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

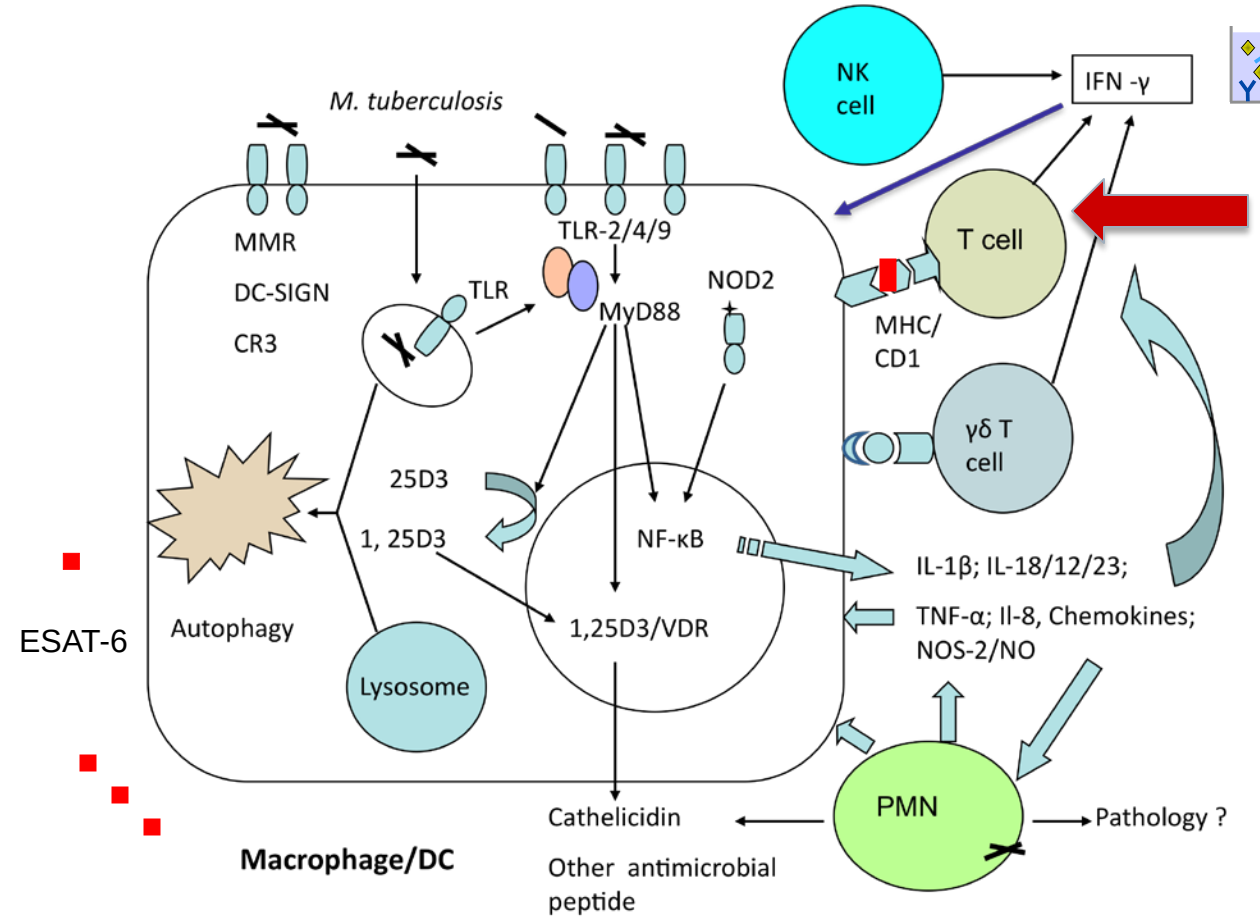
‘How on earth do you keep up- there’s an IGRA paper published every minute…….?’
A PhD student

SRs and meta-analyses

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

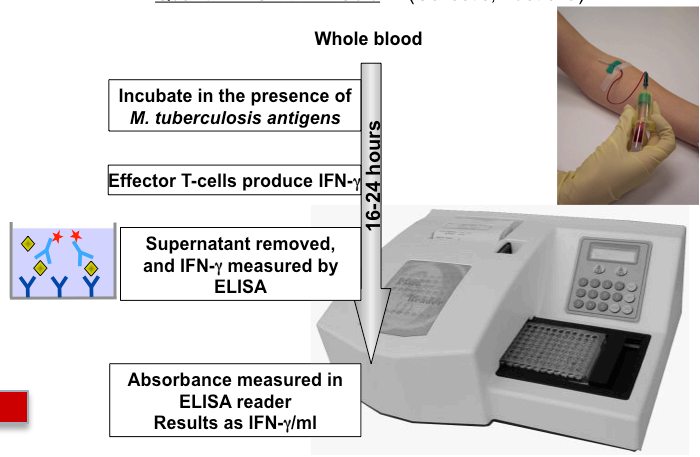
Overview

- 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



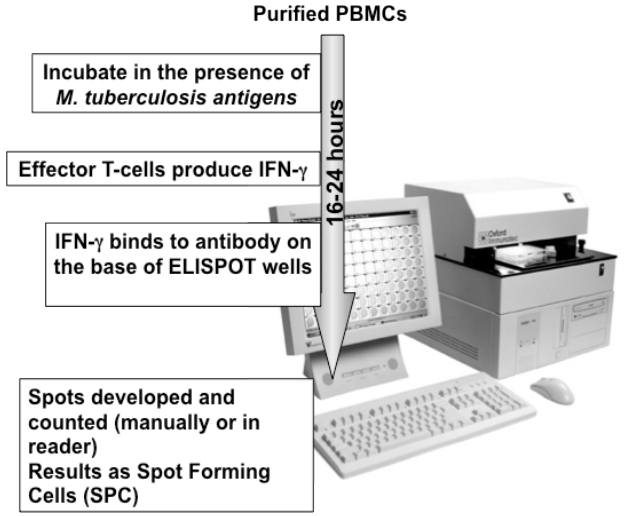
ESAT-6

QuantiFERON®-TB Gold IT (Cellestis, Australia)



