Predictive Value of interferon-gamma release assays for incident active TB disease: A systematic review and meta-analysis

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The 3 *I*'s

***I*soniazid preventive therapy is safe and effective in people living with HIV**

***I*ntensified case finding for TB via symptoms and signs screening**

***I*nfection control for TB is essential to prevent vulnerable patients from getting TB**

2-4 April, 2008, Geneva, Switzerland

Main challenges to IPT roll-out

Testing for 'latent' TB infection

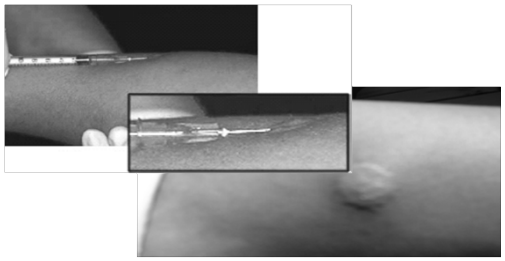
Screening for active TB

Adherence Monitoring

Risk of isoniazid mono-resistance

Testing for 'latent' TB Infection

I. Mantoux



Disadvantages
Poor Sensitivity in HIV infection
Poor Specificity
Reactions read 48-72hrs

Advantages
Cheap
Widely available
Predicts incident TB (RR of 2)
Predicts benefit from IPT

Testing for 'latent' TB Infection

II. T-cell based assays

(Interferon-gamma release assay)

T-SPOT.TB

Oxford Immunotec

Products & Services

'A 21st Century Solution for Latent TB Detection'

QuantiFERON®-TB Gold.
One blood test, One clear answer

The battle: TST vs IGRA

◆TST and IGRA are comparable

◆As "evidence of TB infection", both TST and IGRA are valid tests

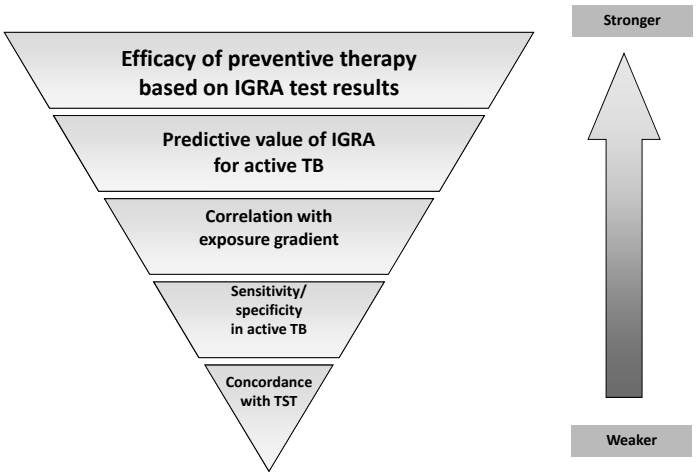
◆Neither TST nor IGRA can distinguish between LTBI and active disease
- Neither stand-alone test is useful in active TB diagnosis
- Neither has great discriminatory value over and above standard tools

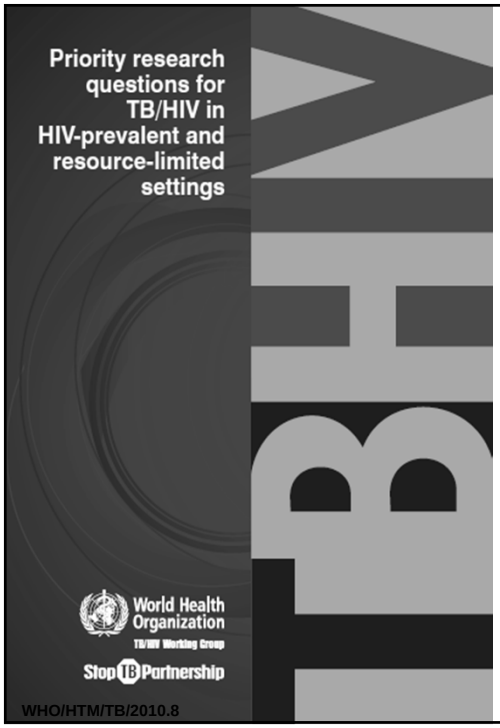
◆Both TST and IGRAs are impacted by HIV but IGRA less so

