**Working Group on New TB Diagnostics**

ANNUAL MEETING

**Thursday, 11th November 2010, 13:00 - 17:00**

International Congress Center, Berlin, Hall 7

# Evidence on IGRAs in Low & Middle Income Countries

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Stop TB Partnership

McGill

# Disclosure

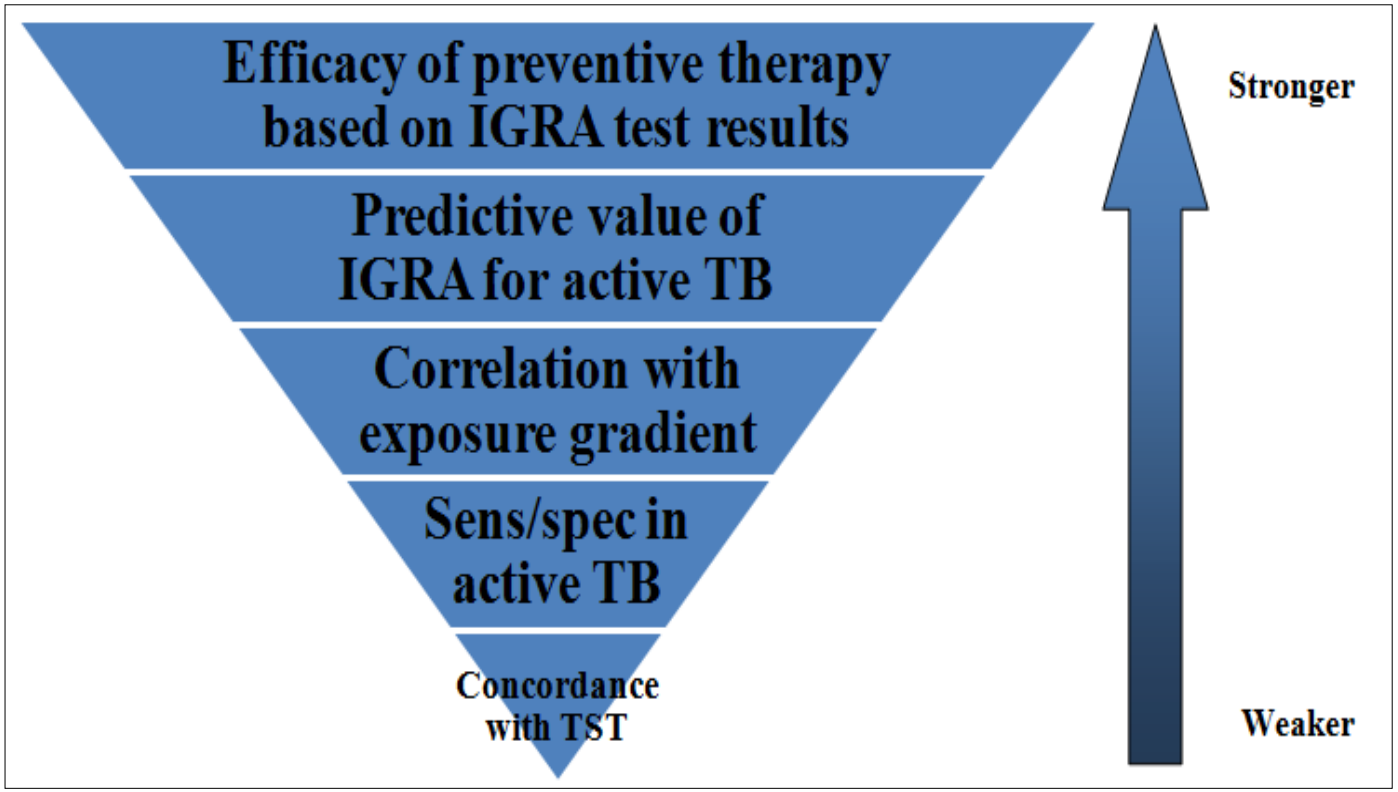
- No industry/financial conflicts

- I co-chair the Stop TB Partnership's New Diagnostics Working Group
- I consult for the Bill & Melinda Gates Foundation
- I have participated in the WHO Expert Group meetings on IGRAs and serodiagnostics

# Rationale

- In recent years, IGRAs have become widely endorsed in high-income countries for diagnosis of LTBI and several guidelines on their use have been issued.
- Currently, there are no guidelines for their use in high TB- and HIV-burden settings, where IGRAs are being promoted, especially in the private sector.
- IGRA performance differs in high- versus low TB and HIV incidence settings
- Majority of IGRA studies have been performed in high-income countries and extrapolation to low- and middle-income settings may not be appropriate.
- WHO Stop TB Department therefore convened a Expert Group meeting on IGRAs on July 20 & 21, 2010
- WHO commissioned 6 systematic reviews on the use of IGRAs in low- and middle-income settings, in pre-defined target groups, with funding support from the TDR and TREAT-TB/Union.

# Hierarchy of evidence on IGRAs developed by the systematic review team and shared with Expert Group prior to the meeting



# Interferon-Gamma Release Assays for Active Pulmonary TB Diagnosis in Adults in Low- and Middle-Income Countries: Systematic Review and Meta-Analysis

John Z. Metcalfe [1,2], Charles K. Everett[1], Karen R. Steingart[2], Adithya Cattamanchi[1,2], Laurence Huang[1,3], Philip C. Hopewell[1,2], Madhukar Pai[4*]

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[2] Curry International National Tuberculosis Center, University of California, San Francisco, USA
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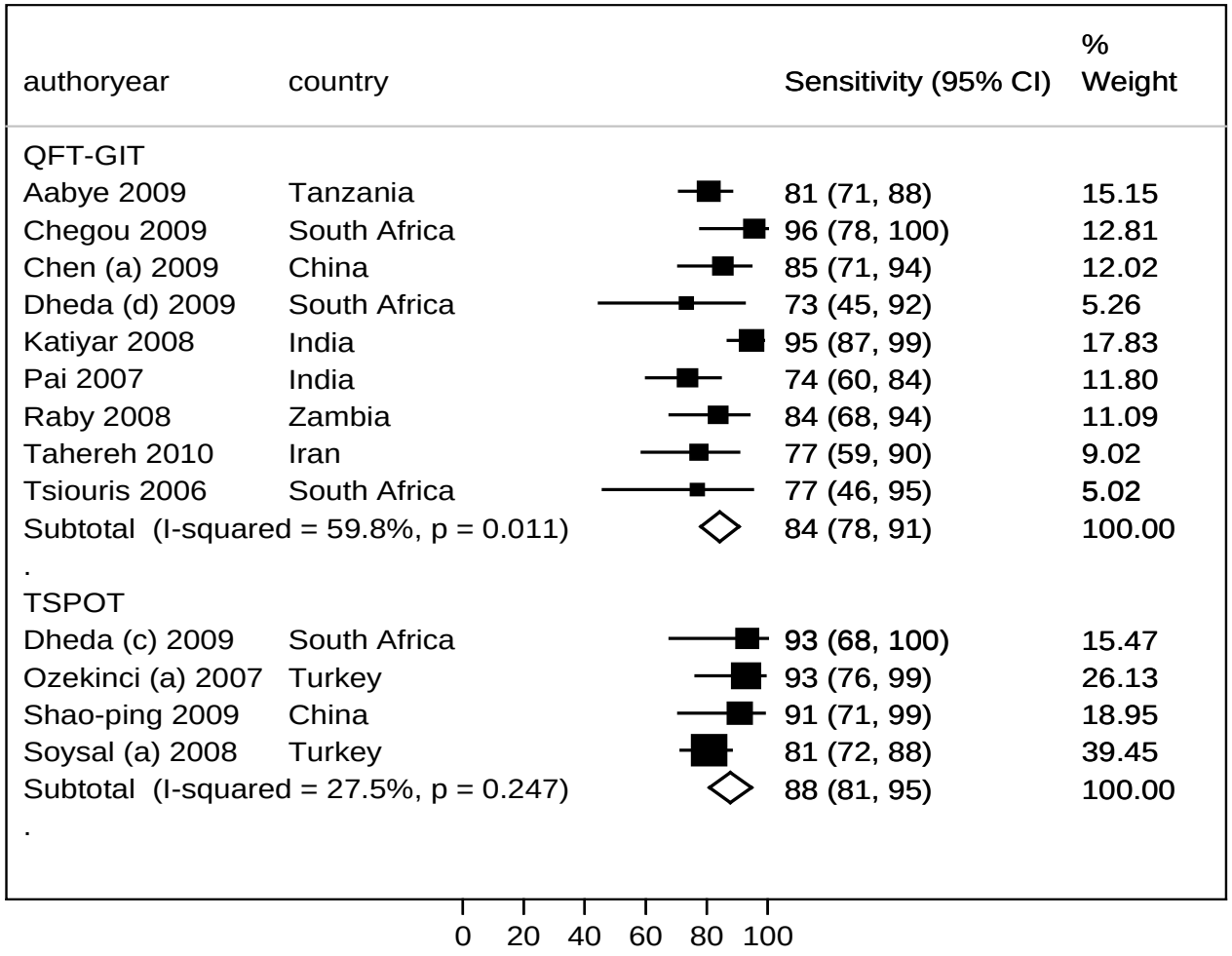
[4] Dept. of Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, Canada