Reviewed in Dheda K, Curr Op Pulm Med, 2009

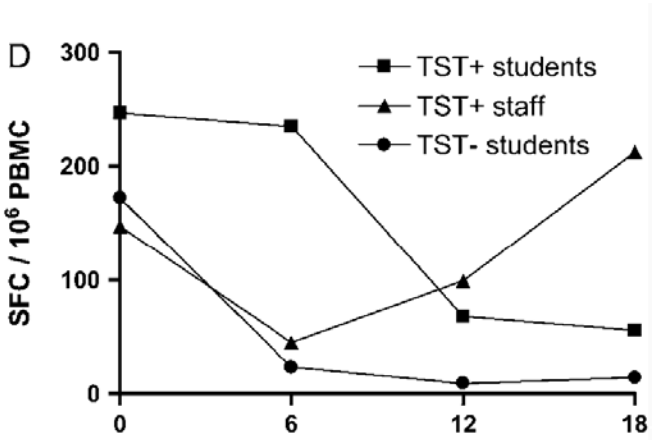
T SPOT TB assay, Oxford Immunotec, UK



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)].

Hill P, PLoS Med, 2007

Perry S, Clin Vaccine Imm, 2008

Pai M, AJRCCM, 2006; Franken WP, Clin Vacc Imm, 2007, Pai M, AJRCCM, 2006

Within-Subject Variability and Boosting of T-Cell Interferon-γ Responses after Tuberculin Skin Testing

Richard N. van Zyl-Smit[1], Madhukar Pai[2], Kwaku Peprah[1], Richard Meldau[1], Jackie Kleck[1], June Juritz[4], Motasim Badri[1], Alimuddin Zumla[5], Leonardo A. Sechi[6], Eric D. Bateman[1], and Keertan Dheda[1,5,7]

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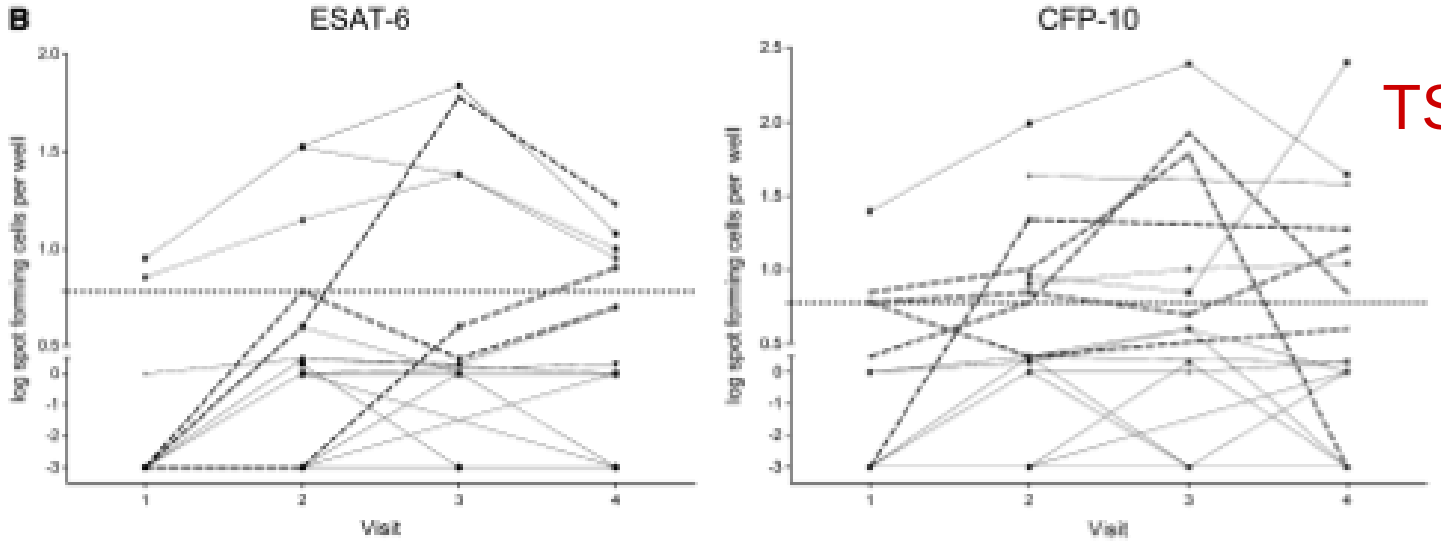


TSPOT-TB

- High week-to-week variability

Innate immunity
No detectable T cell priming (IGRA neg., TST neg.)

Alveolar pneumocytes

Clearance of infection

NK-cells

Neutrophils

NK-T cells

Macrophages

β-defensin

γδ T-cells

Cathelicidin

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

T cell

CD4⁺ T cells

Cytokines

Th1,Th2 & Th17 CD4⁺ T cells

Macrophage

CD1 lipid

CD4 Naive T cell

TLR2 TLR4 TLR9

M.tb

MHC-II

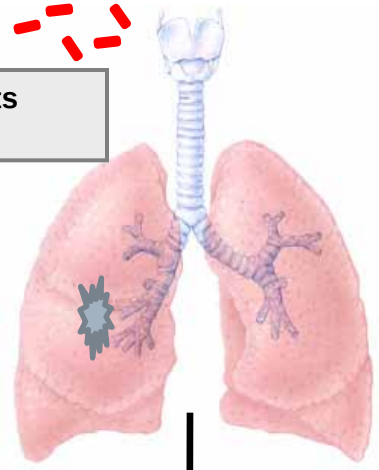
MHC-I

CD8 Naive T cell

CD8⁺ T cells

Treg

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**

In ~ 95 % containment

~ 5 %

~ 2 to 5 %

4. LTBI**

5. Clinically detectable active or subclinical disease

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

7. Reinfection

Schwander and Dheda, AJRCCM, 2011

IGRA

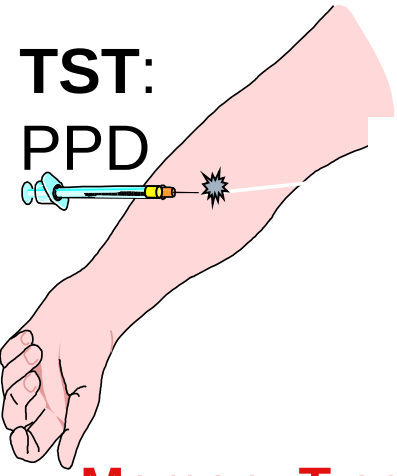
- Both IGRA formats are discordant
- Need phlebotomist (15% of children cannot be bled)
- Indeterminate rates are significant