◆Key differences being:
- IGRA are specific in all settings; TST is specific in BCG unvaccinated or those who get BCG in infancy
- IGRA have logistics that are more convenient
- IGRA require more resources

Courtesy Madhu Pai

Hierarchy of evidence for IGRAs





TB prevention: Gaps

1.6 Priority research questions in the area of TB prevention

- ◆Accuracy and reliability of IGRAs in the diagnosis of latent *M.tb* infection and active TB in HIV-infected adults
- ◆Role of IGRAs in enhancing the effective application of preventive TB therapy in people living with HIV
- ◆Role of IGRAs in monitoring response to latent TB treatment in HIV-infected individuals
- **◆Prognostic ability of IGRAs, compared to the TST, to accurately identify people living with HIV at higher risk for progression from latent to active TB**

Primary Study Questions

- Can IGRA predict the development of incident active TB?
- Is IGRA predictive ability higher than TST?

Secondary Study Questions

- What is the variability in IGRA rates in IPT-treated individuals with TST negative and positive results?
- What is the influence of discordant-concordant TST/IGRA pairs on TB rates?
- Is there an exposure-gradient association between quantitative IGRA results and TB rates?

Outline for rest of talk

- Inclusion Criteria
- Measures of outcome and effect
- Search strategy
- Characteristics of studies
- Study quality
- Main Results
- Summary

Inclusion Criteria

- **Participants, setting and types of studies:**
  - Adults and children without TB at baseline; regardless of HIV infection status
  - Longitudinal studies; in any setting
  - Follow-up of at least 1 year; passively or actively followed-up
- **Index test:**
  - Any IGRA (ELISA/ELISPOT, commercially-licensed or in-house assay)
  - Antigens should include at least one RD1 antigen of *M.tb* (PPD only assays were not eligible)

Inclusion Criteria

- **Target condition (Outcome)**

  Active TB refers to disease caused by *Mycobacterium tuberculosis* (non-tuberculous mycobacterium disease was not considered)

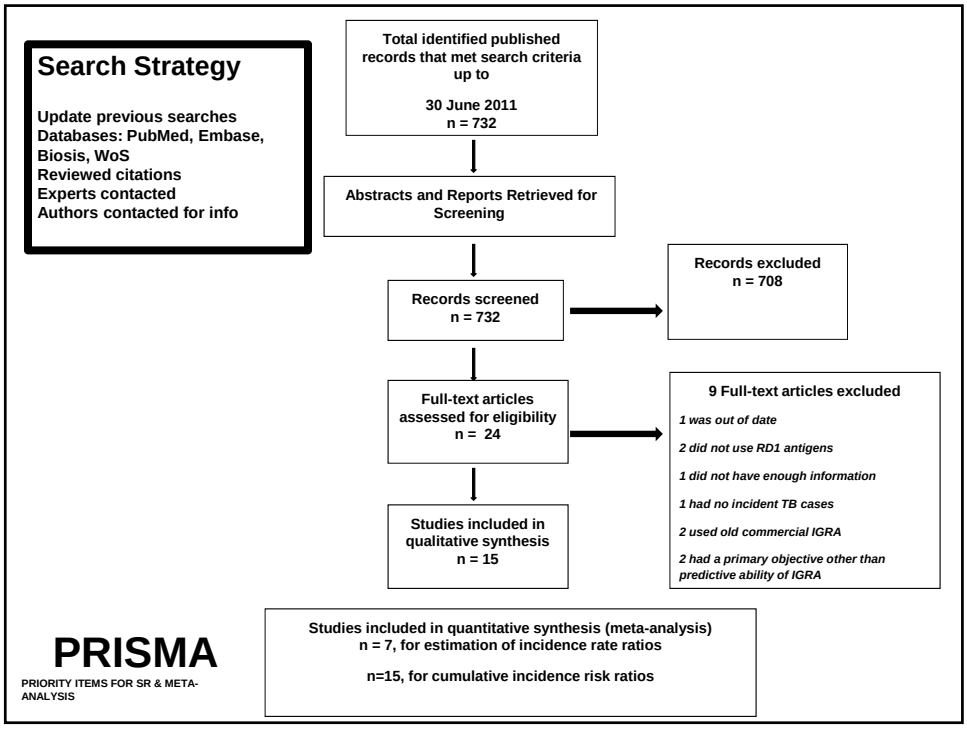
- **Reference standard for TB outcome:**

