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

Lele Rangaka

University of Cape Town, South Africa

mxrangaka@yahoo.co.uk

The 3 I's

Isoniazid preventive therapy is safe and effective in people living with HIV

Intensified case finding for TB via symptoms and signs screening

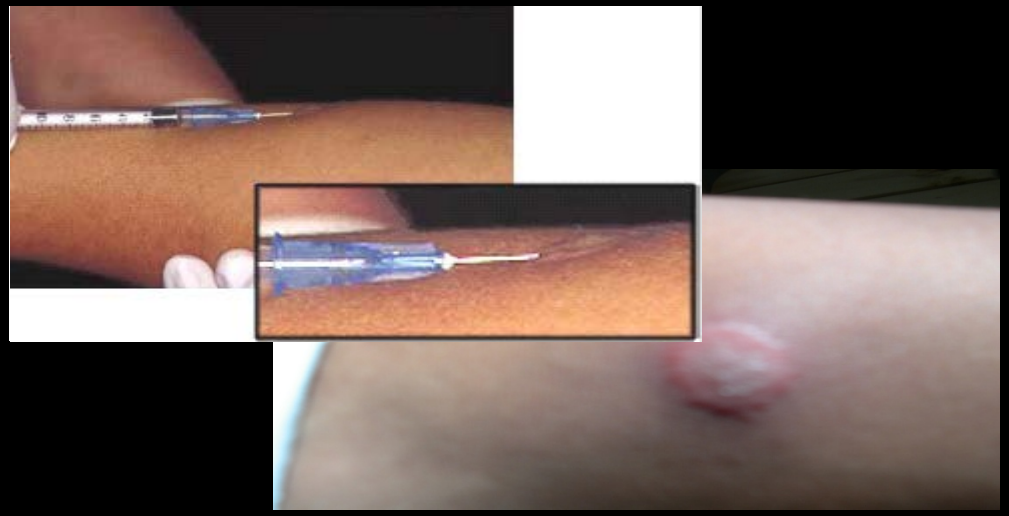
Infection control for TB is essential to prevent vulnerable patients from getting TB

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)

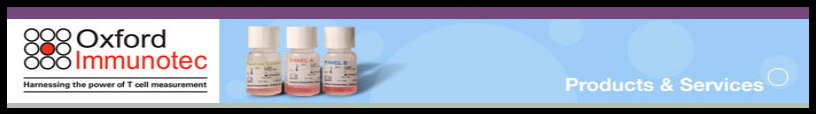
Predicts benefit from IPT

Testing for ‘latent’ TB Infection

II. T-cell based assays

(Interferon-gamma release assay)

T-SPOT.TB



‘A 21st Century Solution for Latent TB Detection’