  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

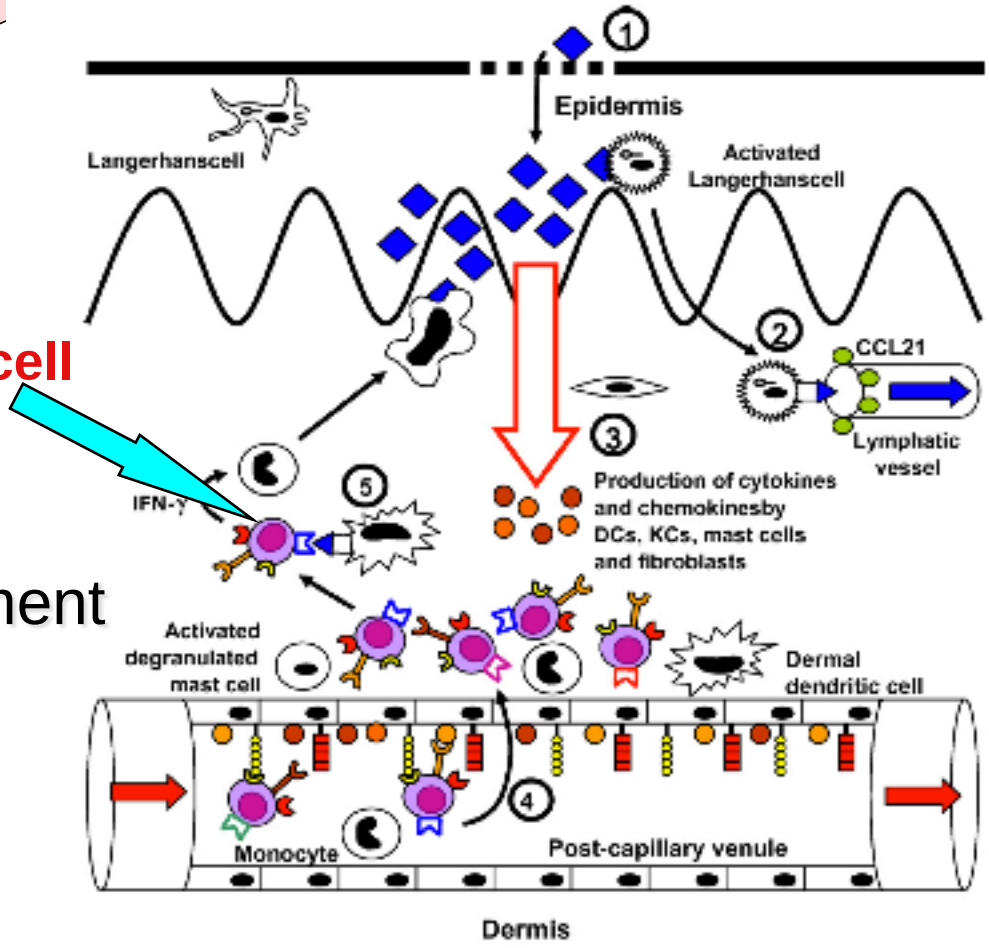
LTBI diagnosis: Mantoux or Tuberculin Skin Test (TST)

TST:
PPD



Memory T cell

Cell recruitment
& activation



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- 28000 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]

    Ferebee SH, Controlled Chemoprophylaxis Trials in TB, A General Review. Adv Tuberc Res, 17, 1970, 28-106

- 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:

INT J TUBERC LUNG DIS 10(11):1192–1204

REVIEW ARTICLE

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

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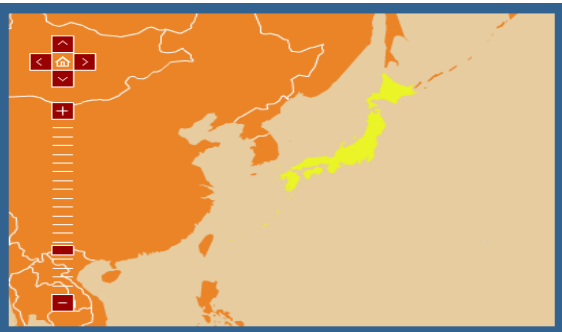
- Analysis of 24 studies with N = 240,243 subjects
- BCG given in infancy- false-positive TST occurs in < 1% of vaccinated subjects > 10 years after BCG vaccination
- When BCG is given after infancy, false-positive TST results due to BCG occur in 21% of vaccinated subjects
- < 2% effect of NTMs on TST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

In India and Africa, BCG has limited effect on TST
In Japan, BCG has a major effect on TST

