at 2 clinics almost 20% of results inconclusive (7% refused phlebotomy, 8% could not be bled, 1% missed lab cutoff, 2% indeterminate
Dewan et al, BMC Infect Dis, 2006
Lab set-up, samples often batched
LTBI diagnosis: Mantoux or Tuberculin Skin Test (TST)

TST: PPD

Cell recruitment & activation

Memory T cell

Vukmanovic-Stejic M, Imm Letters, 2006
Drawbacks of the TST

- Requires return visit for which attendance is poor
- May result in ‘overtreatment’ due to BCG effect
- Results dependent upon observer and technique
- the TST may boost subsequent TST reactions
- Prone to breakage of cold chain and syringe re-use in resource poor setting

BUT plentiful longitudinal and predictive value data
Strong evidence for TST

- IPT is highly efficacious in TST+ subjects and reduces post-exp TB prevalence by 50 to 70%
- 13 studies in 7 countries with > 100,000 participants; 6 trials in household contacts
- Largest USPHS - 28,000 patients - 1st year 77% reduction in TB in the INH arm (highest reduction in 1st 5 years and in those with TST > 10mm [147 TB cases in the placebo and 57 in the INH arm]

Prognostic value of the TST shown strongly in recent Botswana IPT trial in HIV-infected subjects (n= 1655) TST-ve subjects showed no benefit of IPT vs 92% reduction in TST+ve subjects (8 other studies) Thus, TST giving a clinically relevant signal

Samandari T, IUATLD Cancun, 2009
Akolo C, The Cochrane Library, Issue 1, 2010
Specificity and the effect of BCG on the TST:

False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria?

M. Farhat,*† C. Greenaway,** M. Pai,**§ D. Menzies*

* Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, Quebec, Canada; † Massachusetts General Hospital, Harvard University, Boston, Massachusetts, USA; ‡ Division of Infectious Disease and Microbiology, SMBD-Jewish General Hospital, McGill University, Montreal, § Joint Departments of Epidemiology & Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

- Analysis of 24 studies with N = 240,243 subjects
- BCG given in infancy- false-positive TST occurs in < 1% of vaccinated subjects > 10 years after BCG vaccination
- When BCG is given after infancy, false-positive TST results due to BCG occur in 21% of vaccinated subjects
- < 2% effect of NTMs on TST (> 1 million subjects)
In India and Africa, BCG has limited effect on TST.
In Japan, BCG has a major effect on TST.

UK (stopped 2005), Japan, Russia, Japan, Italy (BCG given 6 to 12 years of age)
Limited relevance to most foreign born persons in the USA or UK.
How we grade the strength of evidence supporting the utility of IGRAs:

Efficacy of preventive therapy based on IGRA test results

Predictive value of IGRA for active TB

Correlation with exposure gradient

Sens/spec in active TB

Concordance with TST

NO DATA

IGRA = TST

Along an exposure gradient TST = IGRA (IGRA better in low burden and TST better in high burden)

IGRA = TST

Poor to modest

Stronger

Weaker

Rangaka M, Lancet Infect Dis, 2011


Menzies, Ann Int Med, 2007

Clinical medicine- not diagnostic result but impact important

Substantial for TST
Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis

Molebogeng X Rangaka, Katalin A Wilkinson, Judith R Glynn, Daphne Ling, Dick Menzies, Judith Mwansa-Kambafwile, Katherine Fielding, Robert J Wilkinson, Madhukar Pai

Summary
Background We aimed to assess whether interferon-γ release assays (IGRAs) can predict the development of active tuberculosis and whether the predictive ability of these tests is better than that of the tuberculin skin test (TST).

Methods Longitudinal studies of the predictive value for active tuberculosis of in-house or commercial IGRAs were identified through searches of PubMed, Embase, Biosis, and Web of Science and complementary manual searches up to June 30, 2011. Eligible studies included adults or children, with or without HIV, who were free of active tuberculosis at study baseline. We summarised incidence rates in forest plots and pooled data with random-effects models when appropriate. We calculated incidence rate ratios (IRR) for rates of disease progression in IGRA-positive versus IGRA-negative individuals.