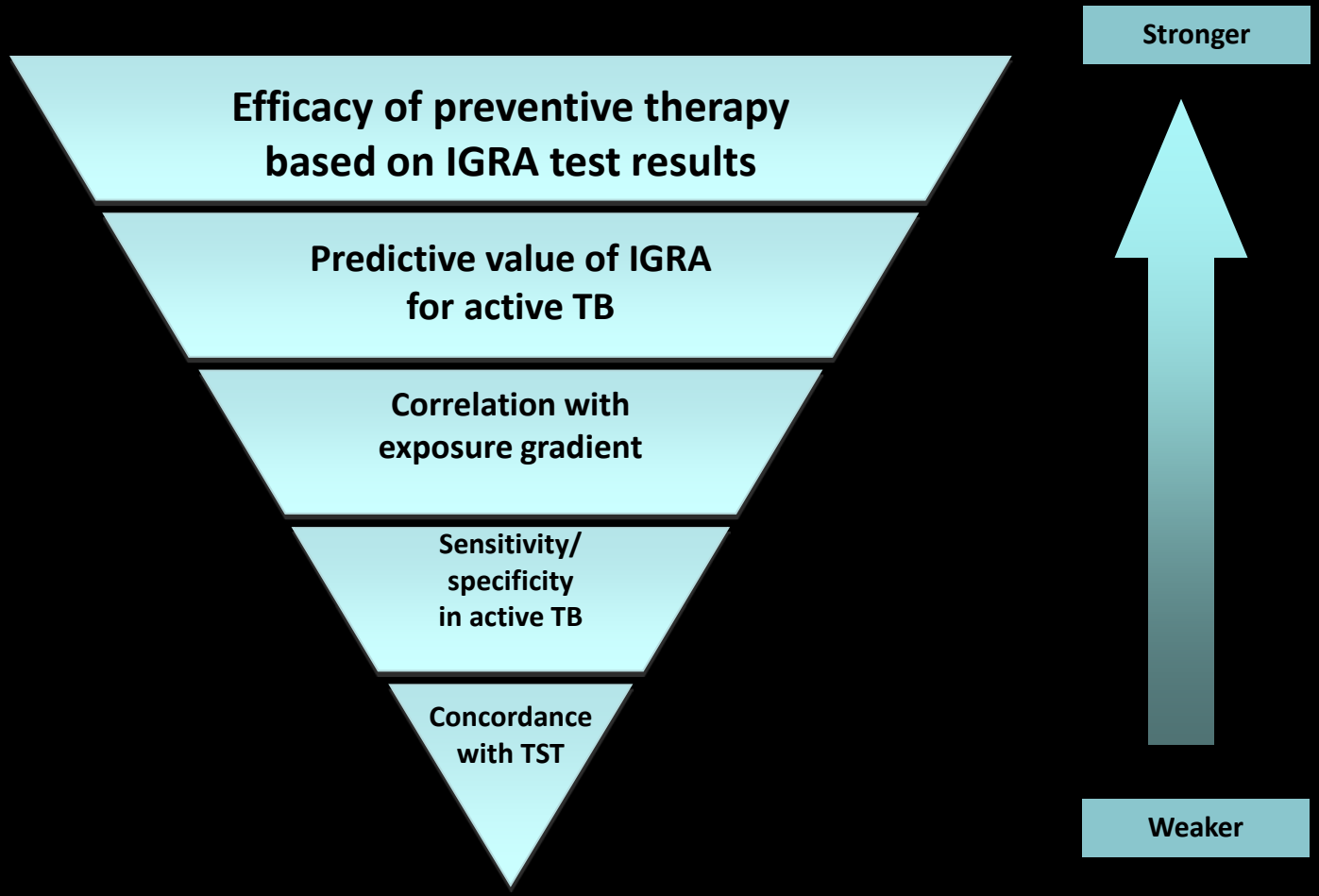
QuantiFERON®-TB Gold.
One blood test, One clear answer