Japan

Country	Japan
Region	..
TB Prevalance per 100,000	29
Number of TB cases per year	37490
Income group (World Bank)	High income: OECD
Current BCG vaccination?	Yes
BCG Recommendation Type	A
Which year was vaccination introduced?	1942/1951
Year BCG stopped?	After birth
Timing of 1st BCG?	No
Multiple BCG?	N/A
Timing of BCG #2	N/A
Timing of BCG #3	N/A
Multiple BCG in the past?	Yes
Timing of old BCG #2	6-13 years (every year if TST negative)
Timing of old BCG #3	N/A
Year booster BCG stopped	stopped in 2003
BCG Strain	Tokyo 172, Japan BCG Laboratory
Is TST done post BCG?	No
Year of BCG cooverage estimate	2006
BCG coverage (%)	98.1
Year of changes to BCG schedule	2005, restricted to those under 6 mo without a preceding TST (?) 1974 restricted to prinary and secondary school entrants who are TST negchanging age of 1st vaccination and age of revaccination (within 4yr and at the age of 7 and 13, if negative of TST.) changing age of 1st vaccination and ceasing revaccination



BCG Recommendation Types

Type	Description
A	This country currently recommends BCG vaccination for everyone at a certain age. (Example: BCG at birth or for school-age children, etc.)
B	This country used to recommend BCG vaccination for everyone, but currently does not.
C	BCG vaccination was never recommended for everyone in this country. (i.e.: never gave BCG or given only to high risk groups such as health care workers.)

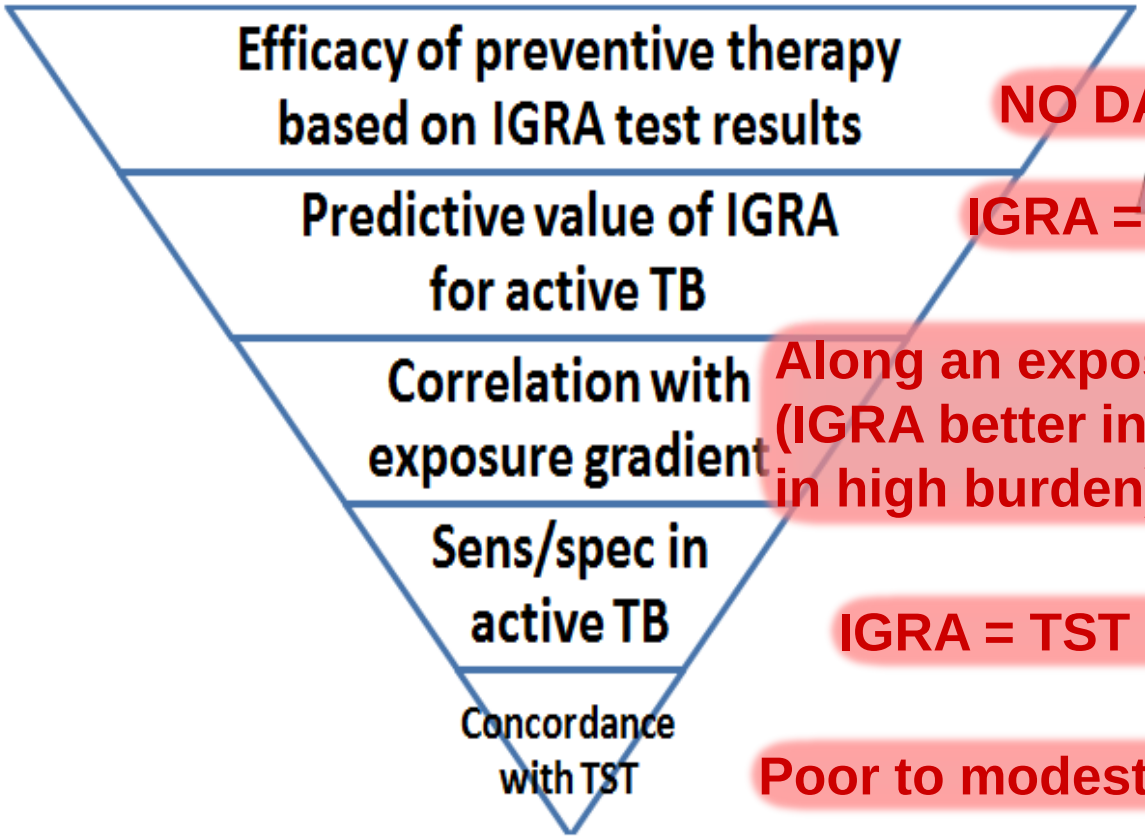
Data Availability

Entry	Description
NA	This entry is not applicable to this country.
(Blank)	This data was not available.

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:



Stronger

NO DATA

IGRA = TST

Rangaka M, Lancet Infect Dis, 2011

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

Dheda K, Curr Op Pulm Med, 2009

IGRA = TST

Menzies, Ann Int Med, 2007

Poor to modest

Weaker

Clinical medicine- not diagnostic result but impact important
Substantial for TST

Predictive value of IGRAs

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.

Rangaka M, Lancet Infect Dis, 2011

	Country (income status)	Age group (years)	Individuals with HIV in cohort (%)	Population	Individuals assessed (n)	Individuals followed up and included in analysis (n)	IPT given (%)*	Tuberculosis diagnoses included
Doherty et al (2002)[30]	Ethiopia (LIC)	Adults (15–65)	No; exclusion criterion	Tuberculosis case-contacts	38	24	No	Smear and culture
Hill et al (2008)[32]	The Gambia (LIC)	Adults and children (0·5–100)	Yes (2%)	Tuberculosis case-contacts	2381	2348	No	TST, smear, and culture
Bakir et al (2008)[27]	Turkey (MIC)	Children (0–16)	Not stated	Tuberculosis case-contacts	1024	908	Yes (76% of 908)	Smear and culture
Aichelburg et al (2009)[26]	Austria (HIC)	Adults (IQR 31–46)	Yes (100%)	Outpatients with HIV	834	822	No	IGRA and culture
Kik et al (2009)[35]	Netherlands (HIC)	Adults (16–45+)	No; exclusion criterion	Tuberculosis case-contacts	433	339	No; exclusion	Smear and culture
Del Corral et al (2009)[28]	Colombia (MIC)	Adults and children (IQR 10–42)	Unknown†	Tuberculosis case-contacts	2060	2060	No	Smear and culture
Lienhardt et al (2010)[37]	Senegal (LIC)	Adults and children (18–71)	Unknown†	Tuberculosis case-contacts	2762	2679	Yes (% NS)	Smear and culture
Yoshiyama et al (2010)[39]	Japan (HIC)	Adults and children (0–60+)	Unknown†	Tuberculosis case-contacts (retrospective)	NS	5676	Yes (20% of 3102)	IGRA‡
Leung et al (2010)[36]	China (MIC)	Adults (mean 60)	Unknown†	Outpatients with silicosis	331	308	Yes (33% of 203)	Smear and culture
Harstad et al (2010)[31]	Norway (HIC)	Adults (18–50+)	Unknown†	Asylum seekers	NS	823	Yes (3%)	IGRA‡
Diel et al (2010)[29]	Germany (HIC)	Adults and children (1–62)	No; exclusion criterion	Tuberculosis case-contacts	1417	1335	Yes (% NS)	TST, IGRA, and culture
Jonnalagadda et al (2010)[33]	Kenya (LIC)	Adults (24–26)	Yes (100%)	HIV cohort with no prior tuberculosis (retrospective)	333	258	No	Self-reported

