# Reference standards for LTBI diagnostics

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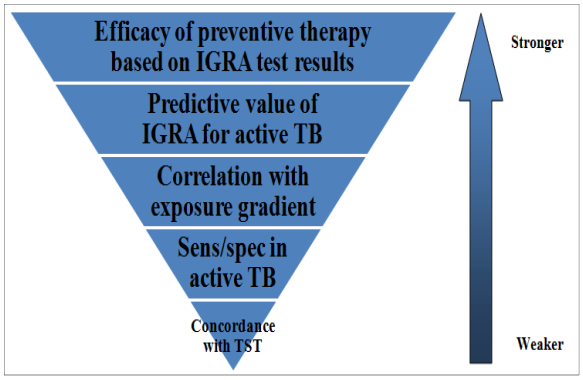
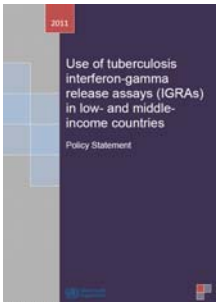
## Latent TB infection (LTBI)

- No gold standard
- Traditionally defined as a positive tuberculin skin test, with no evidence of active TB disease
- TST is known to be imperfect
  - False-positives can occur
  - False-negatives can occur
- IGRAs are newer LTBI tests, but comparing them with TST as gold standard poses problems

Hierarchy of evidence on IGRAs developed by a systematic review team and shared with WHO Expert Group on IGRAs




## Efficacy of preventive therapy based on IGRA results

- No evidence for IGRAs!
- Evidence for IPT based on TST: strong (~60% protection)
  - Latest RCT from Botswana (Samandari et al. Lancet 2011) confirmed the prior observations that IPT works only in TST-positives

## Predictive value of LTBI tests for progression to active TB

- Evidence for TST: historic cohort studies: only modest predictive ability: most TST+ do not progress to disease (i.e. lifetime risk of only 10%)

- Evidence for IGRA: similar to that of TST – based on systematic review of several cohort studies (Rangaka M et al. Lancet Infect Dis 2012)

## 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.

*Lancet Infect Dis* 2012; 12: 45–55

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See Comment page 6

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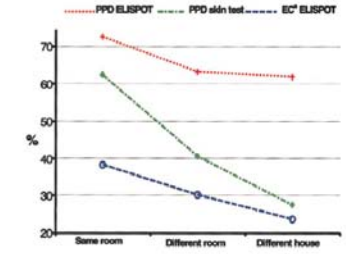
# Performance of IGRAs and TST across a gradient of exposure




| PPD ELISPOT | EC* ELISPOT (n=149) | | EC* ELISPOT (n=340) | | EC* ELISPOT (n=240) | | PPD skin test |
|---|---|---|---|---|---|---|---|
| | POS | NEG | POS | NEG | POS | NEG | |
| POS | 39.2 | 22.1 | 21.2 | 10.6 | 14.6 | 6.5 | POS |
| | 8.1 | 14.1 | 7.1 | 24.4 | 6.9 | 33.7 | NEG |
| NEG | 2.0 | 10.1 | 1.5 | 7.4 | 1.6 | 4.9 | POS |
| | 0.0 | 15.4 | 0.6 | 27.4 | 0.4 | 31.7 | NEG |

*ESAT-6/CFP-10

Hill PC et al. CID 2004

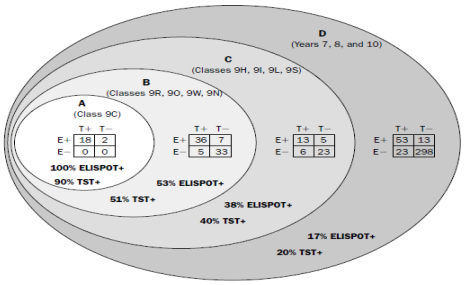



Figure 1: **TST and ELISPOT results for students stratified by decreasing proximity to index case based on school year and class**
T+=TST positive. T−=TST negative. E+=ELISPOT positive. ELISPOT−=ELISPOT negative.
A: students in same class as index case. B: students in classes in same year who regularly shared lessons with index case. C: students in the four remaining classes in same year who shared only weekly school events but no lessons with index case. D: students in different years who shared no school events with index case.