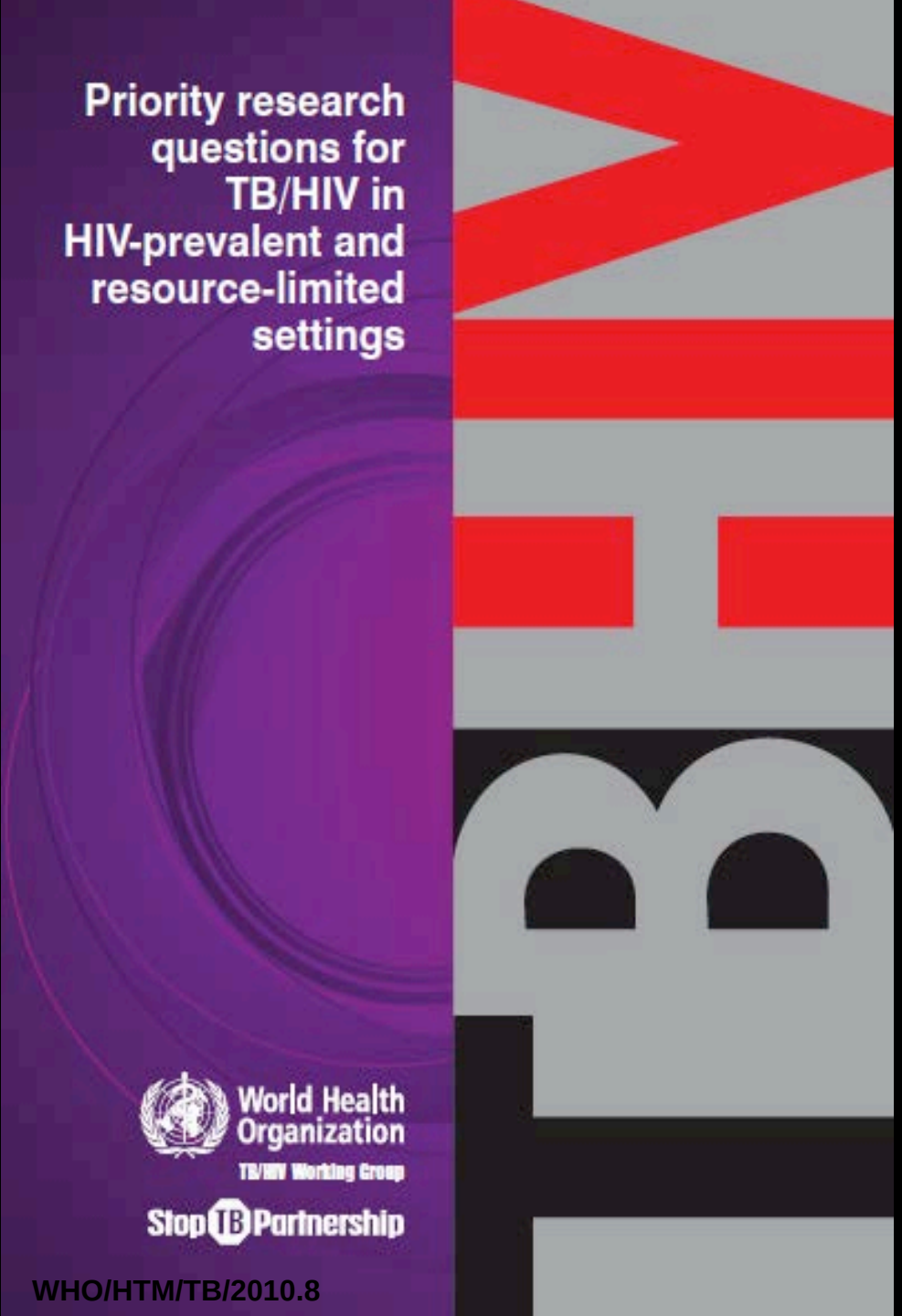
The battle: TST vs IGRA

- 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 stand 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





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**

Study questions

Primary

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

Secondary

- What is the variability in TB rates in IGRA positive and negatives (with TST results) who were treated with IPT?
- What is the influence of discordant-concordant TST/IGRA pairs on TB rates?
- Is there a gradient relationship between quantitative IFN-gamma levels and TB rates?
- What are the outcomes of potential importance or relevance to patients? (False positive or negative accuracy estimates used as proxies)

Outline for rest of talk

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

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/ELIPOT, commercially-licensed or in-house assay)

  Antigens should include at least one RD1 antigen of *M.tb* (PPD only assays were not eligible)

- **Target condition (Outcome)**

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

- **Reference standard for TB outcome:**

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

Inclusion Criteria

- **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

- **Target condition (Outcome)**

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

- **Reference standard for TB outcome:**

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

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

Outline for rest of talk

Inclusion Criteria

Measures of outcome and effect

Search strategy

Characteristics of studies

Study quality

Main Results

Summary

Measures of outcome and effect

Outcome and Effect measures:

- 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 pooled estimates obtained (DerSimonian and Laird)

Patient-relevant outcomes:

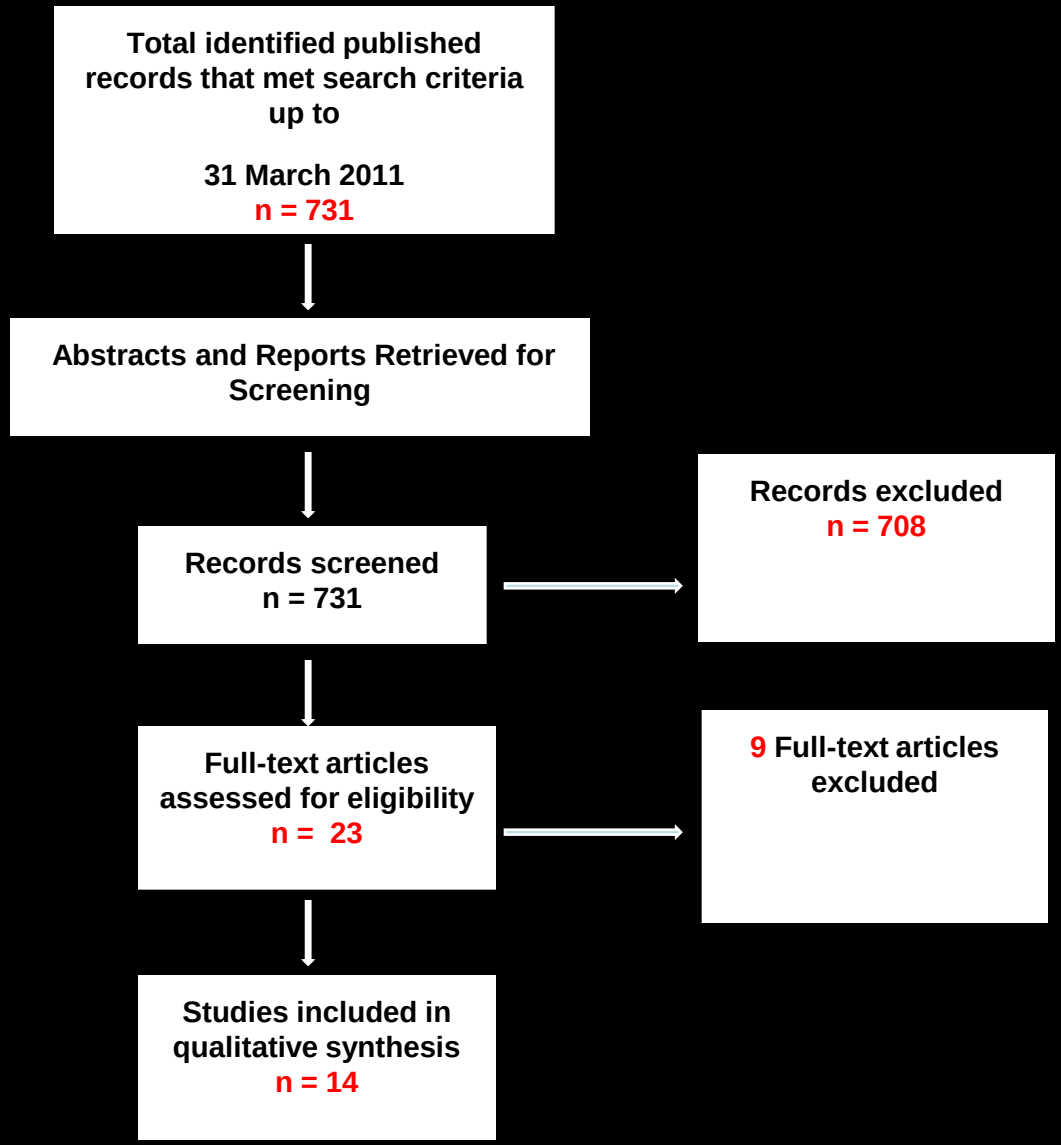
- False negative (1-Senstivity)
- False positive (1-Specificity)

Outline for rest of talk

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

Search Strategy

Update previous searches
Databases: PubMed, Embase, Biosis, WoS
Reviewed citations
Experts contacted
Authors contacted for info



PRISMA

PRIORITY ITEMS FOR SR & META-ANALYSIS

Outline for rest of talk

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

Characteristics of studies

General

- 14 studies
- 4 LIC studies (Ethiopia, Gambia, Senegal, Kenya)
- 5 MIC studies (Turkey, Colombia, China, India, South Africa)
- 5 HIC studies (Austria, Netherlands, Japan, Norway, Germany)
- Combined N=23,673 entered follow-up
- SA study 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)
- 1 HCW cohort (India)
- 1 Asylum seekers (Norway)
- All HIC studies conducted within routine care*

Characteristics of studies

Tests

IGRA

- **9/14 WBA/ELISA – 7/10 QFT-IT**
- **6/14 ELISPOT- 3/6 T.Spot TB**
- **1 study evaluated QFT-IT and T.Spot TB**

TST

- **10/14 performed TST and an IGRA**
- **8/10 compared TST and IGRA as an objective**