Findings 15 studies had a combined sample size of 26,680 participants. Incidence of tuberculosis during a median follow-up of 4 years (IQR 2–6), even in IGRA-positive individuals, was 4–48 cases per 1000 person-years. Seven studies with no possibility of incorporation bias and reporting baseline stratification on the basis of IGRA results showed a moderate association between positive results and subsequent tuberculosis (pooled unadjusted IRR 2.10, 95% CI 1.42–3.08). Compared with test-negative results, IGRA-positive and TST-positive results were much the same with regard to the risk of tuberculosis (pooled IRR in the five studies that used both was 2.11 [95% CI 1.29–3.46] for IGRA vs 1.60 [0.94–2.72] for TST at the 10 mm cutoff). However, the proportion of IGRA-positive individuals in seven of 11 studies that assessed both IGRAs and TST was generally lower than TST-positive individuals.

Interpretation Neither IGRAs nor the TST have high accuracy for the prediction of active tuberculosis, although use of IGRAs in some populations might reduce the number of people considered for preventive treatment. Until more predictive biomarkers are identified, existing tests for latent tuberculosis infection should be chosen on the basis of relative specificity in different populations, logistics, cost, and patients’ preferences rather than on predictive ability alone.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Age group (years)</th>
<th>Individuals with HIV in cohort (%)</th>
<th>Population</th>
<th>Individuals assessed (n)</th>
<th>Individuals followed up and included in analysis (n)</th>
<th>IPT given (%)*</th>
<th>Tuberculosis diagnosed included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hill et al (2008)</td>
<td>The Gambia (LIC)</td>
<td>Adults and children (0.5–100)</td>
<td>Yes (2%)</td>
<td>Tuberculosis case-contacts</td>
<td>2381</td>
<td>2348</td>
<td>No</td>
<td>TST, smear, and culture</td>
</tr>
<tr>
<td>Bakir et al (2008)</td>
<td>Turkey (MIC)</td>
<td>Children (0–16)</td>
<td>Not stated</td>
<td>Tuberculosis case-contacts</td>
<td>1024</td>
<td>908</td>
<td>Yes (76% of 908)</td>
<td>Smear and culture</td>
</tr>
<tr>
<td>Aichelburg et al (2009)</td>
<td>Austria (HIC)</td>
<td>Adults (IQR 31–46)</td>
<td>Yes (100%)</td>
<td>Outpatients with HIV</td>
<td>834</td>
<td>822</td>
<td>No</td>
<td>IGRA and culture</td>
</tr>
<tr>
<td>Del Corral et al (2009)</td>
<td>Colombia (MIC)</td>
<td>Adults and children (IQR 10–42)</td>
<td>Unknown†</td>
<td>Tuberculosis case-contacts</td>
<td>2060</td>
<td>2060</td>
<td>No</td>
<td>Smear and culture</td>
</tr>
<tr>
<td>Lienhardt et al (2010)</td>
<td>Senegal (LIC)</td>
<td>Adults and children (18–71)</td>
<td>Unknown†</td>
<td>Tuberculosis case-contacts</td>
<td>2762</td>
<td>2679</td>
<td>Yes (% NS)</td>
<td>Smear and culture</td>
</tr>
<tr>
<td>Yoshiyama et al (2010)</td>
<td>Japan (HIC)</td>
<td>Adults and children (0–60+)</td>
<td>Unknown†</td>
<td>Tuberculosis case-contacts (retrospective)</td>
<td>NS</td>
<td>5676</td>
<td>Yes (20% of 3102)</td>
<td>IGRA†</td>
</tr>
<tr>
<td>Leung et al (2010)</td>
<td>China (MIC)</td>
<td>Adults (mean 60)</td>
<td>Unknown†</td>
<td>Outpatients with silicosis</td>
<td>331</td>
<td>308</td>
<td>Yes (33% of 203)</td>
<td>Smear and culture</td>
</tr>
<tr>
<td>Harstad et al (2010)</td>
<td>Norway (HIC)</td>
<td>Adults (18–50+)</td>
<td>Unknown†</td>
<td>Asylum seekers</td>
<td>NS</td>
<td>823</td>
<td>Yes (3%)</td>
<td>IGRA†</td>
</tr>
<tr>
<td>Diel et al (2010)</td>
<td>Germany (HIC)</td>
<td>Adults and children (1–62)</td>
<td>No; exclusion criterion</td>
<td>Tuberculosis case-contacts</td>
<td>1417</td>
<td>1335</td>
<td>Yes (% NS)</td>
<td>TST, IGRA, and culture</td>
</tr>
<tr>
<td>Jonnalagadda et al (2010)</td>
<td>Kenya (LIC)</td>
<td>Adults (24–26)</td>
<td>Yes (100%)</td>
<td>HIV cohort with no prior tuberculosis (retrospective)</td>
<td>333</td>
<td>258</td>
<td>No</td>
<td>Self-reported</td>
</tr>
</tbody>
</table>
IGRA and TST were similar wrt the risk of TB (pooled IRR in the 5 studies that used both:

- **2.11 [1.29–3.46]** for IGRA
- **1.60 [0.94–2.72]** for TST at the 10 mm cutoff

TST and IGRAs have weak but similar predictive value and may not help ID those at highest risk of progression to disease.

PPV for TB in IGRA positive individuals is low (< 5%) similar to the TST.
Interferon-γ release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis


ABSTRACT: We conducted a systematic review and meta-analysis to compare the accuracy of the QuantIFERON-TB® Gold In-Tube (QFT-GIT) and the T-SPOT.TB assays with the tuberculin skin test (TST) for the diagnosis of latent Mycobacterium tuberculosis infection (LTBI).

The Medline, Embase and Cochrane databases were explored for relevant articles in November 2009. Specificity, and negative (NPV) and positive (PPV) predictive values of interferon-γ release assays (IGRAs) and the TST, and the exposure gradient influences on test results among bacille Calmette-Guérin (BCG) vaccines were evaluated.

Specificity of IGRAs varied 96–100%. In immunocompetent adults, NPV for progression to tuberculosis within 2 yrs was 97.8% for T-SPOT.TB and 99.9% for QFT-GIT. When test performance of an immunodiagnostic test was not restricted to prior positivity, progression rates to tuberculosis among IGRA-positive individuals followed 19–24 months varied 8–15%, exceeding those reported for the TST (2–3%). In multivariate analyses, the odd ratios for TST positivity following BCG vaccination varied 3–5, whereas IGRA results remained uninfluened and IGRA positivity was clearly associated with exposure to contagious tuberculosis cases.

IGRAs may have a relative advantage over the TST in detecting LTBI and allow the exclusion of M. tuberculosis infection with higher reliability.

KEYWORDS: ECDC, interferon-γ release assay, latent Mycobacterium tuberculosis infection, meta-analysis, systematic review, TBNET

Improvement of diagnostic methods for latent Mycobacterium tuberculosis infection (LTBI) is an important step towards the goal of tuberculosis elimination, as laid out by the WHO Stop TB strategy [1] and The European Centre for Disease Prevention and Control (ECDC) Framework Action Plan to Fight TB in the European Union [2]. As part of reaching this goal, individuals infected with M. tuberculosis need to be identified and offered preventive therapy to stop the progression to active tuberculosis and prevent further M. tuberculosis transmission [3]. Thus, there is a need to develop more accurate methods for the detection of LTBI and to provide evidence-based guidance on the use of such methods before they can be adopted by national tuberculosis screening programmes [4, 5].