- 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

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DOI: 10.1183/09031936.00115110

Interferon-γ release assays for the diagnosis of latent *Mycobacterium tuberculosis* infection: a systematic review and meta-analysis

R. Diel, D. Goletti, G. Ferrara, G. Bothamley, D. Cirillo, B. Kampmann, C. Lange, M. Losi, R. Markova, G.B. Migliori, A. Nienhaus, M. Ruhwald, D. Wagner, J.P. Zellweger, E. Huitric, A. Sandgren and D. Manissero

ABSTRACT: **We conducted a systematic review and meta-analysis to compare the accuracy of the QuantiFERON-TB® Gold In-Tube (QFT-G-IT) 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. Specificities, 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) vaccinees were evaluated.

Specificity of IGRAs varied 98–100%. In immunocompetent adults, NPV for progression to tuberculosis within 2 yrs were 97.8% for T-SPOT®.*TB* and 99.8% for QFT-G-IT. When test performance of an immunodiagnostic test was not restricted to prior positivity of another test, progression rates to tuberculosis among IGRA-positive individuals followed for 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 3–25, whereas IGRA results remained uninfluenced 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 TB7.7). To date, there are two commercially available platforms that measure IFN-γ production following *ex vivo* antigen stimulation [7]: in the QuantiFERON®-TB

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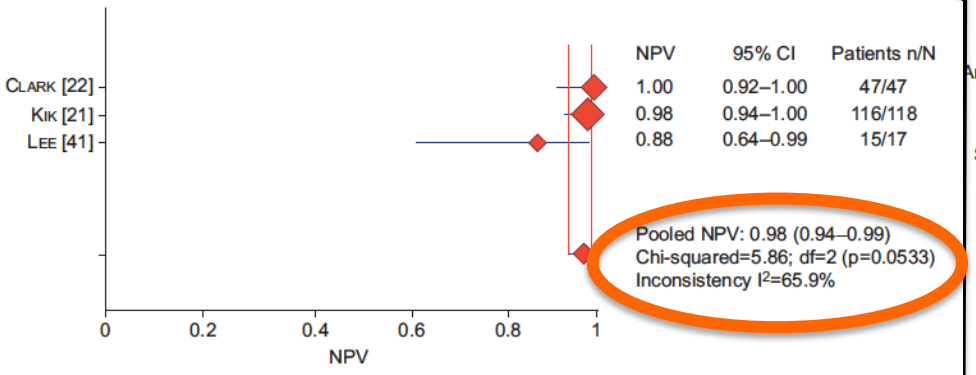
TABLE 2 Positive predictive value (PPV) of commercial interferon-γ release assays (IGRAs) for progression in those with latent *Mycobacterium tuberculosis* infection

First author [ref.]	Study design	Participants	Country (burden)	IGRA(s) used	Age mean±SD[#] yrs	Performance of IGRA and TST testing	Follow-up period months	Later TB cases among untreated IGRA/TST positives n/N (PPV % (95% CI))[¶]	Later TB cases among IGRA/TST-positives with confirmed relationship to index cases by RFLP n/N (%)
Clark [22]	Case–control	201 immune-deficient HIV-1-positive adults	UK (low)	T-SPOT®.*TB*	Median 40 (range 33–46)	NA	24	T-SPOT®.*TB*: 2/20 (10 (0.012–0.32)); TST: NA	NA
Diel [20]	Cohort	601 close contacts of AFB-positive TB cases (66 (10.9%) children <16 yrs)	Germany (low)	QFT-G-IT	27.7±12.0 (range 1–56)	Simultaneously with TST	24 (mean)	QFT-G-IT: 6/41 (14.6 (0.06–0.29)); 5/219 TST-positives >5 mm: (2.3 (0.007–0.052))	QFT-G-IT: 2/6 (33.3); TST: 1/5 (20)
Aichelburg [19]	Cohort	830 HIV-1-positive adults	Austria (low)	QFT-G-IT	39 (interquartile range 32–47)	IGRA first, TST only if QFT-G-IT positive	19 (mean)	QFT-G-IT: 3/36[+] (8.3 (0.018–0.22)); TST: NA	NA
Kik [21]	Cohort	433 adult close immigrant contacts and BCG-vacc. Dutch-born contacts	The Netherlands (low)	QFT-G-IT, T-SPOT®.*TB*	NA	TST first, IGRA only if TST positive (at a cut-off ≥5 mm)[§]	22[/] (median)	QFT-G-IT: 5/178 (2.8 (0.009–0.064)); T-SPOT®.*TB*: 6/181 (3.3 (0.012–0.07)); TST ≥10 mm: 9/288 (3.1 (0.014–0.058))[++]	IGRAs: 3/3 (100)[¶¶]; TST: 6/6 (100)