Outline for rest of talk

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

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

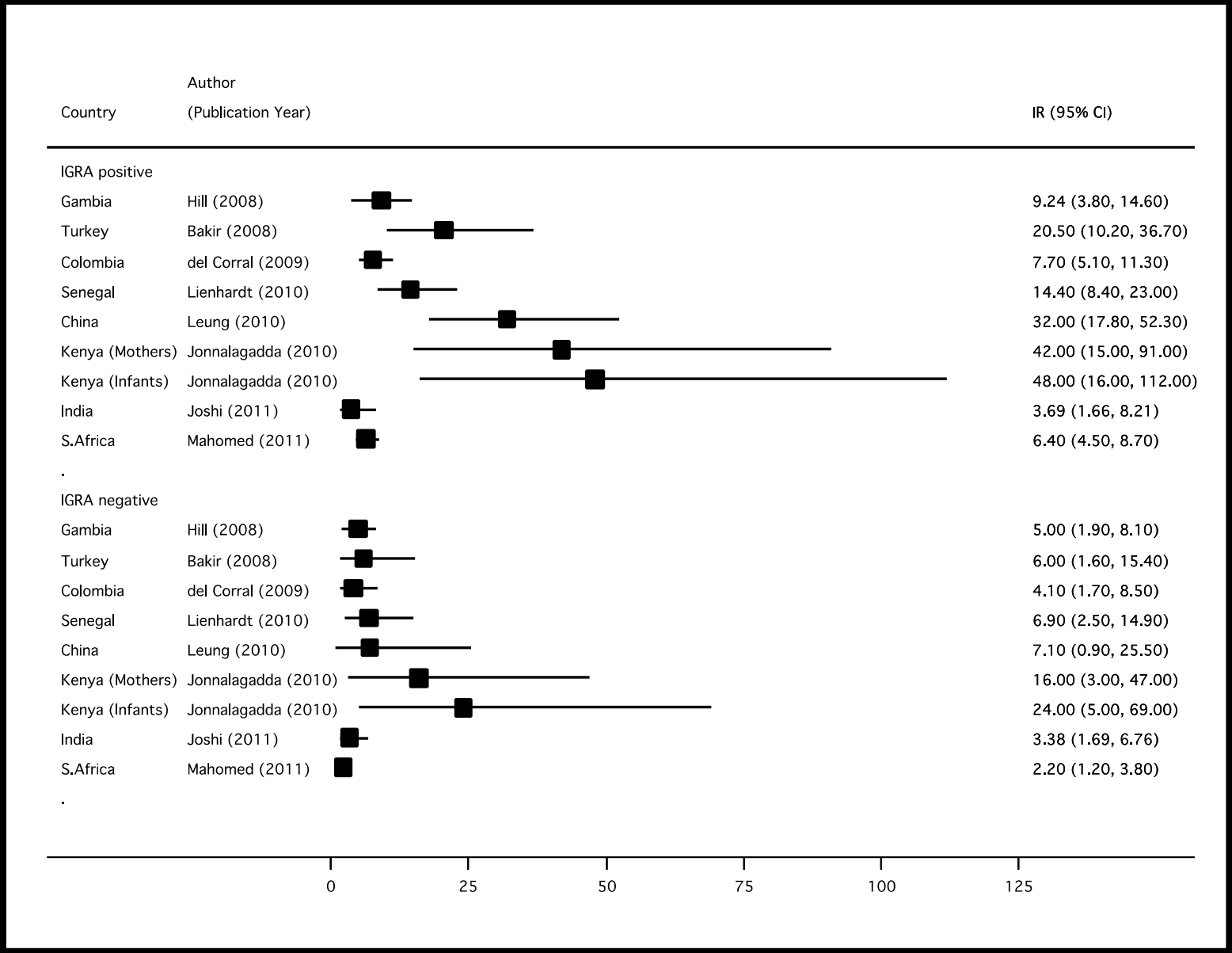
MODIFIED NEWCASTLE-OTTAWA SCALE FOR ASSESSING QUALITY OF OBSERVATIONAL STUDIES FOR SR & META-ANALYSIS

NOS item	Country Income Classification	
	Low/Intermediate Income (n=9)	High Income (n=5)
Selection		
Active TB excluded at baseline	8	3
IGRA incorporated into reference standard (or not reported)	2	5
Comparability		
Adjustment of identified confounders	3	1
Outcome		
Blind assessment and active follow-up by visits to the clinic or home to check for TB	5	0
IGRA incorporated into reference standard (or not reported)	1	5
>50% incident cases culture-confirmed	4	2
≥ 80% of cohort followed	9	3
Outcome reported as incidence rate and rate ratio (person-time)	8	1