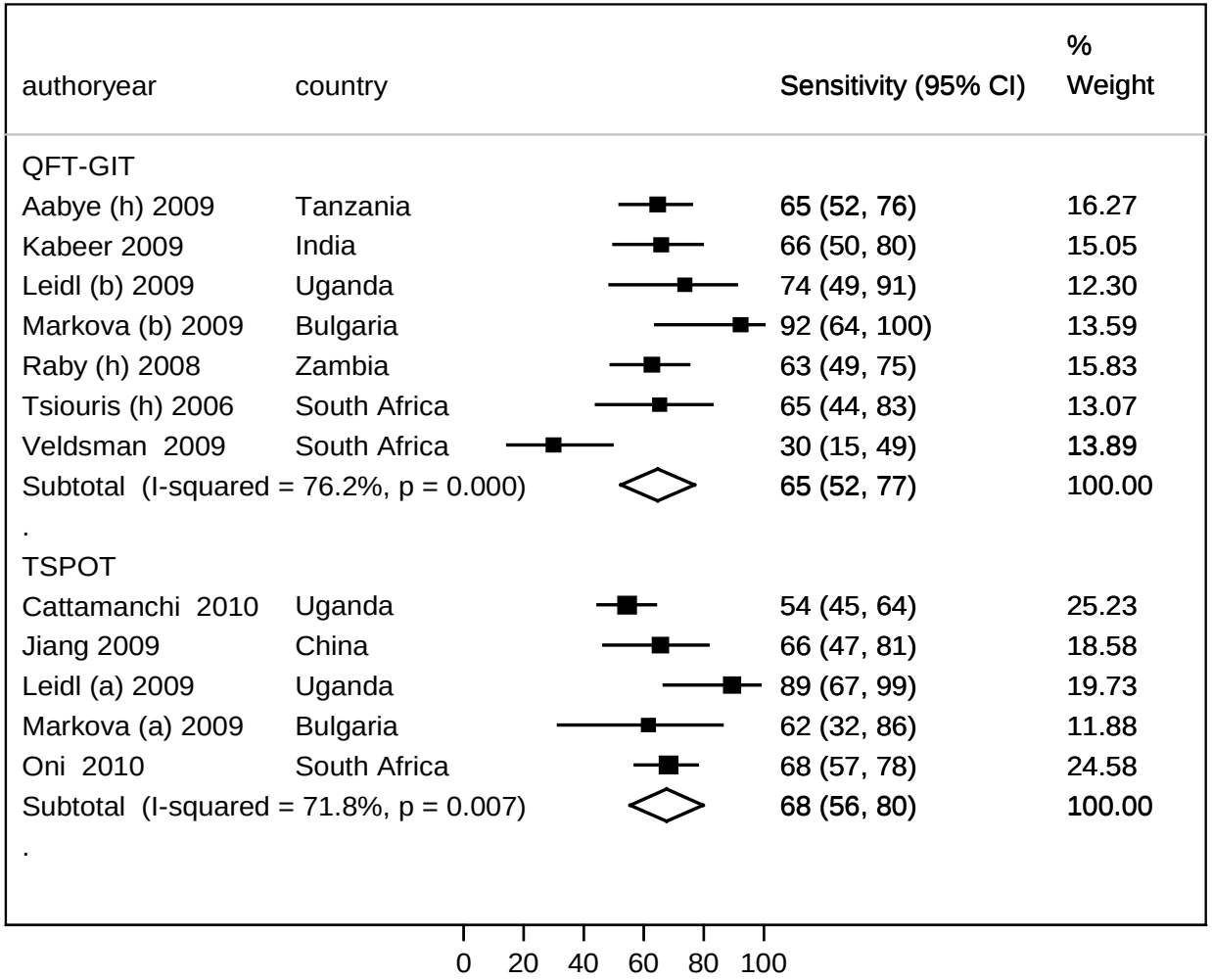
27 studies (17 QFT-GIT, 10 T-SPOT) evaluating 590 HIV-uninfected and 844 HIV-infected TB suspects were included.

Metcalfe JZ et al. Journal Infect Dis (in press)

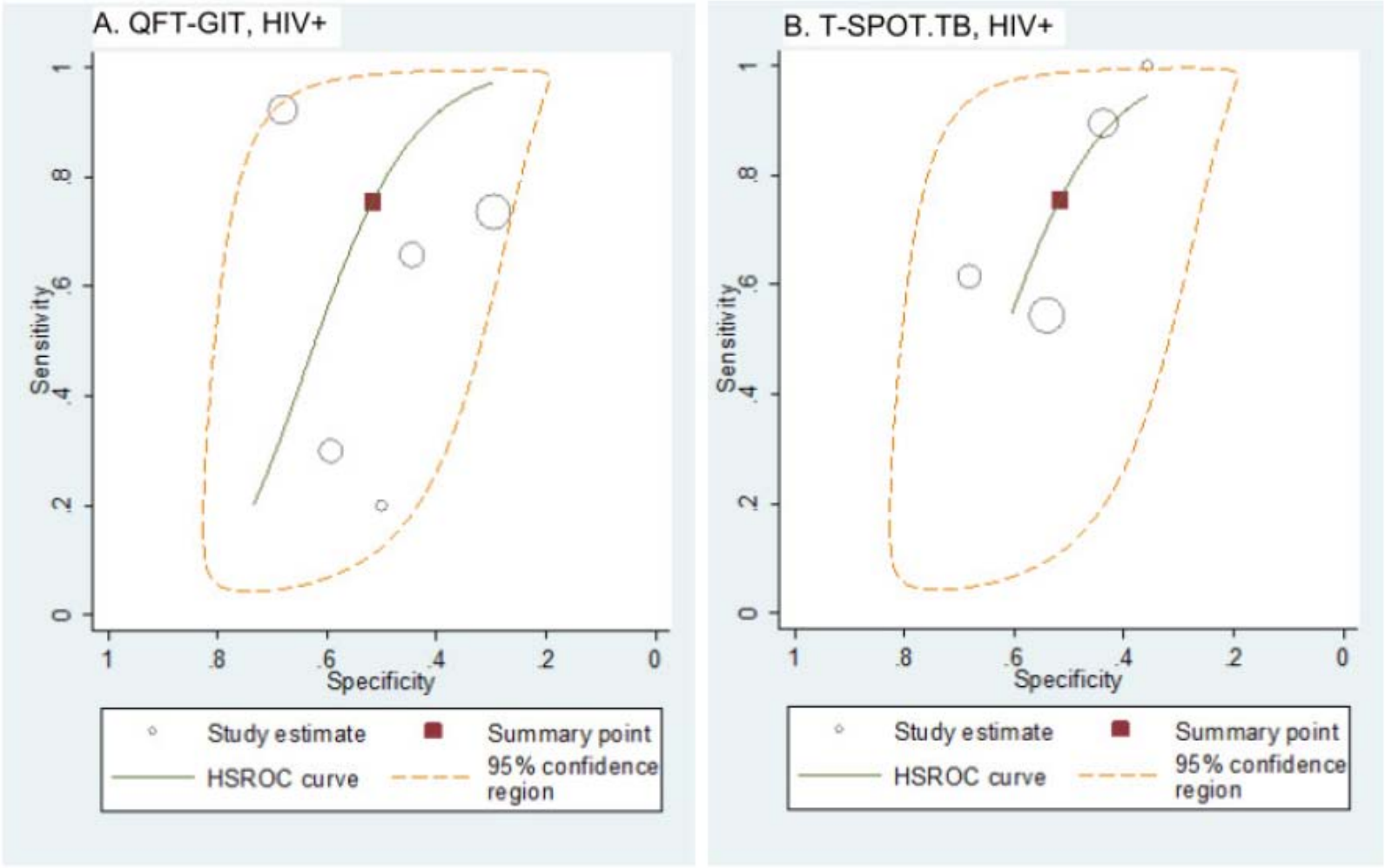
# Sensitivity of QFT-GIT and T-SPOT.TB in HIV-uninfected persons with confirmed active TB in low- and middle-income countries



# Sensitivity of QFT-GIT and T-SPOT.TB in HIV-infected persons with confirmed active TB in low- and middle-income countries



