Interferon-gamma release assays for screening of healthcare workers: a systematic review

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Outline

- HCW Systematic Review
  - Objectives/Background
  - Methods
  - Results
    - Cross-sectional Studies
    - Serial testing Studies
  - Strengths & Limitations/GRADE

- Serial Testing Update
  - New Publications
  - Data from India (4 time points)

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Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review

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► 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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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 value of IGRAs. In particular, data are lacking on

Background

- Health care workers (HCWs) are at increased risk for exposure to TB

- Systematic reviews by Joshi et al. PLoS Med, 2006 and Menzies et al. IJTLD, 2007, reported median prevalence of LTBI in HCWs of:
  - 63% in low and middle income countries (Range: 33-79%)
  - 24% in high income countries (Range: 4-46%)

- Joshi et al found in HCWs in low and middle income countries:
  - an annual risk of LTBI of 0.5%-14.3%
  - annual incidence of TB disease from: 69 to 5,780 per 100,000

Background

- HCWs consistently experience higher rates of active TB than the general population in all settings

- Renewed interest in TB infection control (TBIC) and improving TBIC measures in healthcare facilities

- Routine screening of HCWs for LTBI and/or screening post-exposure can be an important element of controlling TB infection among health care workers and is frequently done in high income countries, low TB incidence countries

Background

- HCW screening is traditionally done using the TST

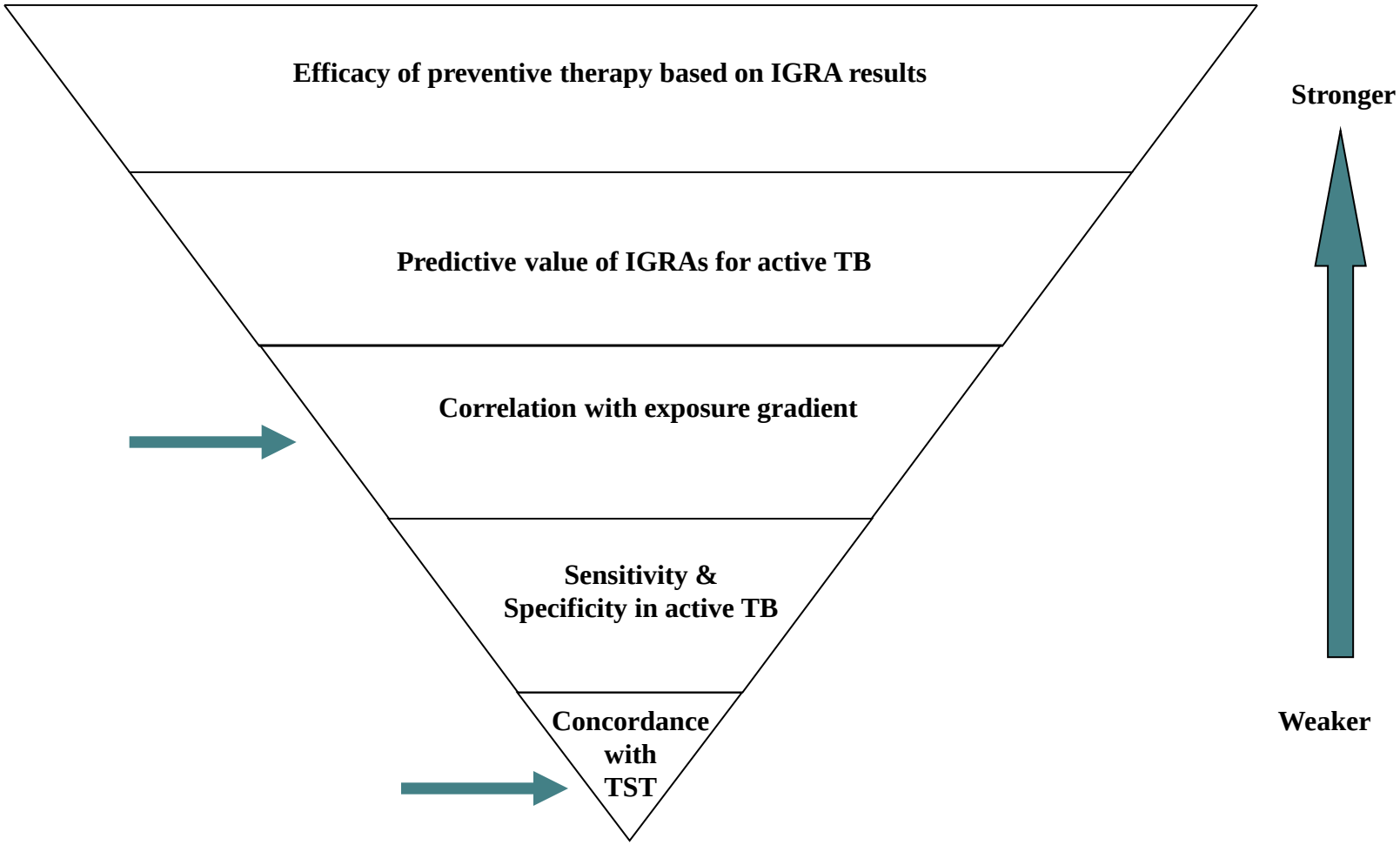
- TST has limitations, and serial testing is complicated by boosting, conversions and reversions