In most areas of Europe, the identification of LTBI relies on the tuberculin skin test (TST). This diagnostic test has been assessed comprehensively in terms of its potential and limitations for use in preventive strategies for tuberculosis elimination [6]. However, the TST does not discriminate between potential infection with M. tuberculosis and prior vaccination with the bacille Calmette-Guérin (BCG), or possible infection with nontuberculous mycobacteria (NTM).

Interferon (IFN)-γ release assays (IGRAs) are in vitro immune tests that have been introduced in recent years as an alternative to the TST for the diagnosis of LTBI. IGRAs are based on the detection of a T-cell immune response towards M. tuberculosis complex specific antigens (early secretory antigenic target (ESAT)-6, culture filtrate protein (CFP)-10 and/or TFB7). To date, there are two commercially available platforms that measure IFN-γ production following ex vivo antigen stimulation [7] in the QuantIFERON-TB...
PPV of IGRAs= 10% in UK (2/20 TB cases/ IGRA+ve)
14% in Germany (6/41) ,
2 to 3% (6/181) in Holland
Negative predictive value (NPV) for progression to TB

T-Spot.TB

QFT-G-IT

Pooled NPV: 0.98 (0.94–0.99)
Chi-squared=5.66; df=2 (p=0.0533)
Inconsistency $I^2=65.9\%$

Pooled NPV: 0.998 (0.994–1.0)
Chi-squared=13.67; df=3 (p=0.0034)
Inconsistency $I^2=78.1\%$
Low burden countries

- LTBI and eliminating the reservoir of disease is a key priority

- Better specificity of IGRAs in those BCG vaccinated after birth, and need for only a single visit, are obvious advantages
Guidelines on interferon-γ release assays for tuberculosis infection: concordance, discordance or confusion?

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1) Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA, 2) Lung Infection and Immunity Unit, Division of Pulmonology and UCT Lung Institute, Department of Medicine, University of Cape Town, Cape Town, South Africa, 3) Department of Infection, University College London Medical School, London, UK, 4) Department of Epidemiology, Biostatistics, and Occupational Health, McGill University and 5) Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, Montreal, QC, Canada

Abstract

Identification of latent tuberculosis (TB) infection and preventive therapy is important for TB control, especially in high-risk populations. Since the advent of interferon-γ release assays (IGRAs), many studies have evaluated their role in the diagnosis of active and latent TB. With the growing evidence base, many guidelines now include IGRAs. We surveyed the literature and contacted experts to identify 33 guidelines and position papers from 25 countries and two supranational organizations. The results show considerable diversity in the recommendations on IGRAs, with four approaches commonly proposed: (i) two-step approach of tuberculin skin test (TST) first, followed by IGRA either when the TST is negative (to increase sensitivity, mainly in immunocompromised individuals), or when the TST is positive (to increase specificity, mainly in bacillus Calmette–Guérin-vaccinated individuals); (ii) Either TST or IGRA, but not both; (iii) IGRA and TST together (to increase sensitivity); and (iv) IGRA only, replacing the TST. Overall, the use of IGRAs is increasingly recommended, but most of the current guidelines do not use objective, transparent methods to grade evidence and recommendations, and do not disclose conflicts of interests. Future IGRA guidelines must aim to be transparent, evidence-based, periodically updated, and free of financial conflicts and industry involvement.

Keywords: Diagnosis, guidelines, immunodiagnostics, interferon-γ release assays, tuberculosis

Article published online: 25 April 2011

Clin Microbiol Infect 2011; 17: 806–814
What do most of the guidelines say?

- >16 countries that have at least one guideline:
  - USA, Canada, UK, Japan, France, Spain, Italy, Germany, Switzerland, Australia, Netherlands, Denmark, Czech Republic, Slovak Republic, Korea and Norway.

