Reference standards for LTBI diagnostics

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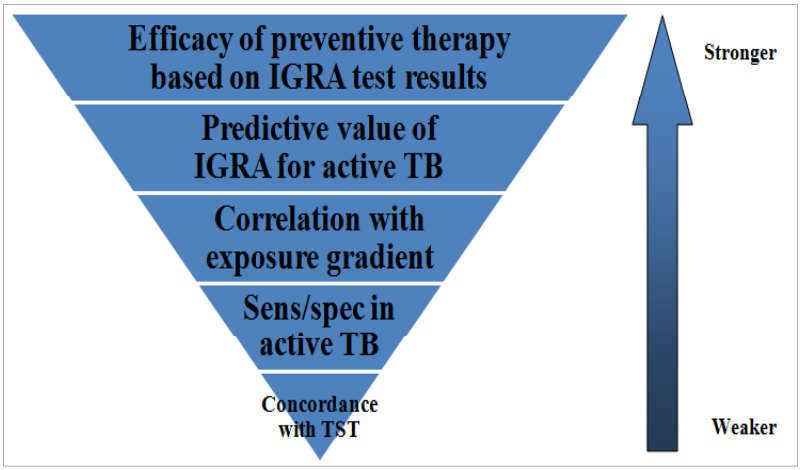
Latent TB infection (LTBI)

- 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

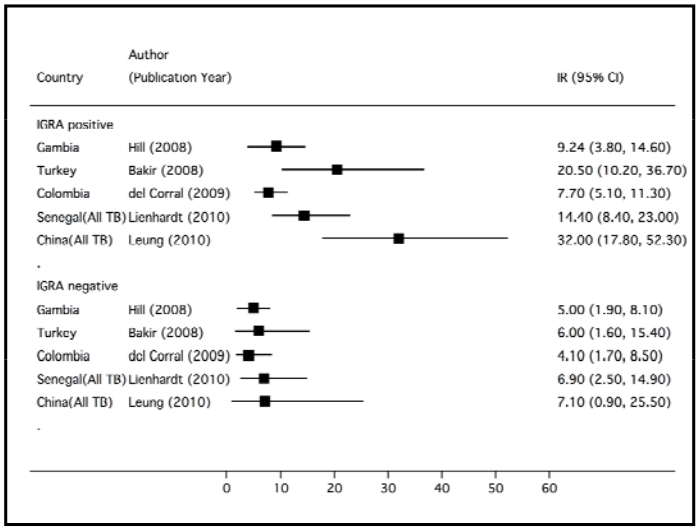


Efficacy of preventive therapy based on IGRA results

- No evidence for IGRAs!
- Evidence for IPT based on TST: strong (~60% protection)

Predictive value: Incidence rates of TB by IGRA status

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



Incidence rate per 1000 person-years

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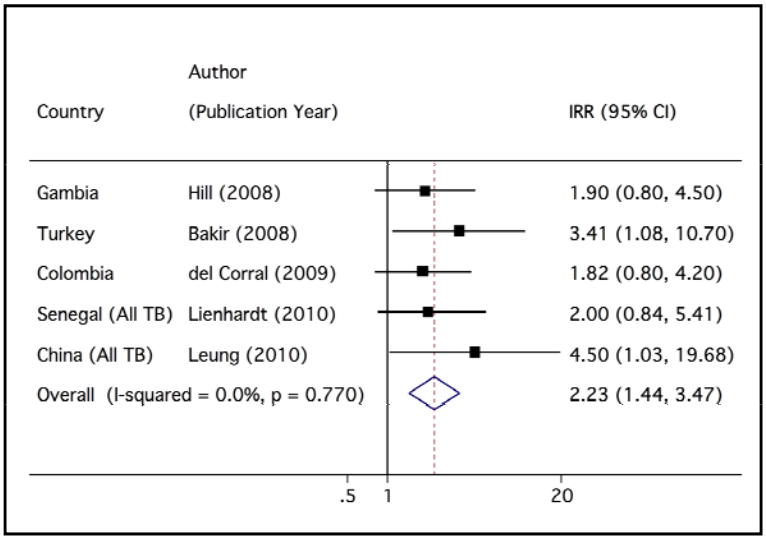
Crude Incidence Rate Ratio for IGRA+ vs. IGRA-