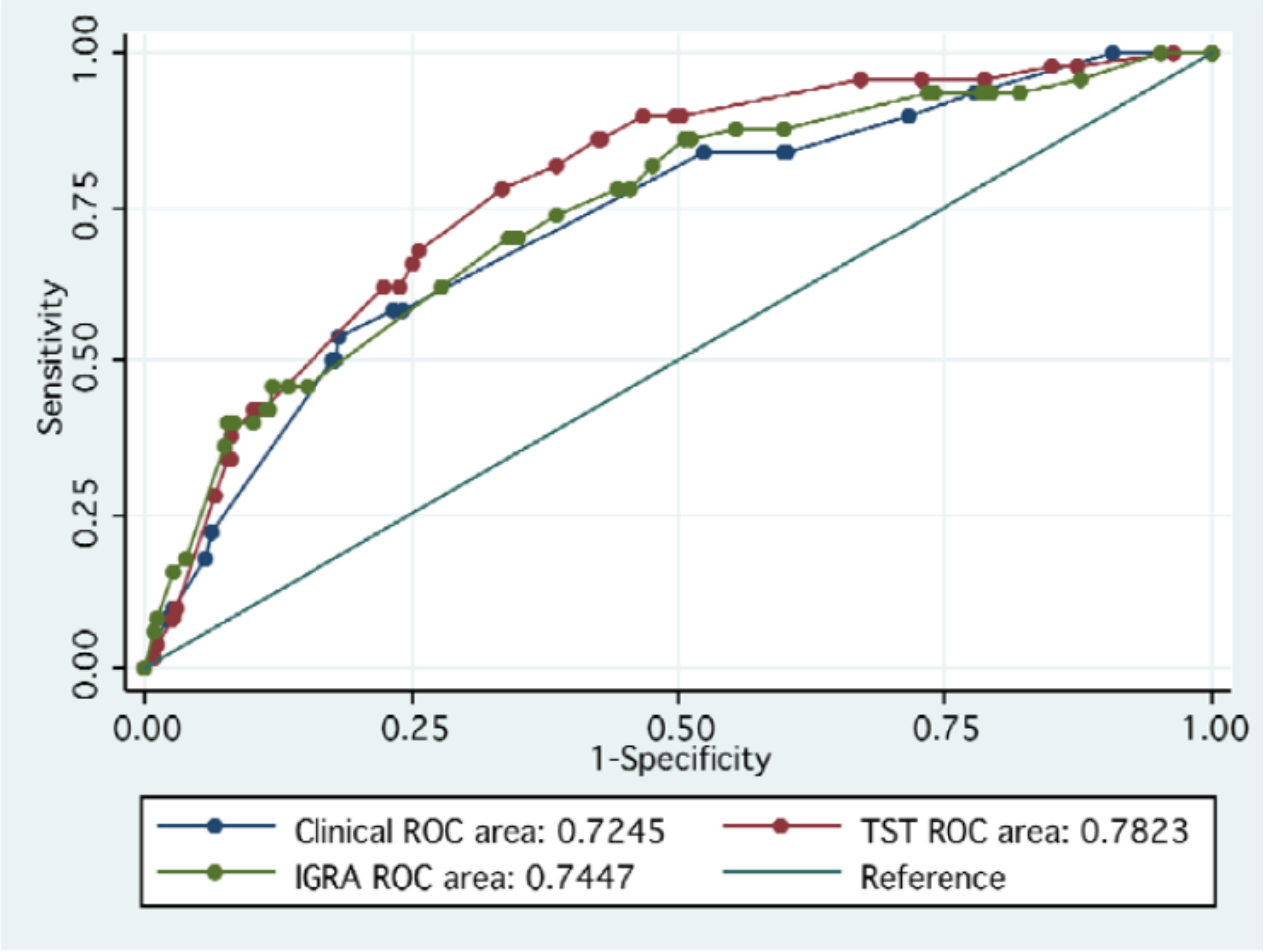
# Hierarchical Summary ROC Plot of Studies that Reported both Sensitivity and Specificity in Active TB Suspects




Metcalfe JZ et al. Journal Infect Dis (in press)

# Added value of IGRA in smear-negative TB work-up

779 sputum smear-negative HIV-infected persons screened for TB prior to IPT




Rangaka MX et al. CDC Late Breaker Session, IUATLD, Berlin 2010

# Take home message

- 1 in 3 HIV-infected patients with active TB will be IGRA-negative
- 1 in 2 patients without active TB will be IGRA-positive
- In low- and middle-income countries, IGRAs are inadequate rule-out or rule-in tests for active TB in adults, especially in the setting of HIV co-infection
- IGRAs do not offer added value beyond conventional tests for active TB

- IGRAs should not replace microbiological tests for active TB

# Interferon-Gamma Release Assays for the Diagnosis of Latent Tuberculosis Infection in HIV-Infected Individuals: A Systematic Review and Meta-analysis

*Adithya Cattamanchi, MD,*† Rachel Smith, MD,* Karen R. Steingart, MD, MPH,† John Z. Metcalfe, MD, MPH,*† Anand Date, MD, MBBS,‡ Courtney Coleman, MPH,‡ Barbara J. Marston, MD,‡ Laurence Huang, MD, MAS,*§ Philip C. Hopewell, MD,*† and Madhukar Pai, MD, PhD‖*

37 studies included 5736 HIV-infected individuals investigated for LTBI

Cattamanchi A et al. JAIDS 2011

# Interferon-Gamma Release Assays for the Diagnosis of Latent Tuberculosis Infection in HIV-Infected Individuals: A Systematic Review and Meta-Analysis

*Adithya Cattamanchi, MD,*† Rachel Smith, MD,* Karen R. Steingart, MD, MPH,† John Z. Metcalfe, MD, MPH,*† Anand Date, MD, MBBS,‡ Courtney Coleman, MPH,‡ Barbara J. Marston, MD,‡ Laurence Huang, MD, MAS,*§ Philip C. Hopewell, MD,*† and Madhukar Pai, MD, PhD‖*

**Objective:** To determine whether interferon-gamma release assays (IGRAs) improve the identification of HIV-infected individuals who could benefit from latent tuberculosis infection therapy.

**Design:** Systematic review and meta-analysis.

**Methods:** We searched multiple databases through May 2010 for studies evaluating the performance of the newest commercial IGRAs (QuantiFERON-TB Gold In-Tube [QFT-GIT] and T-SPOT.*TB* [TSPOT]) in HIV-infected individuals. We assessed the quality of all studies included in the review, summarized results in prespecified subgroups using forest plots, and where appropriate, calculated pooled estimates using random effects models.

**Results:** The search identified 37 studies that included 5736 HIV-infected individuals. In three longitudinal studies, the risk of active tuberculosis was higher in HIV-infected individuals with positive versus negative IGRA results. However, the risk difference was not statistically significant in the two studies that reported IGRA results according to manufacturer-recommended criteria. In persons with active tuberculosis (a surrogate reference standard for latent tuberculosis infection), pooled sensitivity estimates were heterogeneous but higher for TSPOT (72%; 95% confidence interval [CI], 62–81%) than for QFT-GIT (61%; 95% CI, 47–75%) in low-/middle-income countries. However, neither IGRA was consistently more sensitive than the tuberculin skin test in head-to-head comparisons. Although TSPOT appeared to be less affected by immunosuppression than QFT-GIT and the tuberculin skin test, overall, differences among the three tests were small or inconclusive.

**Conclusions:** Current evidence suggests that IGRAs perform similarly to the tuberculin skin test at identifying HIV-infected individuals with latent tuberculosis infection. Given that both tests have modest predictive value and suboptimal sensitivity, the decision to use either test should be based on country guidelines and resource and logistic considerations.

**Key Words:** latent tuberculosis infection, systematic review, interferon-gamma release assay, HIV infection, tuberculin skin test

(*J Acquir Immune Defic Syndr* 2011;56:230–238)

Received for publication September 30, 2010; accepted December 10, 2010.

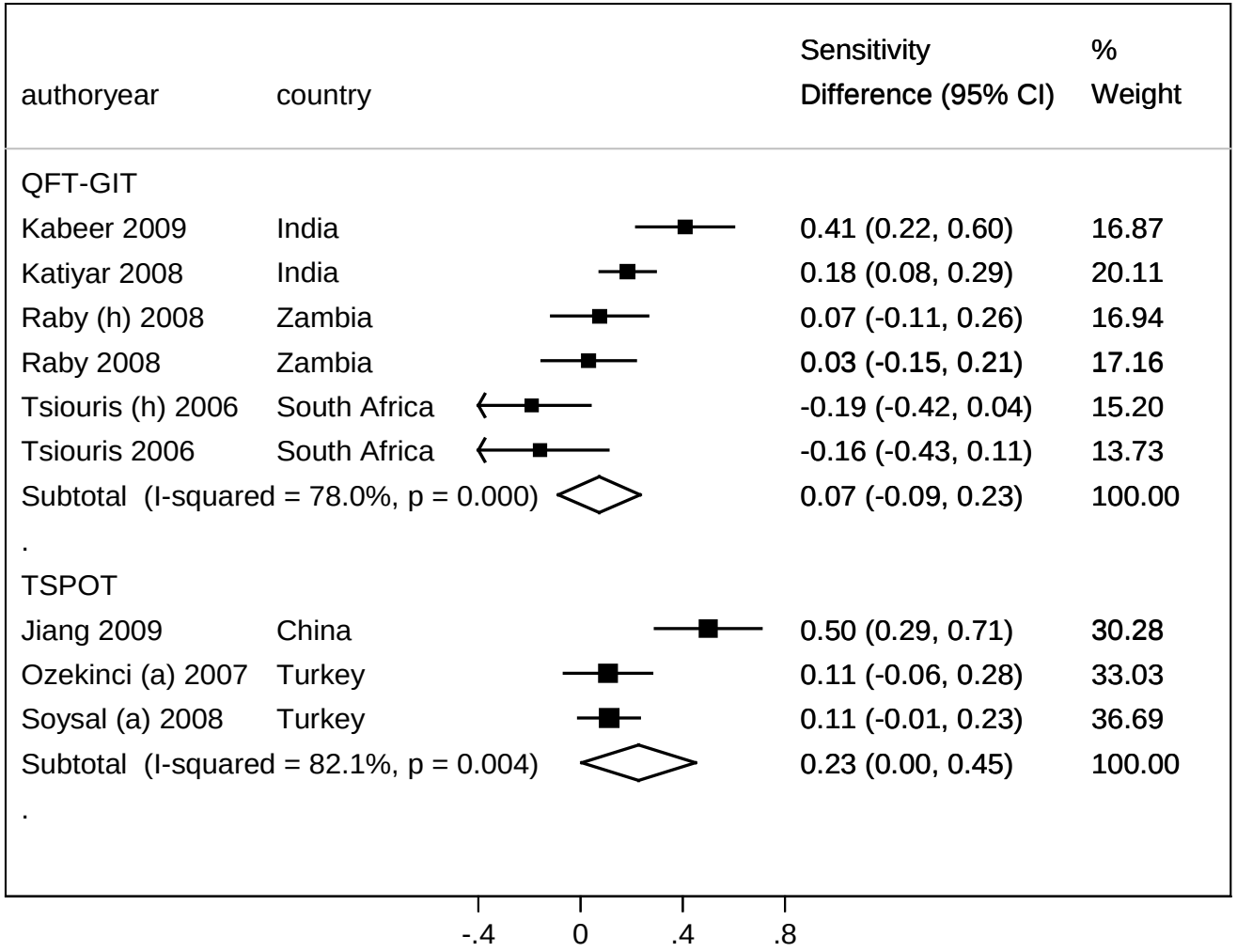
From the *Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California, San Francisco, CA; †Curry International Tuberculosis Center, University of California, San Francisco, San Francisco, CA; ‡Division of Global HIV/AIDS, Centers for Disease

# Key findings

- Both IGRAs have suboptimal sensitivity in HIV-infected persons with culture-confirmed TB
- Neither IGRA was consistently more sensitive than the tuberculin skin test (TST) in head-to-head comparisons.
- While TSPOT appeared to be less affected by immunosuppression than QFT-GIT and TST, overall, differences between the three tests were small or inconclusive.