- Of the countries that have guidelines, 3 main approaches are discernible:
  - TST should be replaced by IGRA (i.e. only IGRA)
  - Either TST or IGRA may be used
  - Two-step approach (dual strategy) of TST first, followed by IGRA

- Some guidelines recommend more than one approach, depending on the risk group tested
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Guideline or position statement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TST alone</strong></td>
<td>WHO, Brazil, ECDC (high-incidence countries)</td>
</tr>
<tr>
<td><strong>TST followed by IGRA, if TST positive</strong></td>
<td>Canada (low-risk contacts), Germany, Italy, Switzerland, Spain, Saudi Arabia, the Netherlands, Norway, Bulgaria, Portugal, Ireland, ECDC (low-incidence countries), and for UK and South Korea only in adults &lt;35 years old</td>
</tr>
<tr>
<td>(either IGRA only in BCG-vaccinated persons or independent of BCG vaccine)</td>
<td></td>
</tr>
<tr>
<td><strong>Both TST and IGRA</strong></td>
<td>Canada (high-risk contacts), Czech Republic, Croatia, Austria, Australia (IGRA may be considered in addition)</td>
</tr>
<tr>
<td><strong>Either TST or IGRA</strong></td>
<td>USA, Denmark, Finland (IGRA preferred if BCG-vaccinated in all three countries), South Korea (only in adults &lt;35 years old), Austria Slovakia, Japan, France</td>
</tr>
<tr>
<td><strong>IGRA alone</strong></td>
<td></td>
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</tbody>
</table>
Interferon-gamma release assays for diagnosis of latent tuberculosis infection: evidence in immune-mediated inflammatory disorders
Rachel Smith\textsuperscript{a,\*}, Adithya Cattamanchi\textsuperscript{b,\*}, Karen R. Steingart\textsuperscript{c}, Claudia Denkinger\textsuperscript{d}, Keertan Dheda\textsuperscript{e}, Kevin L. Winthrop\textsuperscript{f} and Madhukar Pai\textsuperscript{g}

<table>
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<th>Guideline or position statement\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST alone</td>
<td>Brazil</td>
</tr>
<tr>
<td>TST followed by IGRA, if TST positive</td>
<td>Spain, Norway</td>
</tr>
<tr>
<td>TST followed by IGRA, if TST negative</td>
<td>Canada, Italy, Spain, Saudi Arabia</td>
</tr>
<tr>
<td>Either TST or IGRA</td>
<td>Australia-ARA, Denmark (IGRA favoured), South Korea, ECDC, UK (alternatively IGRA alone), USA (if either initial test negative), Portugal, Croatia, Czech Republic, Slovakia, the Netherlands, South Korea, Ireland (TST preferred)</td>
</tr>
<tr>
<td>Both TST and IGRA</td>
<td>Australia-NTAC</td>
</tr>
<tr>
<td>IGRA alone</td>
<td>Germany, Switzerland, Bulgaria, Japan, France, Poland, Austria, Finland, Australia-NTAC</td>
</tr>
<tr>
<td>No recommendations</td>
<td></td>
</tr>
</tbody>
</table>
Major trends

☐ Two-step approach (dual strategy) seems to be the most favored, especially BCG-vaccinated contacts
Within-Subject Variability and Boosting of T-Cell Interferon-γ Responses after Tuberculin Skin Testing


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A

IFN-γ (IU/ml)

Visit days

TST administration

QFT

IFN-γ (IU/ml)

Visit days

TST administration

AJRCCM 2009
Dual strategy is the most cost-effective in several settings

- UK- close contacts and comparing TST vs QFT vs T.SPOT vs TST/QFT vs TST/T.SPOT, considering cases of post-primary TB and ADR’s to INH
Similar conclusions from other studies in UK, Canada, Switzerland and Germany

Oxlade et al, Int J Tuberc Lung Dis, 2007 (Canada- immigrants)
Diel et al, Chest, 2007 (Germany- contacts)
Diel et al, Eur Respir J, 2006 (Germany- contacts)
Wrighton-Smith P et al, Eur Respir J, 2006 (Switzerland- contacts)
NHS NICE guidelines, March 2006 (UK, contacts)
Tuberculin skin test: needs careful interpretation (www.tstin3d.com)