- IGRAs have features that make them attractive for serial testing

- Can IGRAs provide more accurate and realistic estimates of TB infection prevalence and incidence among HCWs?

- Are IGRAs better at identifying incidence of new TB infection than the TST?

Hierarchy of Reference Standards



Objectives

- To summarize the performance characteristics of IGRAs for the detection of LTBI in health care workers (HCWs).

Secondary objectives

1. Compare IGRA performance in HCWs in high or low & moderate TB incidence settings
2. Assess whether IGRAs are better correlated than the TST with occupational exposure to TB in cross sectional studies
3. Estimate rate of IGRA conversions and reversions, and assess whether IGRA conversions are more closely associated with recent occupational exposure than TST conversions
4. Summarize evidence produced by cost-effectiveness analyses and programmatic studies.

Methods: Search Strategy

- PubMed, Embase, Biosis & Web of Science (up to October 1, 2010)*
- Reviewed bibliographies, contacted experts

- Search Terms:
  - ((tuberculosis OR mycobacterium tuberculosis))

  AND
  - ((interferon-gamma release assay*) OR (T-cell-based assay*) OR (antigen-specific T cell*) OR (T cell response*) OR (T-cell response*) OR (interferon*) OR (interferon-gamma) OR (gamma-interferon) OR (IFN) OR (elispot) OR (ESAT-6) OR (CFP-10) OR (culture filtrate protein) OR (Enzyme Linked Immunosorbent Spot) OR T-SPOT.TB OR (Quantiferon* OR Quantiferon-TB))

- *Serial testing update

Methods: Study Selection

- Inclusion Criteria:
  - Screening HCWs for TB using:
  - Commercial IGRA assay: QuantiFERON-TB Gold or In-Tube version AND/OR the TSPOT.TB test