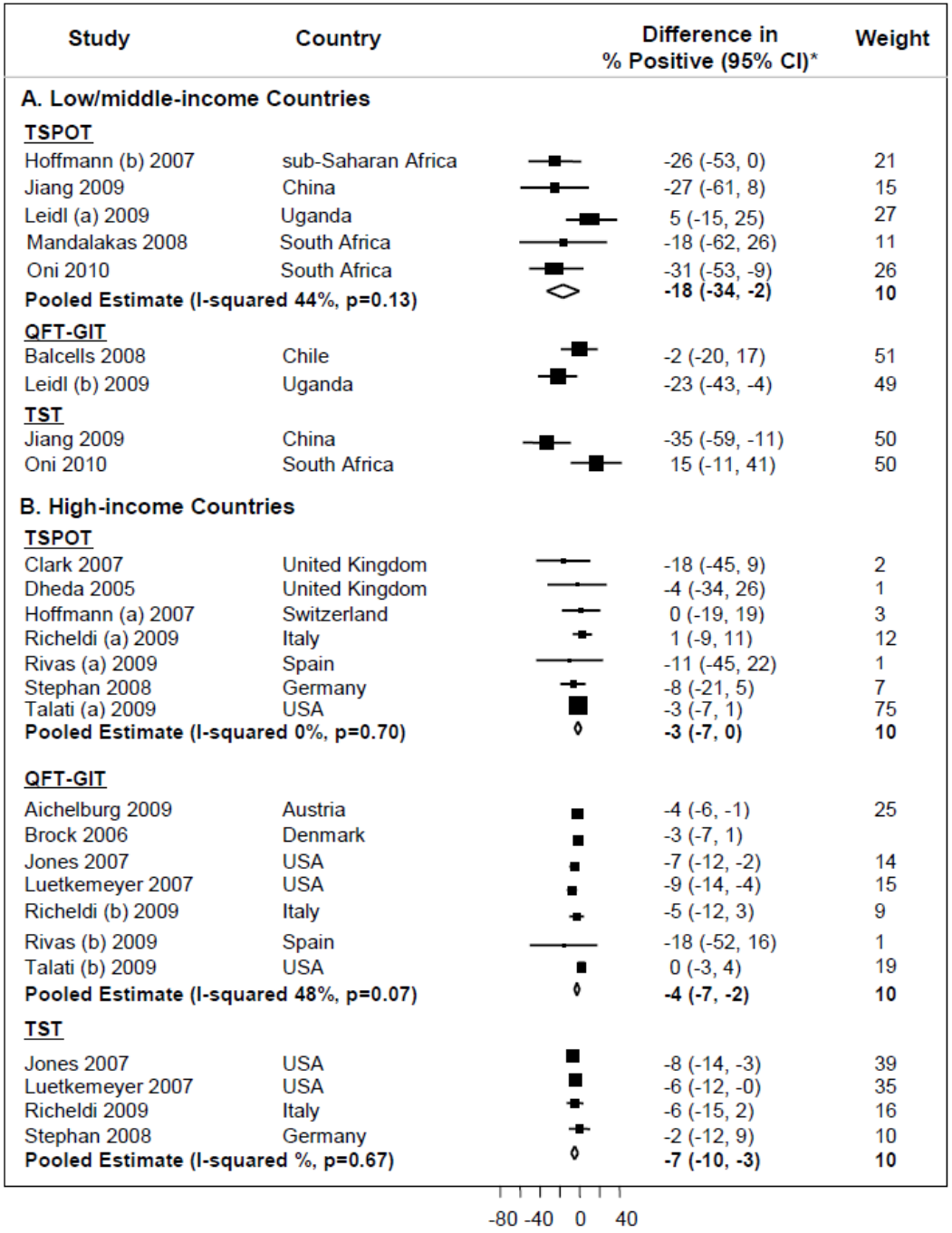
Cattamanchi A et al. JAIDS 2011

# Percent sensitivity difference between IGRA and TST results




There was no significant evidence that either IGRA was more sensitive than the TST for active TB diagnosis, but T-SPOT appeared to be more sensitive.

# Impact of CD4+ cell count on the proportion of positive IGRA results




Difference = (% positive CD4 <200 cells/µl) – (% positive CD4 ≥200 cells/µl)

# Interferon-gamma Release Assays and Childhood Tuberculosis: systematic review and meta-analysis

Mandalakas AM*[1,2], Detjen AK*[2,3], Hesseling AC[2], Benedetti A[4,5,6], Menzies D[4]

Int J Tuberc Lung Dis 2011 (in press)

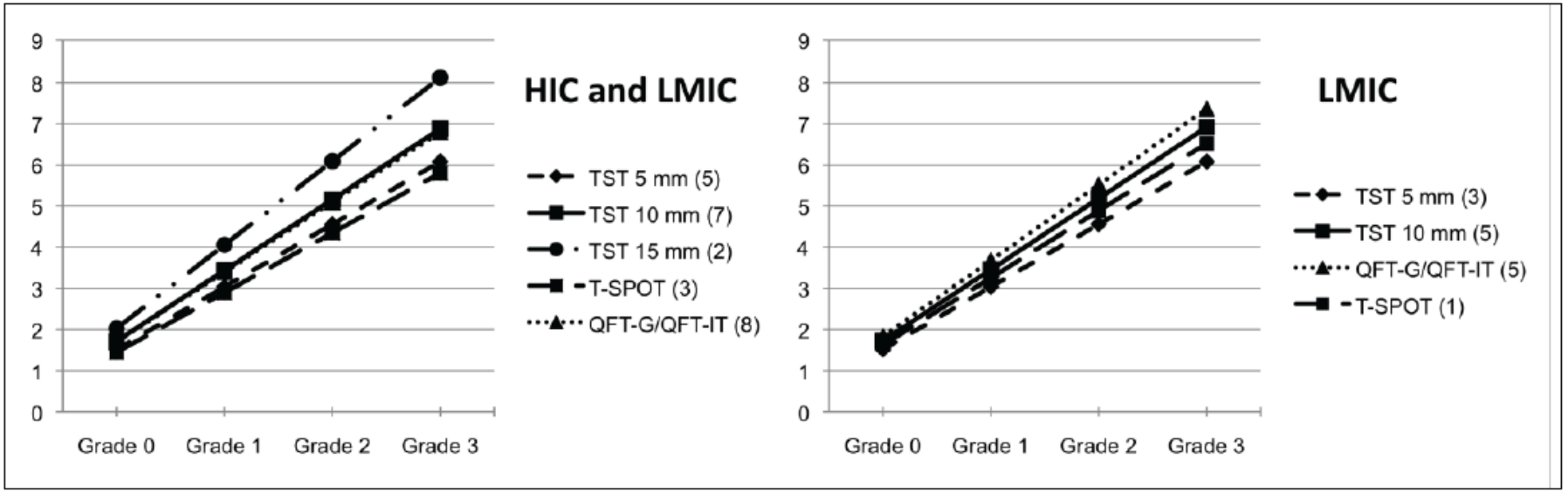
# Key findings

- 33 studies were included (mostly from high income countries)
- For the diagnosis of active TB, the overall sensitivity of both IGRAs and the TST was similar when assessed in children with all categories of active TB combined
  - All tests were suboptimal to rule-out active TB in children
- When assessed across a gradient of exposure, TST and both IGRAs showed a very similar performance
- Overall, available data suggest that TST and IGRAs have similar accuracy for the detection of TB infection or the diagnosis of disease in children

Mandalakas A et al. Int J Tuberc Lung Dis (in press)

# Performance of IGRAs and TST across a gradient of exposure

**Figure 2. Regression slopes for exposure gradients.**




Mandalakas A et al. Int J Tuberc Lung Dis (in press)

# IGRAs in healthcare workers

## 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]

► Additional material and appendix tables A1 and A2 are published online only. To view these files please visit the journal online (http://thorax.bmj.com).

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The findings of this review were presented at a WHO Expert Group Meeting on interferon-gamma release assays in July 2010 organised by the Stop TB Department of the WHO.