Thinking in three dimensions: a web-based algorithm to aid the interpretation of tuberculin skin test results

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†Massachusetts General Hospital, Harvard University, Boston, Massachusetts, USA; †Division of Infectious Disease and Microbiology, Sir Mortimer B Davis Jewish General Hospital, McGill University, Montreal, Canada; §Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada

The Online TST/IGRA Interpreter

Version 3.0

The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of ≥5mm, based on his/her clinical profile. It is intended for adults tested with standard tuberculin (5TU PPDs, or 2 TU RT-23) and/or a commercial Interferon Gamma release assay (IGRA). For more details about the algorithm used, go to the About page. The current version of the algorithm contains modifications of the original version, which was detailed in a paper by Menzies, et al. (2008). For further information see references, or contact dick.menzies@mcgill.ca

Please select the best response for each field:

TST Size: IGRA Result:

Age at immigration (if person immigrated to a low TB incidence country):
Age:
Country of birth:

BCG status:
For more info, visit: BCG World Atlas.
Recent contact with active TB:

If none of these conditions apply, please leave boxes unchecked:

AIDS
Abnormal chest x-ray: fibronodular disease
Chronic renal failure requiring hemodialysis
Diabetes Mellitus (all types)
Recent TB infection (TST conversion ≥ 2 years ago)
Silicosis
Tumor Necrosis Factor (TNF) - alpha inhibitors (e.g. Infliximab/Etanercept)
Young age when infected (0-4 years)

Abnormal chest x-ray: granuloma
Carcinoma of head and neck
Cigarette smoker (>1 pack/day)
HIV infection
Transplantation (requiring immune-suppressant therapy)
Treatment with glucocorticoids
Underweight (< 90% per cent ideal body weight or a body mass index (BMI) ≤ 20)

(Likelihood of true pos test) is: 87.18%
The annual risk of development of active TB = 0.09%. The cumulative risk of active tuberculosis disease, up to age of 80 = 4.18%, risk of drug-induced hepatitis is 0.3%
High Burden settings- active TB is the priority

500 TB suspects in Cape Town- culture= ref standard

QFT-GIT

TSPOT-TB

- Miss 1/3 TB
- Erroneously diagnose active TB in 60% who do not have TB

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR (n=311)</td>
<td>99 (95, 100)</td>
<td>28 (22, 34)</td>
<td>40 (34, 46)</td>
<td>98 (91, 100)</td>
</tr>
<tr>
<td>QFT-GIT (n=362)</td>
<td>76 (68, 83)</td>
<td>42 (36, 49)</td>
<td>44 (38, 51)</td>
<td>74 (66, 82)</td>
</tr>
<tr>
<td>QFT-GIT in smear-negatives (n=263)</td>
<td>73 (56, 85)</td>
<td>42 (35, 49)</td>
<td>18 (13, 25)</td>
<td>89 (82, 95)</td>
</tr>
<tr>
<td>TSPOT-TB (n=372)</td>
<td>84 (77, 90)</td>
<td>46 (39, 52)</td>
<td>47 (40, 53)</td>
<td>84 (76, 90)</td>
</tr>
<tr>
<td>TSPOT-TB in smear-negatives (n=274)</td>
<td>74 (57, 87)</td>
<td>46 (39, 52)</td>
<td>18 (12, 25)</td>
<td>92 (85, 96)</td>
</tr>
</tbody>
</table>

Ling D and Dheda K, Eur Resp J, 2011
IGRA in EPTB (using cells from the site of disease)

- IGRAs not useful in pleural TB (poor specificity)
- Good accuracy in BAL but 1/3 of tests inconclusive
- Works very well in TBM when used in conjunction with CLAT and Gram stain

Dheda K, ERJ, 2009
Dheda K, Thorax, 2009
Patel and Dheda, AJRCCM, 2010
EPTB
unstimulated IFN-g is the most accurate assay

- Pleural TB: SENS = 97 SPEC= 100%
  Dheda K, Eur Resp J, 2009

- TBM: SENS = 95 SPEC= 99%
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Interferon-gamma release assays and childhood tuberculosis: systematic review and meta-analysis

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SUMMARY

BACKGROUND: Children infected with Mycobacterium tuberculosis have significant risk of developing tuberculosis (TB) and can therefore benefit from preventive therapy.