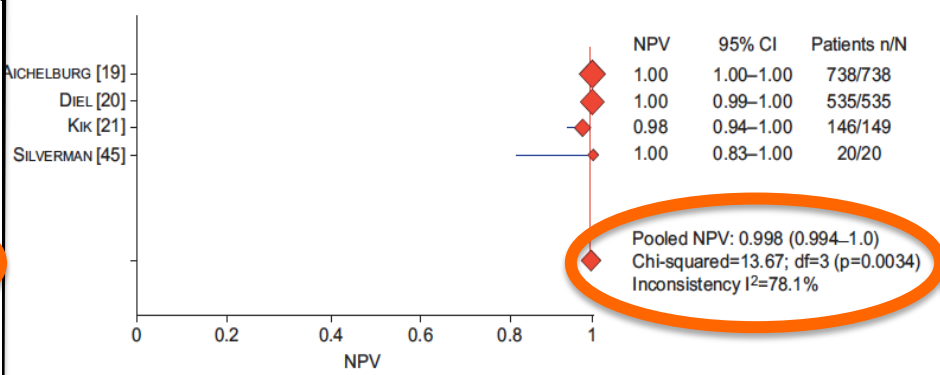
PPV of IGRAs= 10% in UK (2/20 TB cases/ IGRA+ve)
14% in Germany (6/41) ,
2 to 3% (6/181) in Holland

Negative predictive value (NPV) for progression to TB

T-Spot.TB



QFT-G-IT



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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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
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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 discernable:
  - 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 2. Guidelines on IGRAs: recommendations for contact investigation in adults

Recommendation	Guideline or position statement[a]
TST alone	WHO, Brazil, ECDC (high-incidence countries)
TST followed by IGRA, if TST positive (either IGRA only in BCG-vaccinated persons or independent of BCG vaccine)	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 <35 years old
Both TST and IGRA	Canada (high-risk contacts), Czech Republic, Croatia, Austria, Australia (IGRA may be considered in addition)
Either TST or IGRA	USA, Denmark, Finland (IGRA preferred if BCG-vaccinated in all three countries), South Korea (only in adults <35 years old), Austria
IGRA alone	Slovakia, Japan, France

Interferon-gamma release assays for diagnosis of latent tuberculosis infection: evidence in immune-mediated inflammatory disorders

Rachel Smith[a,*], Adithya Cattamanchi[b,*], Karen R. Steingart[c], Claudia Denkinger[d], Keertan Dheda[e], Kevin L. Winthrop[f] and Madhukar Pai[g]

TABLE 5. Guidelines on IGRAs: recommendations for LTBI screening in persons on TNF-α inhibitors

Recommendation	Guideline or position statement[a]
TST alone	Brazil
TST followed by IGRA, if TST positive	Spain, Norway
TST followed by IGRA, if TST negative	Canada, Italy, Spain, Saudi Arabia
Either TST or IGRA	Australia-ARA, Denmark (IGRA favoured), South Korea
Both TST and IGRA	ECDC, UK (alternatively IGRA alone), USA (if either initial test negative), Portugal, Croatia, Czech Republic, Slovakia, the Netherlands, South Korea, Ireland (TST preferred)
IGRA alone	Germany, Switzerland, Bulgaria, Japan, France, Poland, Austria
No recommendations	Finland, Australia-NTAC

Major trends

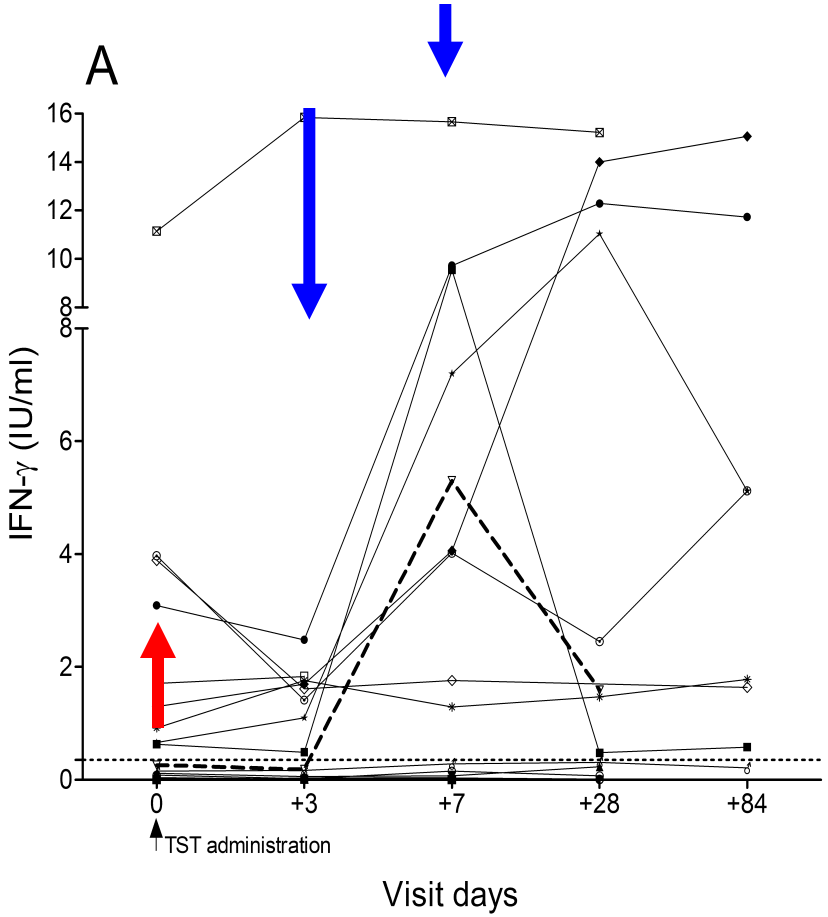
- Two-step approach (dual strategy) seems to be the most favored, especially BCG-vaccinated contacts