Received 25 May 2010
Accepted 2 December 2010

**ABSTRACT**

Healthcare workers (HCWs) are at increased risk of exposure to tuberculosis (TB). Traditionally, screening for latent TB infection (LTBI) is done using the tuberculin skin test (TST). Interferon-gamma release assays (IGRAs) are now increasingly being used for diagnosis of LTBI, but their role in HCW screening is unclear. A systematic review was conducted of all IGRA studies in HCWs to summarise their performance in cross-sectional and serial testing settings. By searching four electronic databases and other sources, all available studies using any one of the commercial IGRA assays in HCWs were retrieved and screened. 50 unique studies were identified which met the inclusion criteria including five from high TB incidence settings. Among 24 cross-sectional studies in low TB incidence settings, the pooled prevalence of positive IGRA using either test was significantly lower than for a positive TST. However, in high-incidence settings (n=2) there were no consistent differences in the prevalence of positive tests. IGRAs showed good correlation with occupational risk factors for TB exposure in low-incidence settings. Only 10 studies assessed use of IGRA for serial testing and all showed large variation in the rates of conversions and reversions, with no data suggesting that IGRAs are better at identifying the incidence of new TB infection than the TST. The use of IGRAs instead of TST for one-time screening may result in a lower prevalence of positive tests and fewer HCWs who require LTBI treatment, particularly in low TB incidence settings. However, the use of IGRAs for serial testing is complicated by lack of data on optimum cut-offs for serial testing and unclear interpretation and prognosis of conversions and reversions. Further longitudinal research will be required to inform guidelines on serial testing using IGRAs.

In many high-income countries, periodic screening of HCWs for LTBI is an important component of TBIC programmes.[4] Traditionally, the prevalence of LTBI and incidence of new TB infection (ie, conversion) among HCWs has been estimated using the tuberculin skin test (TST), a test with known limitations.[5–7] Recently, interferon-gamma release assays (IGRAs) have emerged as alternatives for the diagnosis of LTBI.[8–10] Two IGRAs are commercially available—the QuantiFERON-TB Gold In-Tube (QFT) assay (Cellestis Ltd, Carnegie, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Abingdon, UK). With the development of new national guidelines incorporating IGRAs, their use is steadily increasing.[11]

IGRAs have features that make them attractive for repeated screening: they are ex vivo blood-based tests that, in contrast to the TST, can be repeated any number of times without sensitisation or boosting, they require only one visit and do not need a baseline two-step protocol.

There is strong evidence from systematic reviews that IGRAs, especially QFT, have excellent specificity that is unaffected by BCG vaccination, while the T-SPOT.TB shows improved sensitivity for active TB over both the TST and QFT.[7 12 13] However, reviews have suggested that IGRA performance differs in high versus low TB incidence settings, with relatively lower sensitivity in high-incidence countries.[8 14]

Despite the substantial body of literature on IGRAs, almost all the available studies have limitations—namely, lack of a gold standard for LTBI, cross-sectional design, use of sensitivity and specificity as surrogates for patient-important outcomes, and lack of adequate data on predictive/prognostic

Thorax, 2011

# Predictive Value of interferon-gamma release assays for incident active TB disease in low,middle and high-income countries: A systematic review

MX Rangaka, KA Wilkison, D. Ling, JR Glynn, J. Mwansa, K Fielding, D. Menzies, RJ Wilkinson, M. Pai

University of Cape Town, Cape Town, South Africa

London School of Hygiene and Tropical Medicine, London, U.K

McGill University, Montreal, Canada



Rangaka MX et al. Under review.

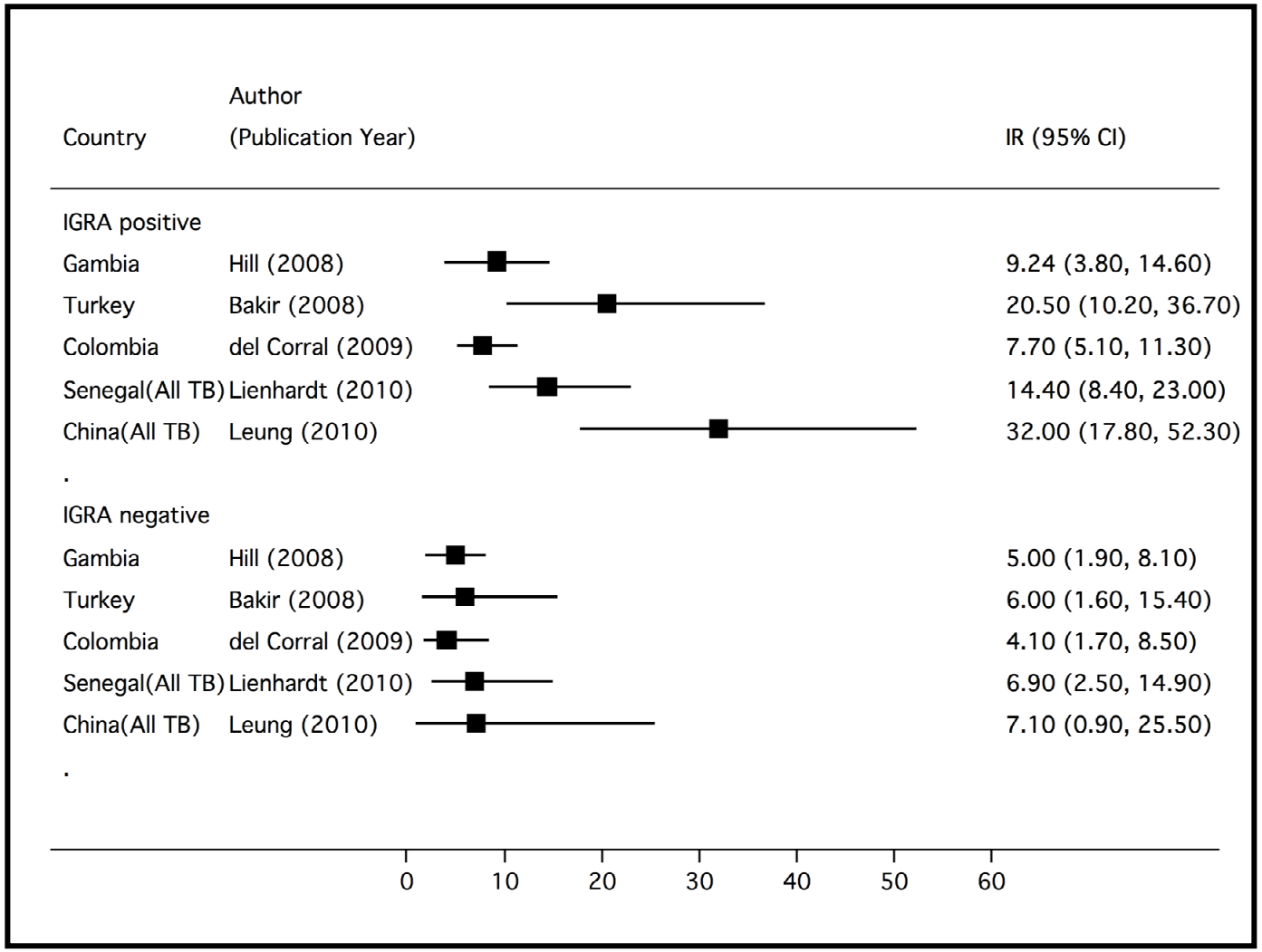
# 11 Cohort studies were included (mostly contacts)