Ewer K et al. Lancet 2003

- Systematic review by Mandalakas et al. IJTLD 2011

INT J TUBERC LUNG DIS 15(8):1018–1032
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REVIEW ARTICLE

**Interferon-gamma release assays and childhood tuberculosis: systematic review and meta-analysis**

A. M. Mandalakas,*† A. K. Detjen,‡§ A. C. Hesseling,† A. Benedetti,‡¶# D. Menzies‖

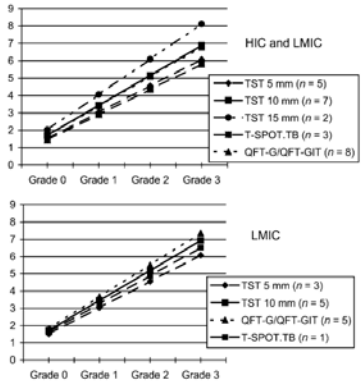


**Figure 2** Regression slopes for exposure gradients. The slopes are estimated from the regression of the logs of ORs of each successive higher exposure compared to the least exposed group. Hence, a steeper slope represents a greater change in the log ORs as exposure increases. A greater change in the log OR in response to increasing exposure (i.e., steeper slope) suggests that a test is better able to detect infection. A random effects model was used to calculate regression slopes for TST 10 mm and QFT. A fixed effects model was used to calculate the slopes for TST 5 mm, 15 mm and T-SPOT.*TB*. HIC = high-income country; LMIC = low- and middle-income country; TST = tuberculin skin test; QFT-G = QuantiFERON® Gold; QFT-GIT = QuantiFERON® Gold In-Tube; OR = odds ratio.

## Sensitivity and specificity in active TB (where active TB is the surrogate reference standard for LTBI)

Eur Respir J 2011; 37: 100–111
DOI: 10.1183/09031936.00114810
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Interferon-γ release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis

M. Sester*, G. Sotgiu#, C. Lange, C. Giehl, E. Girardi, G.B. Migliori, A. Bossink, K. Dheda, R. Diel, J. Dominguez, M. Lipman, J. Nemeth, P. Ravn, S. Winkler, E. Huitric, A. Sandgren and D. Manissero

Interferon-γ Release Assays for Active Pulmonary Tuberculosis 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] and Madhukar Pai[4]

Both concluded that IGRAs cannot be used to rule in or rule out active TB

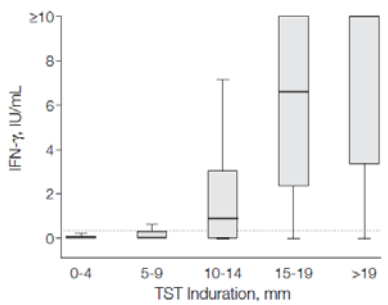
## Concordance (agreement) between TST and IGRA

**Table 3.** Agreement Between TST and IFN-γ Assay Results (n = 719)

| Results* | TST Cutpoint, mm ≥5 | ≥10 | ≥15 |
|---|---|---|---|
| Positive TST/positive IFN-γ assay | 259 | 226 | 148 |
| Negative TST/negative IFN-γ assay | 254 | 359 | 412 |
| Positive TST/negative IFN-γ assay | 177 | 72 | 19 |
| Negative TST/positive IFN-γ assay | 29 | 62 | 140 |
| Agreement, % | 71.4 | 81.4 | 77.9 |
| κ (95% CI) | 0.45 (0.39-0.51) | 0.61 (0.56-0.67) | 0.51 (0.44-0.57) |

Abbreviations: CI, confidence interval; IFN-γ, interferon γ; TST, tuberculin skin test.
*IFN-γ assay cutpoint was at least 0.35 IU/mL.

**Figure 3**. Correlation Between TST and IFN-γ Assay Responses (n=719)




Pai M et al. JAMA 2005

# In the absence of a gold standard

- Latent class analysis may be helpful

INT J TUBERC LUNG DIS 12(8):895–902
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## Improving the estimation of tuberculosis infection prevalence using T-cell-based assay and mixture models

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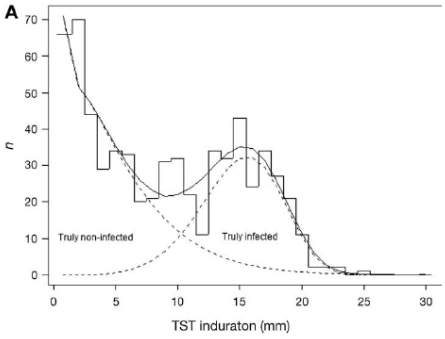