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

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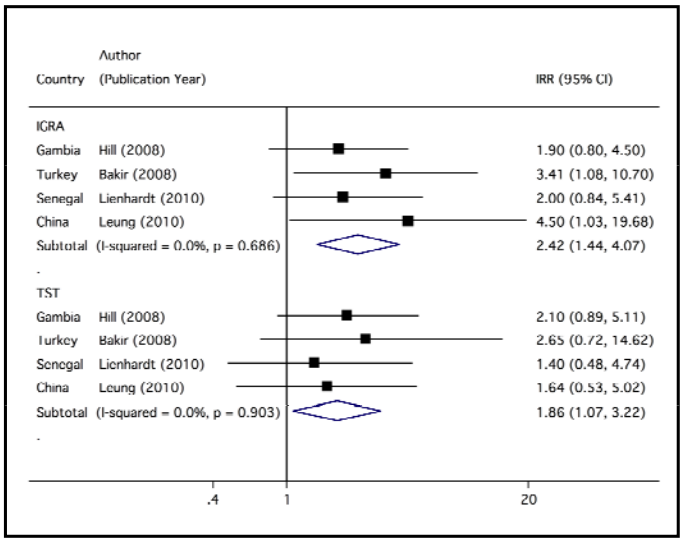
Results:IGRA vs TST: Which has greater predictive ability?



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

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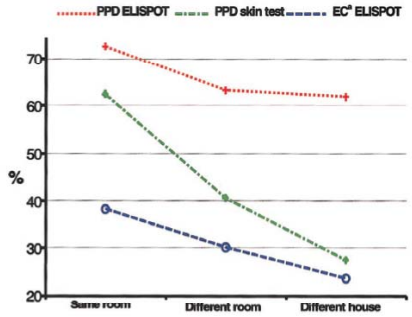
Performance of IGRAs and TST across a gradient of exposure



PPD ELISPOT	EC* ELISPOT (n=149)		EC* ELISPOT (n=340)		EC* ELISPOT (n=246)		PPD skin test
	POS	NEG	POS	NEG	POS	NEG	
POS	28.2	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

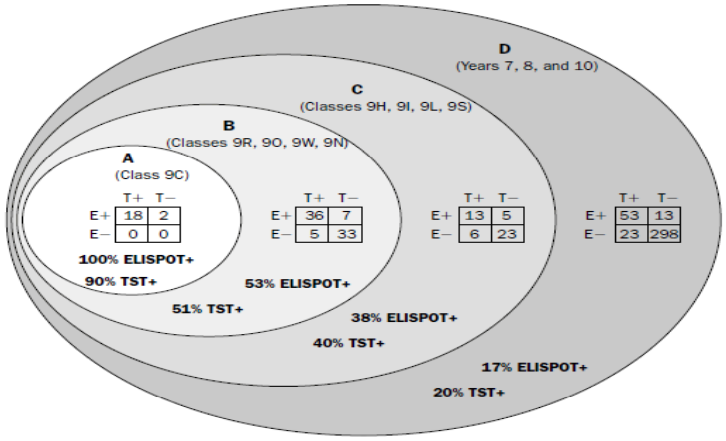
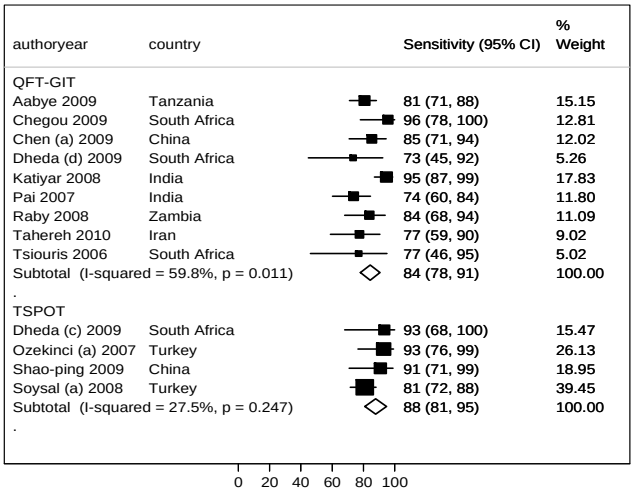