5 ELISPOT (2 T.SPOT-TB) 7 WBA/ELISA (5 QFT-Gold In Tube )

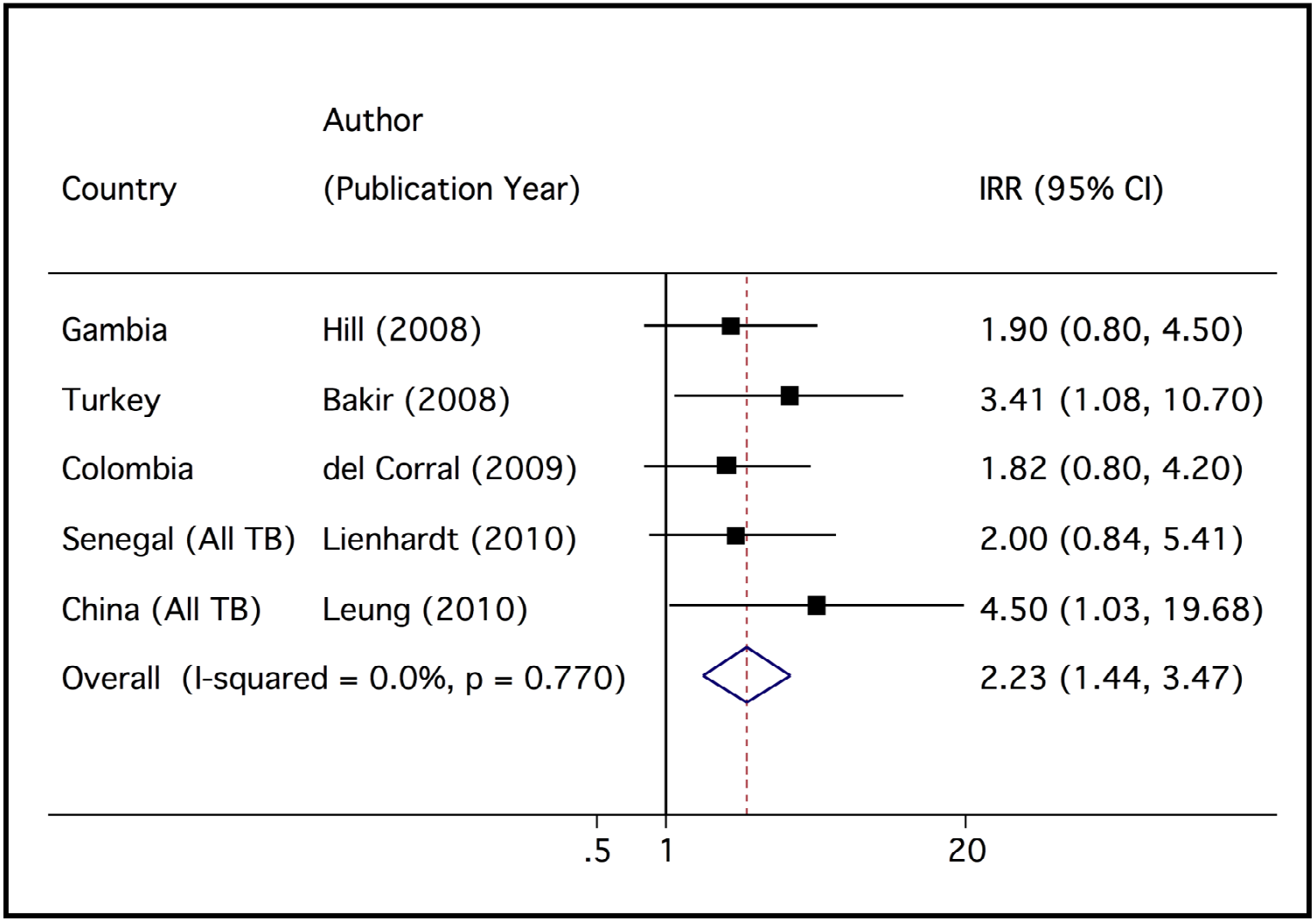
| Country, Year published, Income Class. | Adults or Children (Age distribution) | HIV infected sample (%) | àStudy Design | Original N evaluated | àN entered follow-up | *IPT given: % | TB diagnoses included |
|---|---|---|---|---|---|---|---|
| Ethiopia 2001, LIC [24] | Adults (15-65) | No; exclusion | TB case-contacts | 38 | 24 | No | Smear & culture |
| Gambia 2008, LIC [29] | Adults and Children (0.5-25+) | Yes (2%) | TB case-contacts | 2381 | 2348 | No | TST, smear & culture |
| Turkey 2008, MIC [23] | Children (0-16) | Not stated | TB case-contacts | 1024 | 908 | 1Yes: 76% | Smear & culture |
| Austria 2009, HIC [25] | Adults (IQR:31-46) | Yes (100%) | HIV infected outpatients | 834 | 822 | 2No. | IGRA & Culture |
| Netherlands 2009, HIC [26] | Adults (16-45+) | No; exclusion | TB case-contacts | 433 | 339 | No; exclusion | Smear & culture |
| Colombia 2009, MIC [27] | Adults and Children (<4-65+) | Unknown | TB case-contacts | 2060 | 2060 | No | Smear & culture |
| Senegal 2010, LIC [28] | Adults and Children (IQR:10-31) | Unknown | TB case-contacts | 2762 | 2679 | Yes: % Not stated | Smear & culture |
| Japan 2010, HIC [33] | Adults and Children (0-60+) | Unknown | Retrospective; TB case-contacts | Not stated | 5676 | 3Yes: 20% of 3102 | **IGRA |
| China 2010, MIC [30] | Adults (mean 60) | Unknown | Silicosis outpatients | 331 | 308 | 4Yes: 33% of 203 | Smear & culture |
| Norway 2010, HIC [31] | Adults (18-50+) | Unknown | Asylum seekers | Not stated | 823 | 5Yes: 3% | **IGRA |
| Germany 2010, HIC [34] | Adults and Children (0-50+) | No; exclusion | TB case-contacts | 1417 | 1335 | 5Yes: Total started not stated | TST, IGRA & culture |