OBJECTIVE: To assess the value of interferon-gamma release assays (IGRAs) and the tuberculin skin test (TST) in the diagnosis of TB infection and disease in children.

METHODS: Thirty-three studies were included, assessing commercial IGRAs (QuantiFERON®-TB [QFT] and T-SPOT.®TB) and TST. Reference standards for infection were incident TB or TB exposure. Test performance for disease diagnosis was evaluated in studies assessing children with confirmed and/or clinically diagnosed TB, compared to children where TB was excluded.

RESULTS: Two small studies measured incident TB in children tested with QFT and found weak positive predictive value. Association of test response with exposure —categorized dichotomously or as a gradient—was similar for all tests. The sensitivity and specificity of all tests were similar in diagnosing the disease. Stratified analysis suggested lower sensitivity for all tests in young or human immunodeficiency virus infected children.

CONCLUSIONS: Available data suggest that TST and IGRAs have similar accuracy for the detection of TB infection or the diagnosis of disease in children. Heterogeneous methodology limited the comparability of studies and the interpretation of results. A rigorous, standardized approach to evaluate TB diagnostic tests in children is needed.

KEY WORDS: tuberculosis; pediatrics; TB infection; IGRAs; tuberculin skin test
Research agenda in high burden settings

- LTBI diagnosis in HIV-infected persons
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200 HIV-infected persons; CD4 380 (range 25-1227)

**TST as ‘Gold Standard’**

- IGRA’s only identify ≈2/3 of TST positive subjects
- IGRA’s identified 30% of subjects who were TST-ve

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>59.5%</td>
<td>67.5%</td>
<td>29.3%</td>
<td>88%</td>
</tr>
<tr>
<td>TSPOT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST-QFT</td>
<td>78.1%</td>
<td>62.1%</td>
<td>33.3%</td>
<td>92.1%</td>
</tr>
</tbody>
</table>
Research agenda in high burden settings

- LTBI diagnosis in HIV-infected persons
- Predictive tool in HIV-infected persons
- Serial testing of HCWs

Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review

Alice Zwerling,¹ Susan van den Hof,²,³ Jerod Scholten,² Frank Cobelens,²,³ Dick Menzies,¹ Madhukar Pai¹
Low burden settings:

• LTBI priority
• IGRA’s useful in BCG vaccinated subjects (after birth), cost effective and only a single visit is required. Thus, IGRA’s have relative advantage over the TST.
• Testing strategy is variable and controversial - most popular is the dual strategy, i.e. TST followed by IGRA
• Nevertheless, TST alone still acceptable as a test for LTBI
• IMID, most sensible approach is to do both tests for maximal sensitivity but false negative results interpreted clinical context

• Which test – IGRA or TST or what combination will depend on the available resources, logistics and national guidelines
• Clinical risk stratification is crucial and more emphasis needs to be put on compliance and completion of chemoprophylaxis.
High burden settings:

- Currently no clear role for IGRA’s in high burden settings.
- Not useful for active TB (blood)
- For extrasanguinous fluids IGRA’s have limited utility, except perhaps for TB meningitis
- Nevertheless, unstimulated interferon gamma performs equally well or better than IGRA’s for extrapulmonary TB.

IGRA and TST are both imperfect tests with a low predictive value for active TB and better predictive tools are required (latency antigens, HBHA, other antigens).
Funding Agencies:

- EUFP7
- EDCTP
- South African National Research Foundation
- NIH Fogerty
- Discovery
- EDCTP
- South African MRC