B

| Observed data | | |
|---|---|---|
| | QFT-G + | QFT-G – |
| TST + | 226 | 62 |
| TST – | 72 | 359 |

| Truly infected | | |
|---|---|---|
| | QFT-G + | QFT-G – |
| TST + | y11 | y10 |
| TST – | y01 | y00 |

| Truly non-infected | | |
|---|---|---|
| | QFT-G + | QFT-G – |
| TST + | 226-y11 | 62-y10 |
| TST – | 72-y01 | 359-y00 |

**Table 1** Prior information on sensitivity and specificity of tuberculin skin test and QuantiFERON-TB Gold In-Tube tests*

| Parameter | Prior distribution (95%CrI) |
|---|---|
| TST sensitivity | 75–90 |
| TST specificity | 70–90 |
| QFT-G sensitivity | 75–90 |
| QFT-G specificity | 95–100 |

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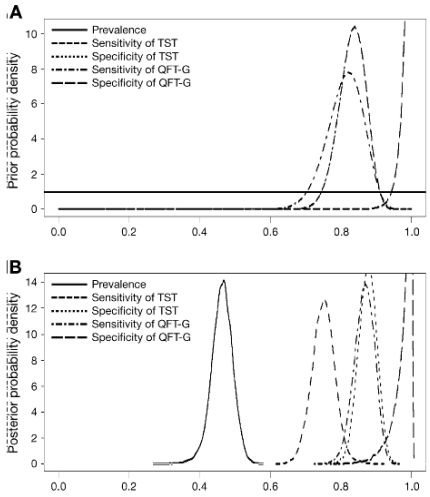


**Table 2** Estimates of LTBI prevalence from the different methods

| Method used to estimate prevalence | LTBI prevalence % | 95%CI or CrI % |
|---|---|---|
| Cut-off point based analysis of TST data | | |
| TST (≥5 mm cut-off point) | 60.7 | 57.1–64.2 |
| TST (≥10 mm cut-off point) | 41.4 | 37.7–44.9 |
| TST (≥15 mm cut-off point) | 23.2 | 20.1–26.3 |
| Cut-off point based analysis of QFT-G data | | |
| QFT-G (IFN-γ ≥ 0.35 IU/ml, manufacturer's cut-off point) | 40.1 | 36.6–43.7 |
| Mixture analysis of continuous TST data | | |
| Mixture model of TST (assuming Weibull distributions for both infected and cross-reacting subgroups) | 36.5 | 28.5–47.0 |
| LCA of TST and QFT-G data | | |
| LCA (using prior information on TST and QFT-G) | 45.4 | 40.1–49.7 |

LTBI = latent tuberculosis infection; CI = confidence interval; CrI = credible interval; TST = tuberculin skin test; QFT-G = QuantiFERON-TB Gold In-Tube assay; LCA = latent class analysis.

INT J TUBERC LUNG DIS 12(8):895–902


# Other IGRA studies with latent class analyses

ELSEVIER
Journal of Clinical Epidemiology

ORIGINAL ARTICLE

A statistical method was used for the meta-analysis of tests for latent TB in the absence of a gold standard, combining random-effect and latent-class methods to estimate test accuracy

Mohsen Sadatsafavi[a], Neal Shahidi[b], Fawziah Marra[c], Mark J. FitzGerald[d], Kevin R. Elwood[e,f], Na Guo[a], Carlo A. Marra[a,g]

Research articles

ESTIMATING DIAGNOSTIC ACCURACY OF TESTS FOR LATENT TUBERCULOSIS INFECTION WITHOUT A GOLD STANDARD AMONG HEALTHCARE WORKERS

E Girardi [girardi@inmi.it][1], C Angeletti[2], V Puro[3], R Sorrentino[3], N Magnavita[4], D Vincenti[5], S Carrara[6], D Butera[6], A M Ciufoli[6], S Squarcione[6], G Ippolito[3], D Goletti[1,7]

Practice of Epidemiology

Interpreting Tuberculin Skin Tests in a Population With a High Prevalence of HIV, Tuberculosis, and Nonspecific Tuberculin Sensitivity

Peter J. Dodd*, Kerry A. Millington, Azra C. Ghani, Junior Mutsvangwa, Anthony E. Butterworth, Ajit Lalvani, and Elizabeth L. Corbett