# Results: Incidence rates of TB by IGRA status

Majority of IGRA positives did not progress to TB disease during follow-up

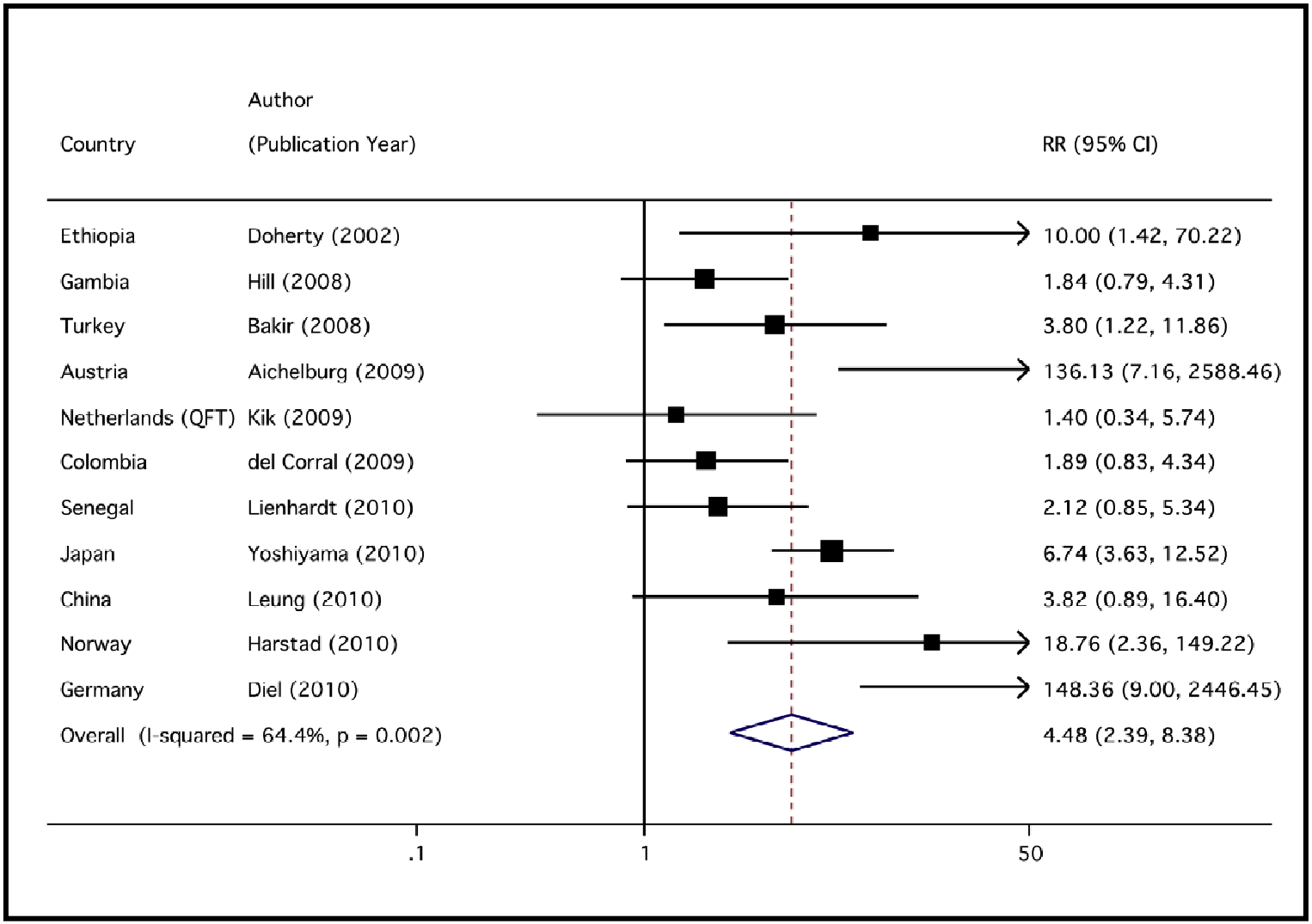


# Results: Crude Incidence Rate Ratio for IGRA+ vs. IGRA-

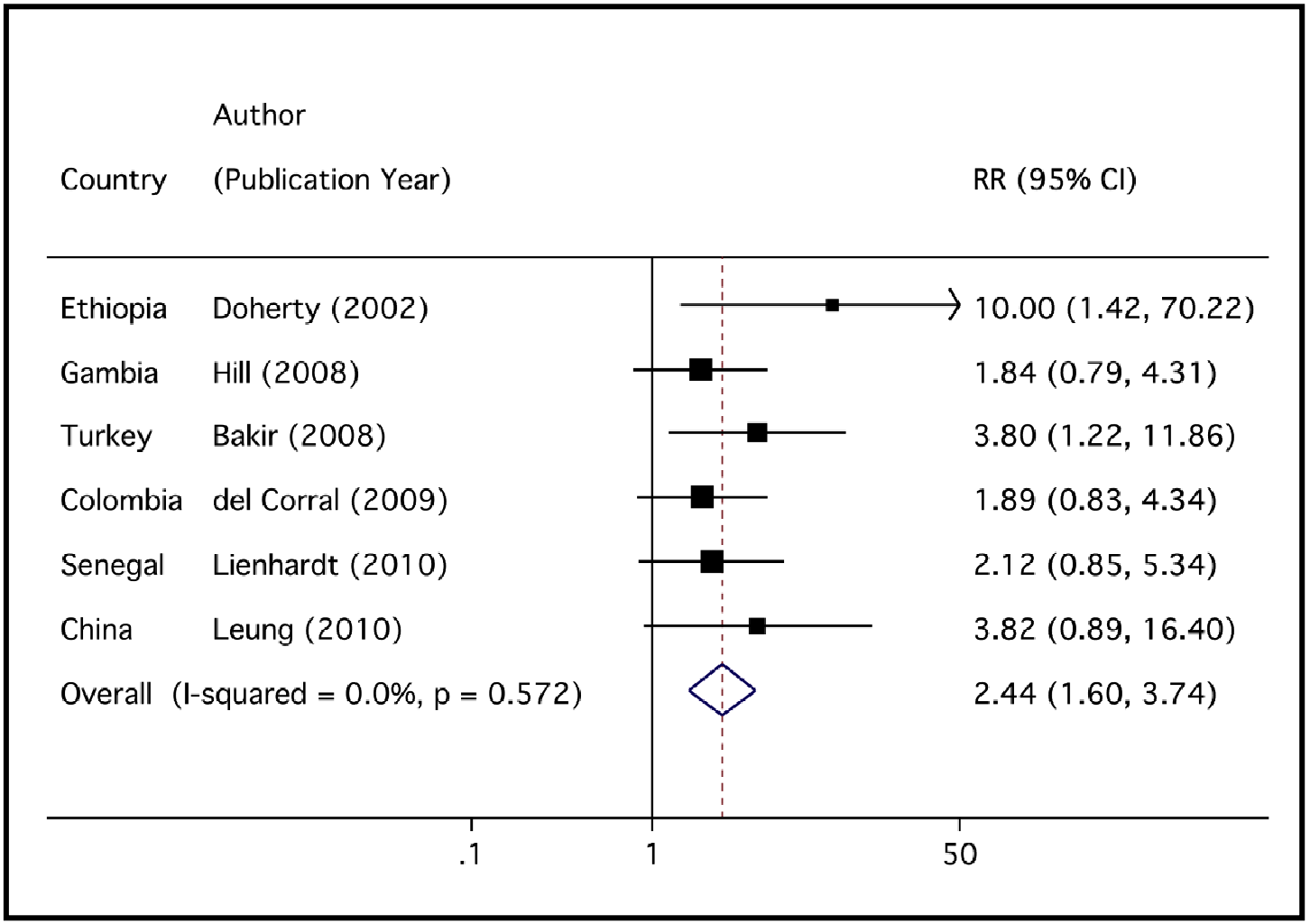



IGRA positives have moderate association with incident TB compared to IGRA negatives

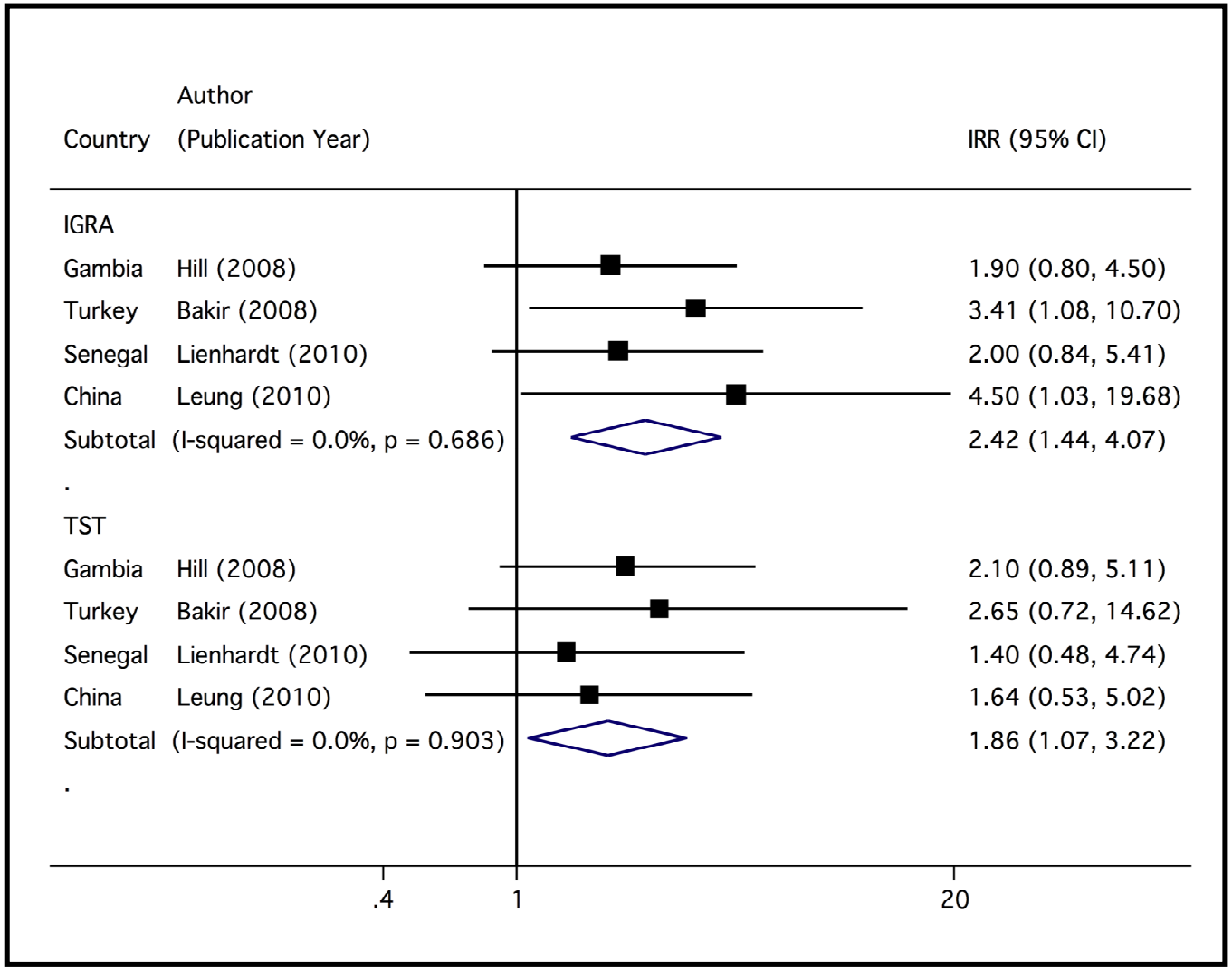
# Results: Cumulative Incidence Risk Ratio for IGRA+ vs. IGRA-



# Results: Cumulative Incidence Risk Ratio for TB (IGRA+ vs. IGRA-) No incorporation/work-up bias studies



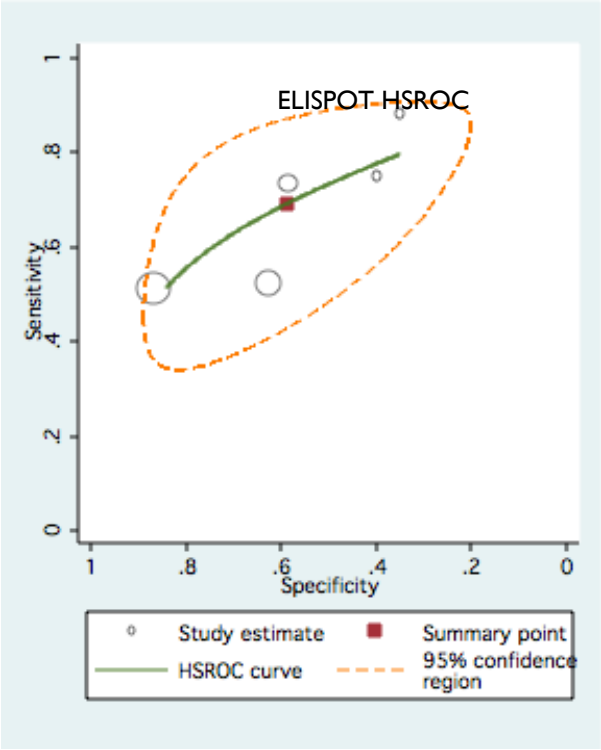
# Results:IGRA vs TST: Which has greater predictive ability?

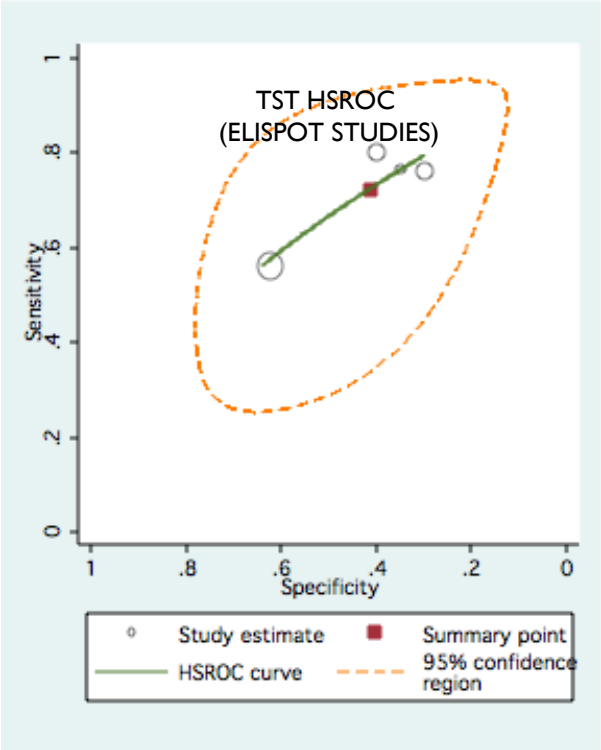



IGRA+ and TST+ have a similar strength of association with subsequent TB compared to test negative individuals

# Results:IGRA vs TST: Patient-relevant Outcomes
# HSROC summary estimates of sensitivity, specificity…

| Test | N at analysis (No. of studies) | Sensitivity % (95% CI) | Specificity % (95% CI) | FPR (1- Specificity) % (95% CI) |
|---|---|---|---|---|
| ELISPOT Studies | | | | |
| ELISPOT | 4,144 (5) | 73 (58-84) | 48 (38-58) | 52 (42-62) |
| TST | 4,638 (5) | 72 (58-83) | 41 (30-54) | 59 (46-70) |