  Any incident active TB disease: smear/culture-confirmed or not

Measures of outcome and effect

- **Incidence rates of TB**
- **Incidence rate ratios, IRR for effect: rates in IGRA+ vs. IGRA-**
- **Risk ratios also presented (not all studies reported person-time results)**
- **Crude rather than adjusted estimates reported***

Random effects model to pool estimates (DerSimonian and Laird)



Characteristics of studies

General

- 4 LIC (Ethiopia, The Gambia, Senegal, Kenya)
- 5 MIC (Turkey, Colombia, China, India, South Africa)
- 6 HIC studies (Austria, Netherlands, Japan, Norway, Germany, Portugal)-All conducted within routine care*
- Combined N=26,680 entered follow-up
- SA study was the largest (11,988 PY)
- Median study period of 3 years (IQR: 2-5)

Characteristics of studies

Population

- 8 TB case-contact studies (Ethiopia, Gambia, Senegal, Colombia, Germany, Turkey, Japan, Netherlands)
- 2 HIV cohorts (Austria, Kenya)
- 1 Silicosis cohort (China)
- 2 HCW cohort (India, Portugal)
- 1 Asylum seekers (Norway)

Characteristics of studies

Tests

IGRA

- 10/15 WBA/ELISA – 8/10 QFT-IT
- 6/15 ELISPOT- 3/6 T.Spot TB
- 1 study evaluated QFT-IT and T.Spot TB

TST

- 11/15 performed TST and an IGRA
- 8/11 compared TST and IGRA as an objective

Study Quality

NOS Item	Features	Modification
Selection	Representativeness of the exposed cohort; Selection of the non-exposed cohort; Ascertainment of exposure; Demonstration that outcome of interest was not present at start of study.	Assessment of whether IGRA results were incorporated into the diagnosis of active TB at baseline. Whether methods to exclude TB included microbiological tools (smear and/or culture)
Comparability	With respect to whether the studies had adjusted effect measures for potential confounders.	
Outcome	Assessment of outcome; Study follow up length and adequacy.	Assessment of whether IGRA results were incorporated into the diagnosis of active TB during follow-up. Whether methods to exclude TB included microbiological tools (smear and/or culture)

NOS

MODIFIED NEWCASTLE-OTTAWA SCALE FOR ASSESSING QUALITY OF OBSERVATIONAL STUDIES FOR SR & META-ANALYSIS

Study Quality

	Low or intermediate income (n=9)	High income (n=6)
Selection		
Representative sample	9	6
IGRA positive and negative from same source population	9	6
Assay described in detail	9	6
Active tuberculosis excluded at baseline*	8	4
Methods include smear and culture†	..	..
Whole or random sample screened for tuberculosis	0	0
IGRA incorporated into reference standard (or not reported)‡	2	6
Comparability		
Adjustment of identified confounders‡	3	1
Outcome		
Blind assessment and active follow-up by regular visits to the clinic or home to check for tuberculosis§	5	0
IGRA incorporated into reference standard (or not reported)¶	1	6
>50% incident cases culture-confirmed‖	4	4
Study follow-up at least 1 year	9	6
≥80% of cohort followed up**	9	4
Outcome reported as incidence rate and rate ratio (person-time incidence)††	8	1