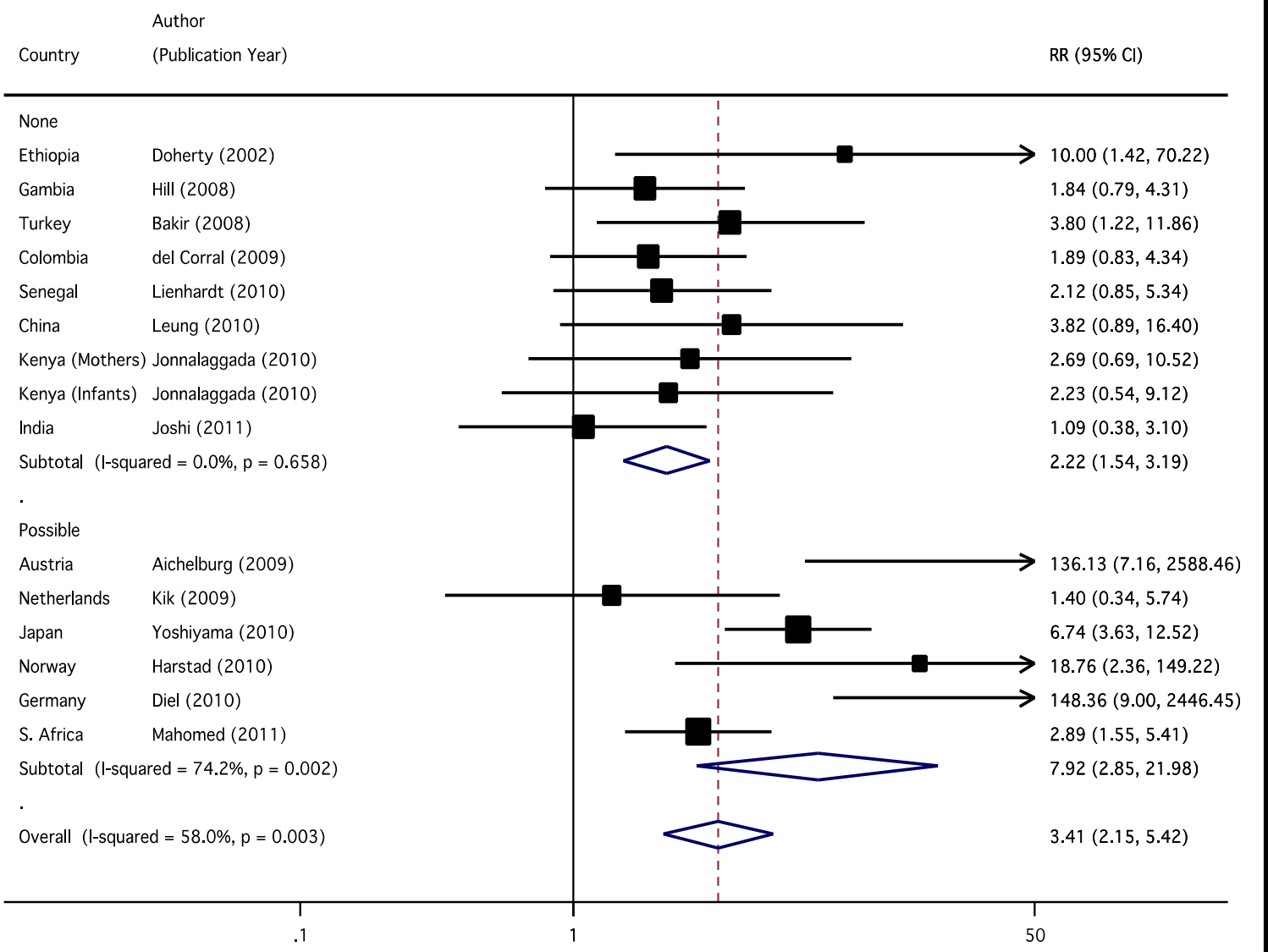
Outline for rest of talk

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