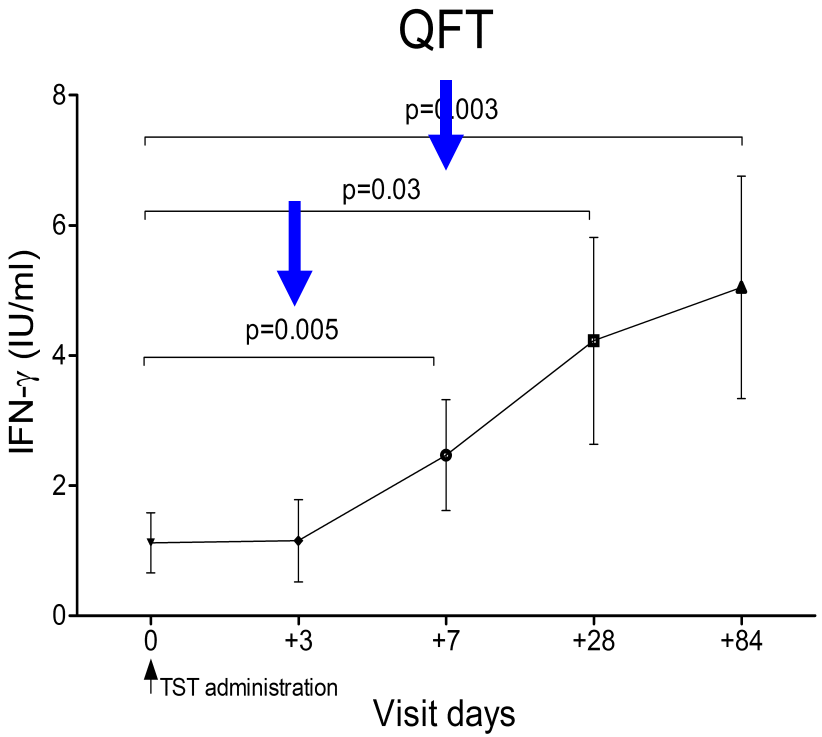
Within-Subject Variability and Boosting of T-Cell Interferon-γ Responses after Tuberculin Skin Testing

Richard N. van Zyl-Smit[1], Madhukar Pai[2], Kwaku Peprah[1], Richard Meldau[1], Jackie Kleck[1], June Juritz[4], Motasim Badri[1], Alimuddin Zumla[5], Leonardo A. Sechi[6], Eric D. Bateman[1], and Keertan Dheda[1,5,7]

[1]Lung Infection and Immunity Unit, Division of Pulmonology and UCT Lung Institute Department of Medicine, University of Cape Town, Cape Town, South Africa; [2]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada; [3]Department of Radiology, University of Cape Town and Groote Schuur Hospital, and [4]Department of Statistical Sciences, University of Cape Town, Cape Town, South Africa; [5]Centre for Infectious Diseases and International Health, Royal Free and University College Medical School, London, United Kingdom; [6]Dipartimento di Scienze Biomediche, University of Sardinia, Sassari, Italy; and [7]Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa

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

Pooran et al. BMC Pulmonary Medicine 2010, 10:7
http://www.biomedcentral.com/1471-2466/10/7

RESEARCH ARTICLE Open Access

Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost effectiveness analysis

Anil Pooran[1,4], Helen Booth[2†], Robert F Miller[2,3], Geoff Scott[2†], Motasim Badri[4], Jim F Huggett[1†], Graham Rook[1†], Alimuddin Zumla[1,2†], Keertan Dheda[1,2,4,5*]

- 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)

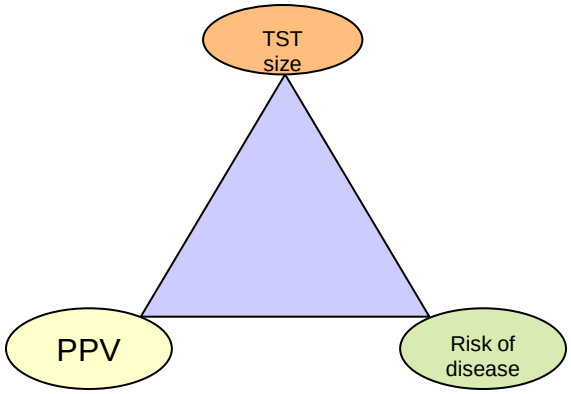
Tuberculin skin test: needs careful interpretation (www.tstin3d.com

INT J TUBERC LUNG DIS 12(5):498–505

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

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

* Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, Canada; † Massachusetts General Hospital, Harvard University, Boston, Massachusetts, USA; ‡ Division of Infectious Disease and Microbiology, Sir Mortimer B Davis Jewish General Hospital, McGill University, Montreal, § Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada



(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%

- http://www.tstin3d.com/en/calc.html
- http://www.tstin3d.com/en/about.html
- http://www.tstin3d.com/en/disclaimer.html
- http://www.tstin3d.com/en/references.html
- http://www.tstin3d.com/en/links.html

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 (5 TU 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:

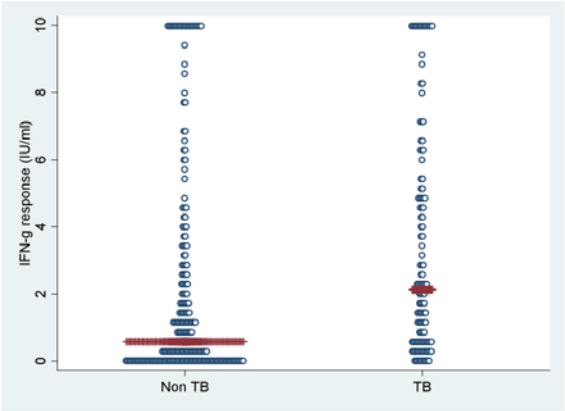
Please select all the conditions that currently apply to the patient:
(If none of these conditions apply, please leave boxes unchecked)