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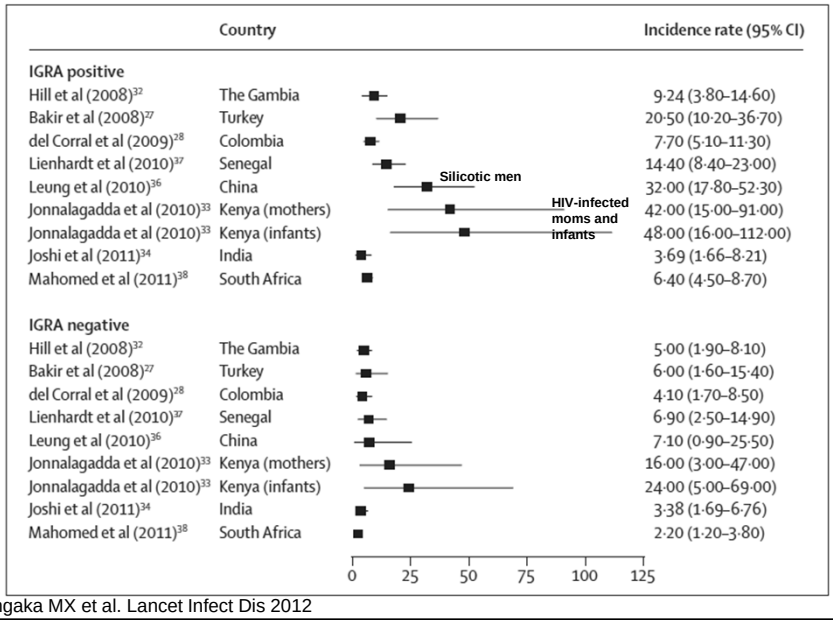
Incidence rates of TB



8/15

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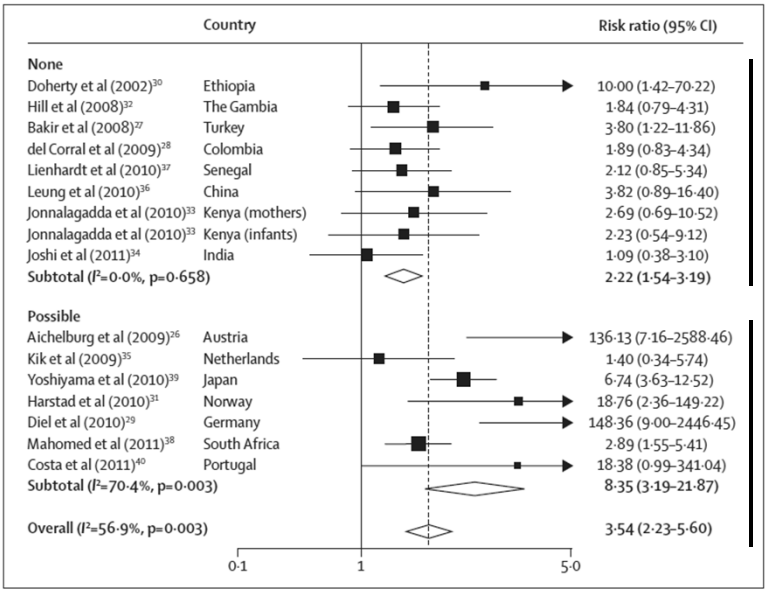
Association between IGRA and incident TB: RR

15/15



All L/MIC

All HIC
1 MIC

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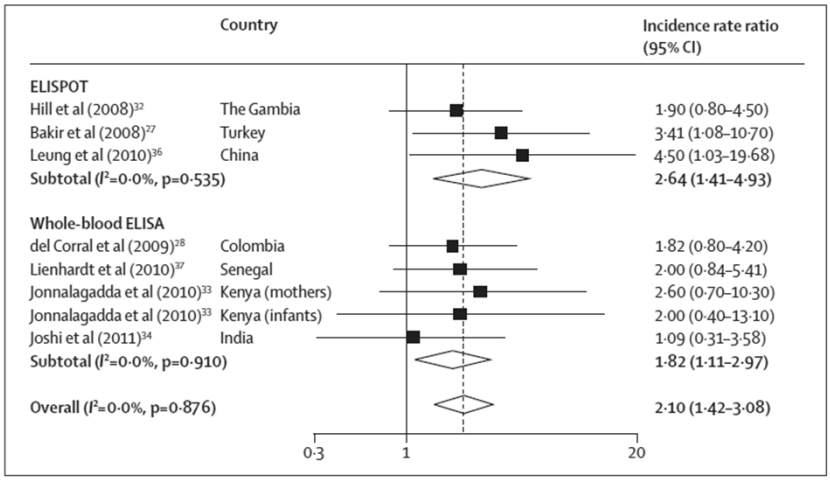
Association between IGRA and incident TB: IRR



All L/MIC (7)