Incidence rates of TB



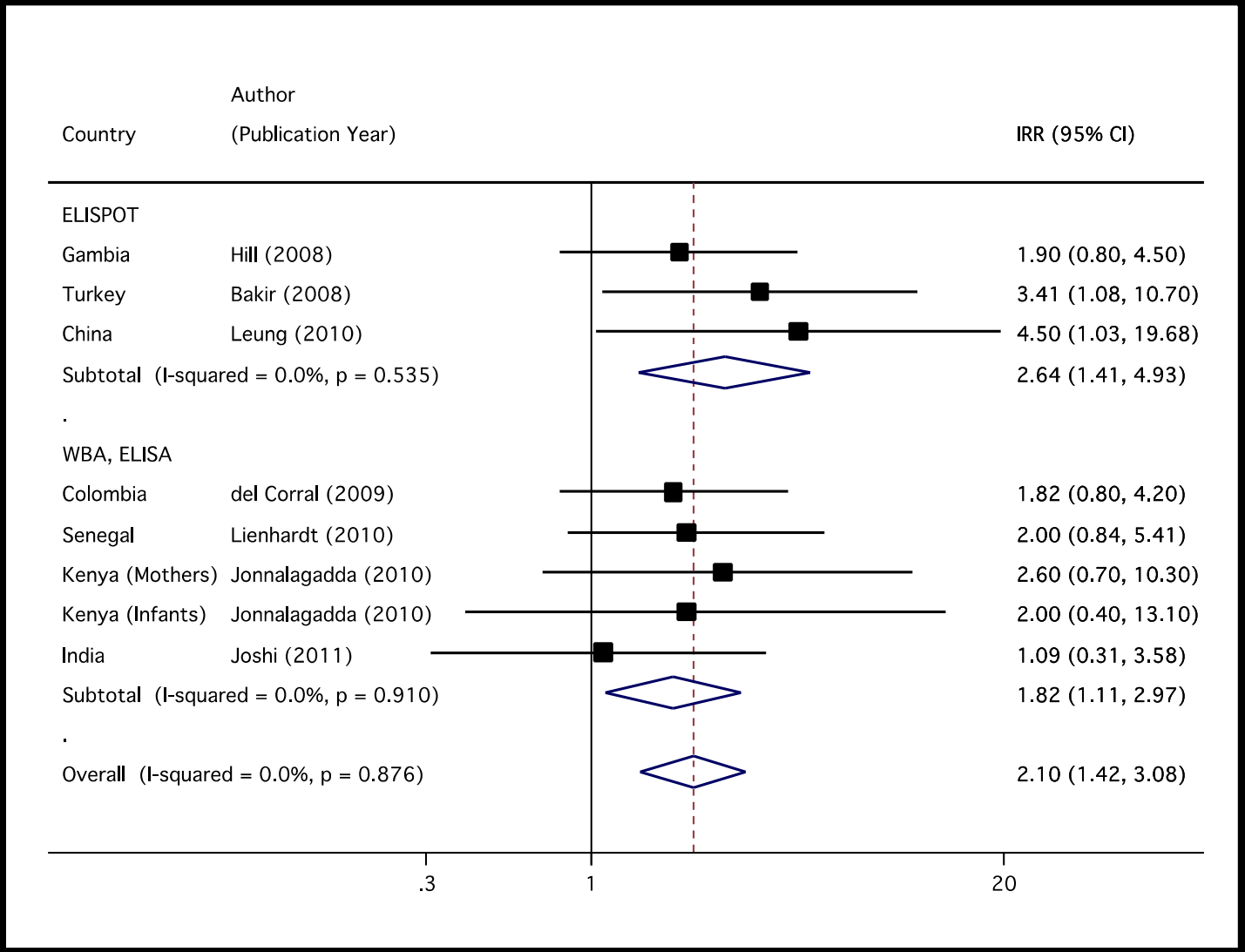
Association between IGRA and incident TB: RR