Figure 1: **TST and ELISPOT results for students stratified by decreasing proximity to index case based on school year and class**
T+=TST positive. T−=TST negative. E+=ELISPOT positive. ELISPOT−=ELISPOT negative.
A: students in same class as index case. B: students in classes in same year who regularly 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

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



Cattamanchi A et al. JAIDS (in press)

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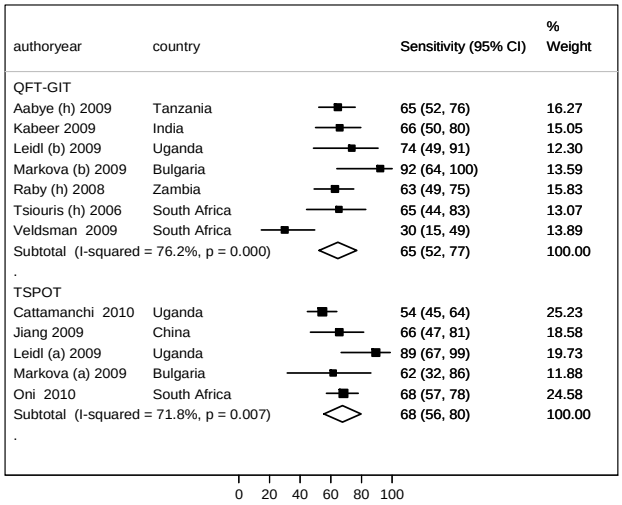


Cattamanchi A et al. JAIDS (in press)

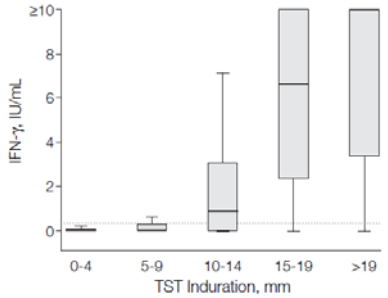
Concordance (agreement) between TST and IGRA

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

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Improving the estimation of tuberculosis infection prevalence using T-cell-based assay and mixture models

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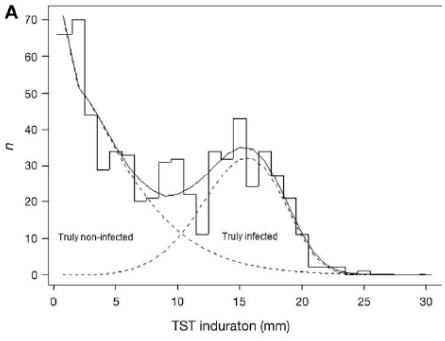

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Observed data		
	QFT-G +	QFT-G –
TST +	226	62
TST –	72	359

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

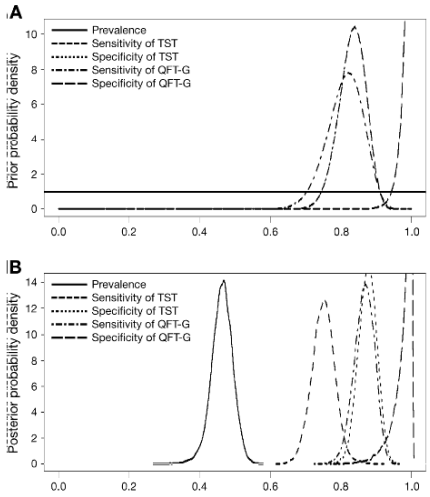

Table 2 Estimates of LTBI prevalence from the different methods

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.

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