AIDS	Abnormal chest x-ray: granuloma
Abnormal chest x-ray: fibronodular disease	Carcinoma of head and neck
Chronic renal failure requiring hemodialysis	Cigarette smoker(>1 pack/day)
Diabetes Mellitus (all types)	HIV infection
Recent TB infection (TST conversion ≤ 2 years ago)	Transplantation (requiring immune-suppressant therapy)
Silicosis	Treatment with glucocorticoids
Tumor Necrosis Factor (TNF)-alpha inhibitors(e.g. Infliximab/Etanercept)	Underweight (< 90 per cent ideal body weight or a body mass index (BMI) ≤ 20)
Young age when infected (0-4 years)	

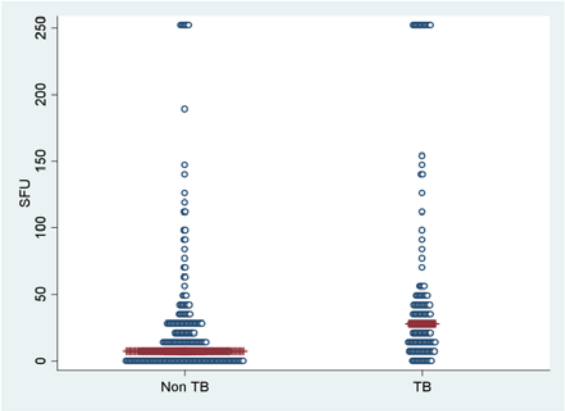
High Burden settings- active TB is the priority

Dheda K, Curr Op Pulm Med, 2009

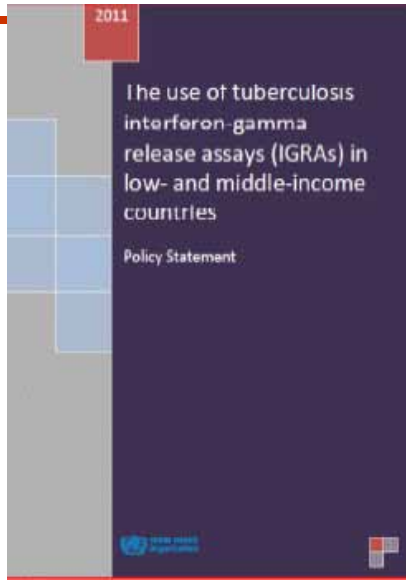
500 TB suspects in Cape Town- culture= ref standard



QFT-GIT



TSPOT-TB



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

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

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

Eur Respir J 2009; 34: 1–9
DOI: 10.1183/09031936.00005309

Utility of quantitative T-cell responses *versus* unstimulated interferon-γ for the diagnosis of pleural tuberculosis

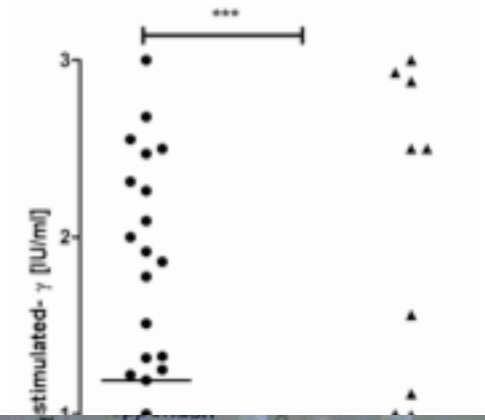
K. Dheda*,#, R.N. van Zyl-Smit*, L.A. Sechi*, M. Badri*, R. Meldau*, S. Meldau*, G. Symons*, L. Semple*, A. Maredza*, R. Dawson*, H. Wainright*, A. Whitelaw*, Y. Vallie*, P. Raubenheimer*, E.D. Bateman* and A. Zumla#

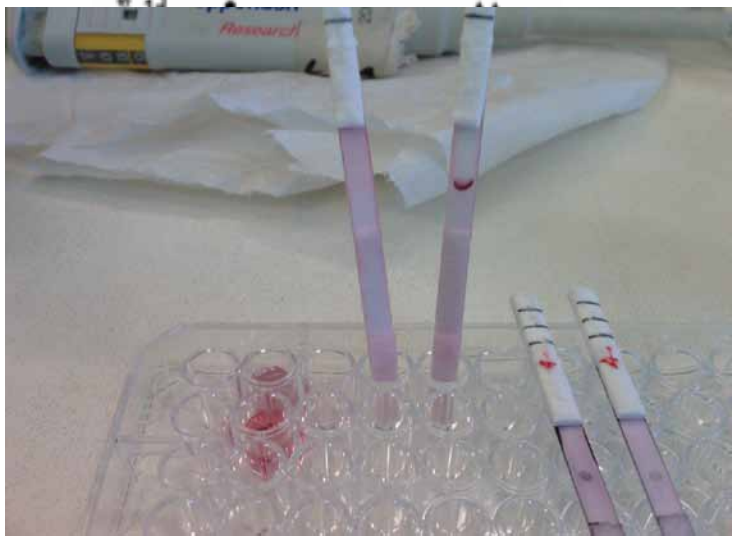
- Pleural TB: SENS = 97 SPEC= 100%

Dheda K, Eur Resp J, 2009

- TBM: SENS = 95 SPEC= 99%

Patel V, Dheda K, J Clin Micro, 2011





- Peritoneal TB: SENS = 97 SPEC= 100%

Sharma SK, J Interf & Cytokine Research, 2006

- Pericardial TB: high SENS and SPEC

Reuter H, QJM, 2006

Children

INT J TUBERC LUNG DIS 15(8):1018–1032

doi:10.5588/ijtld.10.0631
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REVIEW ARTICLE

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

  Samandari T, Lancet, 2010

  Akolo C, The Cochrane Library, Issue 1, 2010

  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

	Sensitivity	Specificity	PPV	NPV
TST-TSPOT	59.5%	67.5%	29.3%	88%
TST-QFT	78.1%	62.1%	33.3%	92.1%

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 Pai[1]

Low burden settings:

Summary

- 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 extrasangunous 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).

M Pai and C Lange

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Discovery

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South African National Research Foundation

EDCTP

South African MRC