# Results:IGRA vs TST: Patient-relevant Outcomes
# % Scored Positive by IGRA and TST at analysis

| Country | N at analysis tested with IGRA | % IGRA positive (95% CI) | N at analysis tested with TST | % TST positive (95% CI) |
|---|---|---|---|---|
| WBA/ELISA Studies | | | | |
| Ethiopia | 24 | 38 (19-59) | N/A | N/A |
| Austria | 775 | 5 (3-7) | N/A | N/A |
| Netherlands (QFT) | 327 | 54 (49-60) | N/A | N/A |
| Colombia | 1973 | 66 (64-68) | N/A | N/A |
| Japan | 3102 | 14 (12-15) | N/A | N/A |
| Norway | 823 | 30 (27-33) | ‡823 | ‡100 |
| Germany | 954 | 21 (18-23) | 954 | 63 (60-66) |
| ELISPOT Studies | | | | |
| Gambia | 1736 | 37 (35-40) | †2230 | 38 (36-40) |
| Turkey | 908 | 42 (39-45) | 908 | 61 (58-64) |
| Netherlands (TSpot.TB) | 299 | 61 (55-66) | ‡299 | ‡100 |
| Senegal (All TB) | 893 | 57 (54-60) | 893 | 70 (67-73) |
| China (All TB) | 308 | 66 (61-71) | 308 | 66 (61-71) |

# Conclusions

- All existing LTBI tests (TST and IGRAs) appear to have only modest predictive value and may not help identify those who are at highest risk of progression to disease.
- Based on the evidence thus far, IGRAs appear to have similar predictive value as the TST.
- In some settings, the % IGRA+ will be less than % TST+, reducing the number needed for IPT
- Incidence rates of TB, even in IGRA positive individuals, are low, suggesting that a vast majority (>95%) of IGRA+ individuals do not progress to TB disease during follow-up. This is similar to the TST.
- IFN-g alone is not sufficient as a biomarker for disease progression
- The search for predictive biomarkers must continue

# 2015: new target for predictive LTBI test

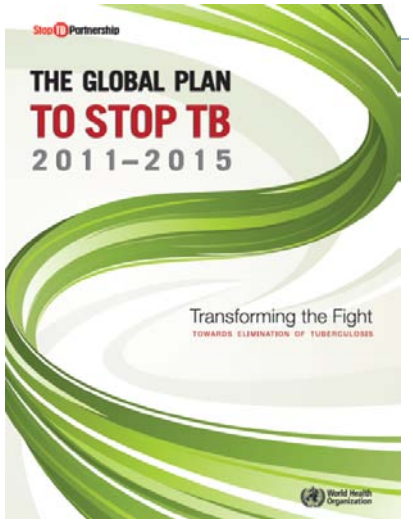
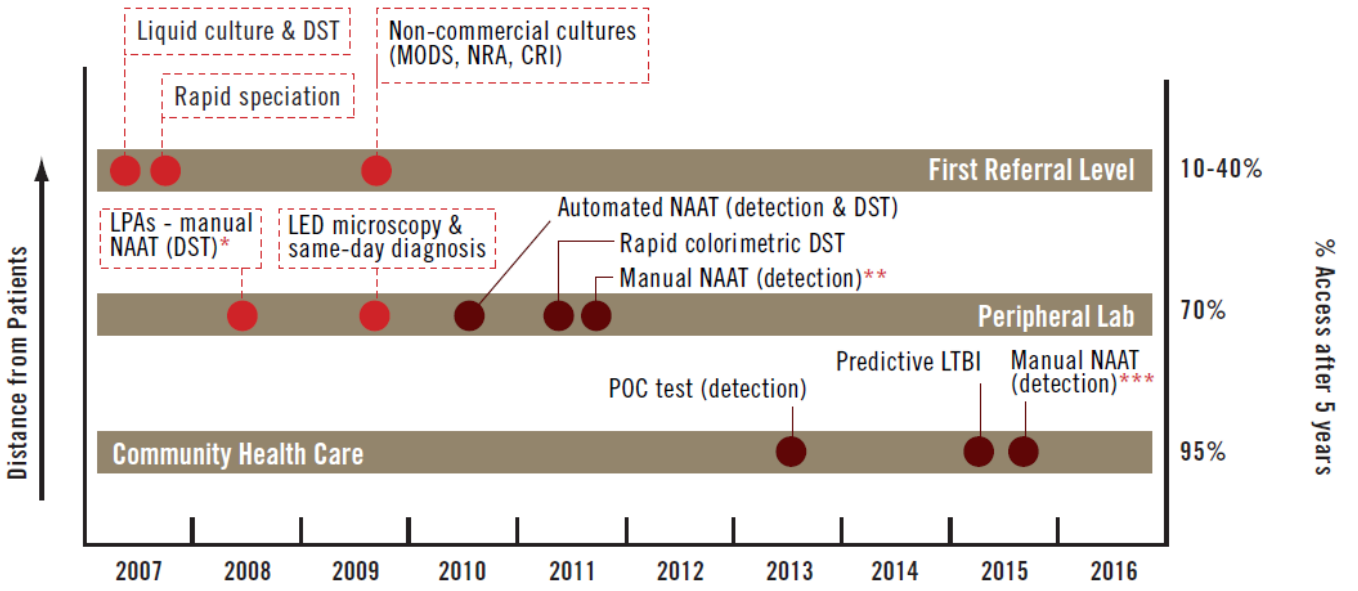



FIGURE 2 TARGETS FOR INTRODUCTION OF TESTS, LEADING TO SUSTAINABLE ADOPTION, 2006–2015




**Abbreviations**
DST: Drug Susceptibility Test
NAAT: Nucleic Acid Amplification Test
LTBI: Latent TB Infection
POC: Point of Care
MODS: Microscopic observation drug-susceptibility
NRA: Nitrate reductase assay
CRI: Colorimetric redox indicator assay
LED: Light-emitting diode
LPA: Line probe assay

* Manual NAAT: technology for MTB Drug Susceptibility Testing
** Manual NAAT: technology for MTB detection at the Peripheral Lab
*** Manual NAAT: technology for MTB detection at the Community Health Care Level

Technologies in boxes: endorsed by WHO

# Updated NDWG pipeline for diagnostics

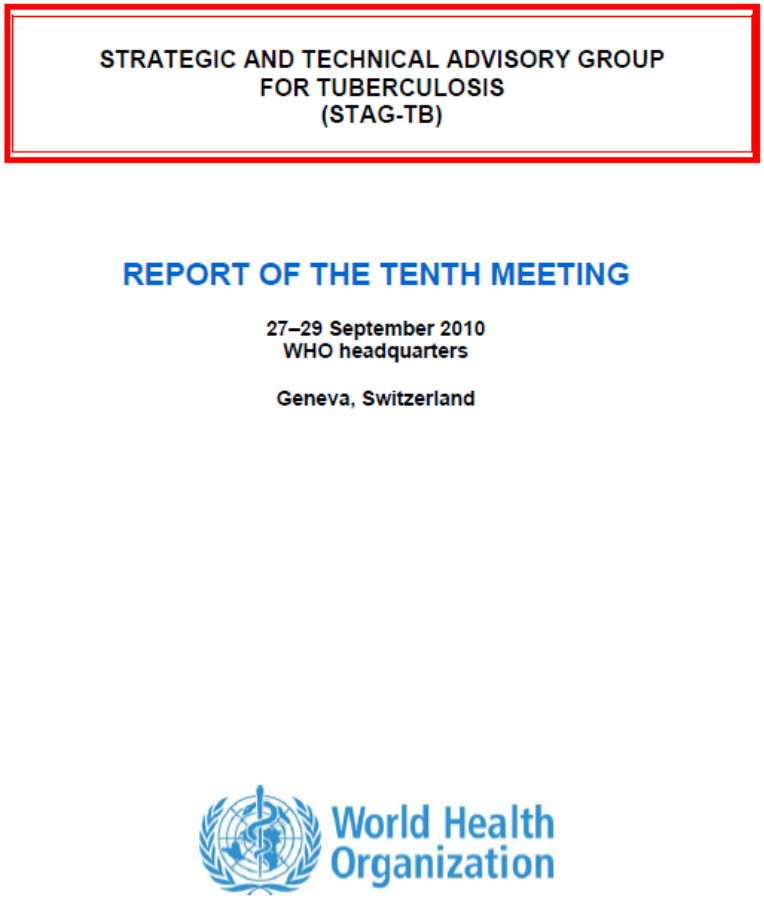
# IGRAs: resources and operational issues in low and middle income countries

- Benefits and desired effects
- Risks or undesired effects
- Resource implications (cost, lab capacity, power outages, temperature monitoring, portable incubators, etc)
- Values and preferences


All of these, plus evidence from systematic reviews and expert opinion was used to formulate recommendations which were endorsed by STAG in September 2010
WHO policy is forthcoming

# STAG TB report, published in Dec 2010

- http://www.who.int/tb/advisory_bodies/stag_tb_report_2010.pdf



STRATEGIC AND TECHNICAL ADVISORY GROUP
FOR TUBERCULOSIS
(STAG-TB)

REPORT OF THE TENTH MEETING

27–29 September 2010
WHO headquarters

Geneva, Switzerland

World Health Organization

# Thank you


- Karin Weyer, Stop TB Department of WHO
- Andy Ramsay, TDR
- Rick O'Brien, FIND
- WHO Expert Group on IGRAs
- All the systematic reviewers, in particular, Karen Steingart, Adithya Cattamanchi, John Metcalfe, Lele Rangaka, Alice Zwerling, Anna Mandalakas, Anne Detjen & Dick Menzies