All L/MIC

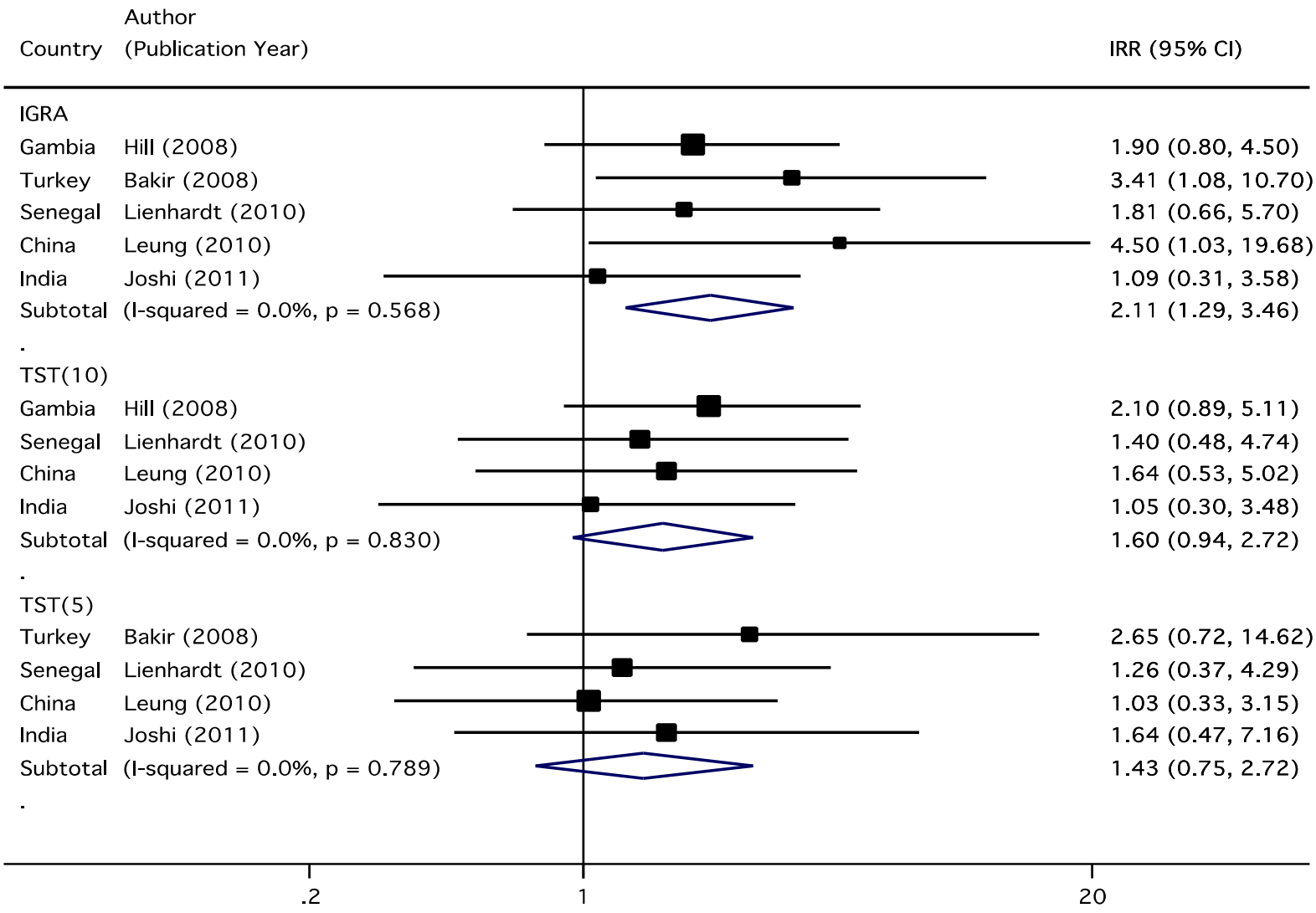
All HIC
1 L/MIC

Association between IGRA and incident TB: IRR



7/14
All L/MIC

IGRA vs TST: Which has greater ‘predictive ability’



Patient-relevant outcomes: % scored positive by IGRA vs. TST

Country	N tested with IGRA	% IGRA positive (95% CI)	N tested with TST	% TST positive (95% CI)
WBA/ELISA				
Netherlands (QFT), HIC	327	54 (49-60)	‡327	*5mm cutoff: ‡100
Norway, HIC	823	30 (27-33)	‡823	*6mm cutoff: ‡100
Germany, HIC	954	21 (18-23)	954	*5mm cutoff: 63 (60-66)
South Africa, MIC	5,244	51 (50-52)	5,244	*5mm cutoff: 55 (54-57) 10mm cutoff: 42 (41-44)
ELISPOT				
Turkey, MIC (25)	908	42 (39-45)	908	*5mm cutoff: 61 (58-64)
Netherlands (TSpot.TB), HIC (33)	299	61 (55-66)	‡299	*5mm cutoff: ‡100
Senegal (All TB), LIC (35)	893	57 (54-60)	893	5mm cutoff: 83 (81-86) *10mm cutoff: 70 (67-73)

- 7 out of 10 studies
- % scored positive with IGRA may be less
- Cutoff dependent

Patient-relevant outcomes: False positives and False negatives (TST vs IGRA)

- **4 studies without incorporation bias**
- **All Elispot studies**
- **Comparable FP and FN estimates for IGRA and TST**

Summary FP estimate for IGRA: 50% (95% CI 42-59)
Summary FP estimate for TST: 59% (95% CI 46-70)

Summary FN estimate for IGRA: 28% (95% CI 18-42)
Summary FN estimate for TST: 28% (95% CI 17-42)

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

4/10 studies that performed IGRA and TST:
Discordant pairs have similar rates
Confidence intervals overlap

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

Could not be assessed: No studies

Results: Variability in TB rates by quantitative IGRA levels

Could not be assessed: Not enough studies

Limitations

Publication Bias

4 known unpublished studies not included

1 published study

Other unknown

Conclusions

- 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.


HIV
POSITIVE
HIV
POSITIVE
HIV