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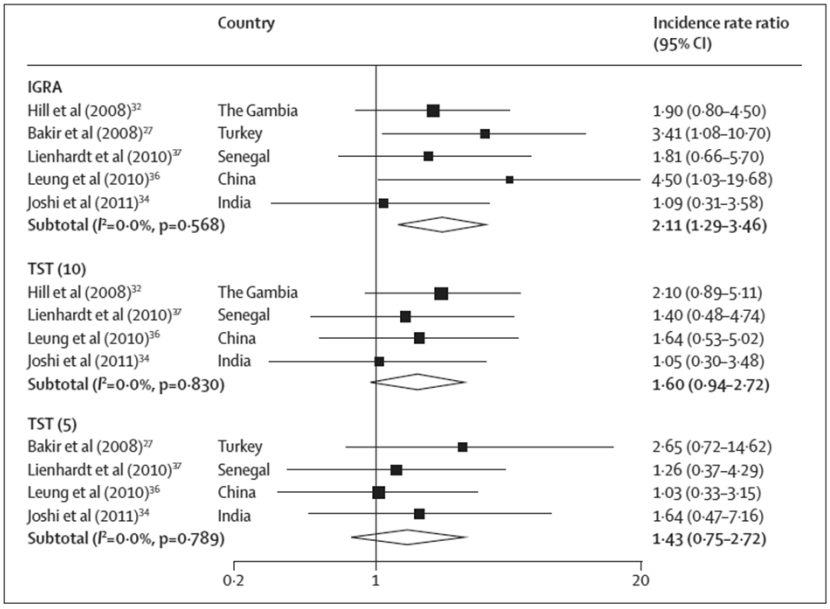
IGRA vs TST battle: Which has greater 'predictive ability'



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Results: Variability in IGRA rates in IPT-treated individuals with TST negative and positive results

Could not be assessed: No studies

Results: Influence of discordant/concordant TST/IGRA pairs on TB rates

4/10 studies that performed IGRA and TST:
Discordant pairs where IGRA was positive had higher rates
Confidence intervals overlap

Results: Exposure gradient relationship between quantitative IGRA levels and TB rates

Could not be assessed: Not enough studies (1)

Limitation

Publication Bias

3 known unpublished studies not included

But..there may be others

INT J TUBERC LUNG DIS e-publication ahead of print 8 February 2012

http://dx.doi.org/10.5588/ijtld.11.0416

SHORT COMMUNICATION

Development of tuberculosis in immunocompromised patients with a positive tuberculosis-specific IGRA

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SUMMARY

There is a lack of data on the predictive value of tuberculosis (TB) specific interferon-gamma release assays (TIGRAs) for both immunocompetent and immunocompromised individuals. We retrospectively followed up 460 such patients after QuantiFERON®-TB Gold In-Tube (QFT-GIT) testing (mean follow-up 28 months) by reviewing patient charts. A total of 1/38 QFT-GIT-positive and no QFT-GIT-negative patients developed active TB. The incidence rate of progression to active TB assessed retrospectively in these patients after positive TIGRA was therefore low (1.2 events/100 person-years). The need for careful follow-up and prophylactic therapy after positive TIGRA in this patient group needs to be evaluated prospectively.

KEY WORDS: tuberculosis; interferon-gamma release assay; risk of progression

Retrospective study of immunocompromised and immunocompetent individuals

460 tested with QFT-GIT

Only 1/38 QFT-GIT positive patients developed TB (1 HIV-infected was not on IPT)

Summary

- TST and IGRA have modest predictive value for incident TB
- IGRAs appear to have similar predictive value as the TST
- Both may not help identify those at highest risk of progression to disease
- Decision to choose one test over another may be based on difference in specificity across populations, logistics, cost and patient important outcomes rather than predictive ability alone.

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How can we squeeze predictive value out of IGRAs?

1. Only test those who are at high risk
2. Incorporate biomarkers with other known risk factors (age, recent conversion, HIV etc.) into a composite scoring system to generate multivariable risk prediction models
3. Use a higher cut-off for prediction (as compared to diagnosis)
4. Use serial testing to resolve underlying phenotypes
5. Identify new biomarkers and measure an array of biomarkers (biosignature)

Courtesy M.Pai

THE LANCET Infectious Diseases

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

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