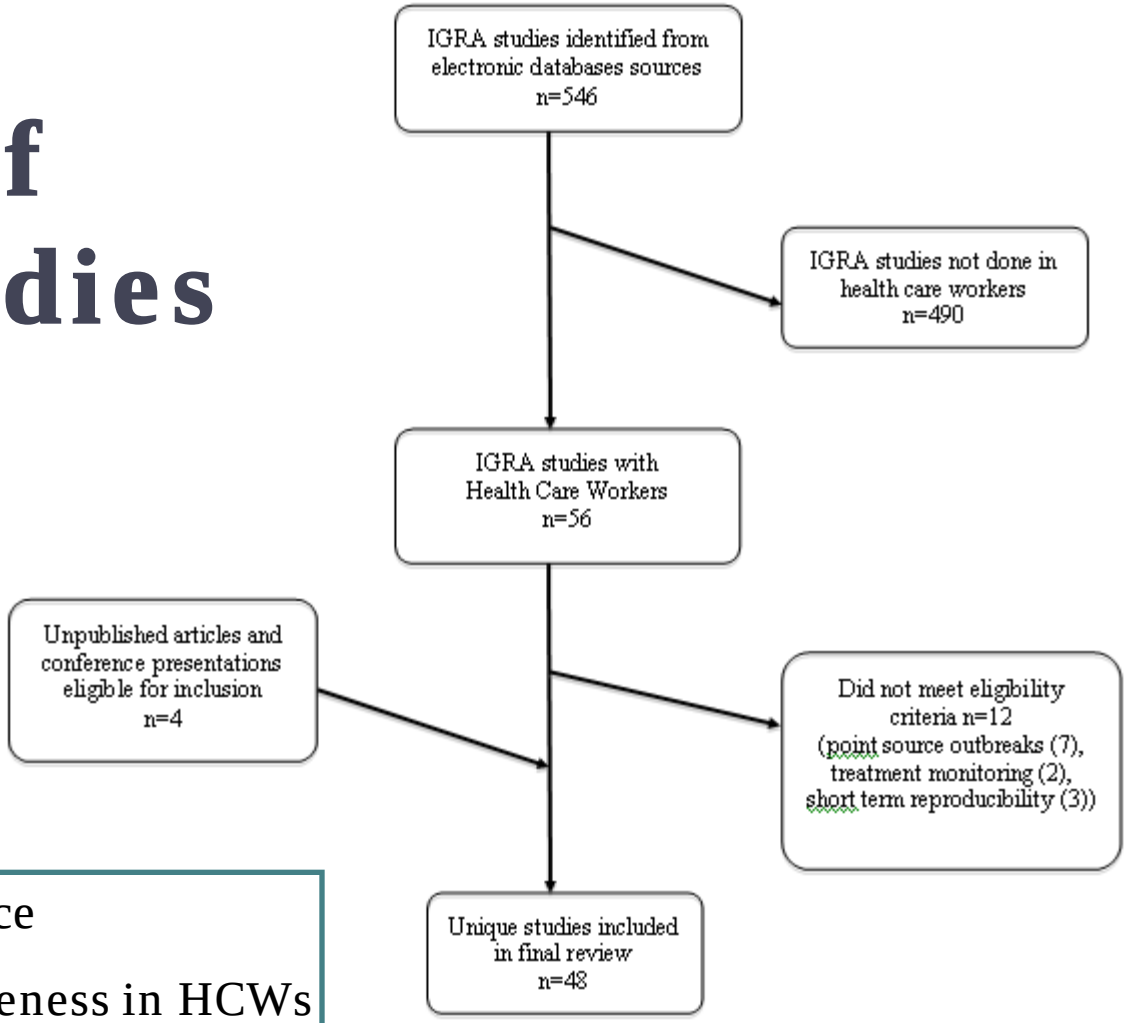
- Exclusion Criteria:
  - Case reports & case series
  - Studies with n≤10 participants
  - Reviews and commentaries
  - Letters with no original data
  - Studies evaluating IGRAs for treatment monitoring
  - Reproducibility studies (serial testing within 1 month)
  - Non-commercial in-house assays
  - IGRA testing in nosocomial outbreak/point source exposure

Quality Assessment

- Studies are not assessing sensitivity/specificity, therefore QUADAS is not appropriate to evaluate these studies

  - Study Design (cross-sectional versus longitudinal)
  - Use of standardized assays and PPD
  - Duration of follow-up in longitudinal studies
  - Selection and recruitment of study population

Flow chart of included studies



- 44 studies on IGRA performance
- 3 studies on IGRA cost-effectiveness in HCWs
- 3 studies on feasibility of IGRAs in HCWs

Study Characteristics

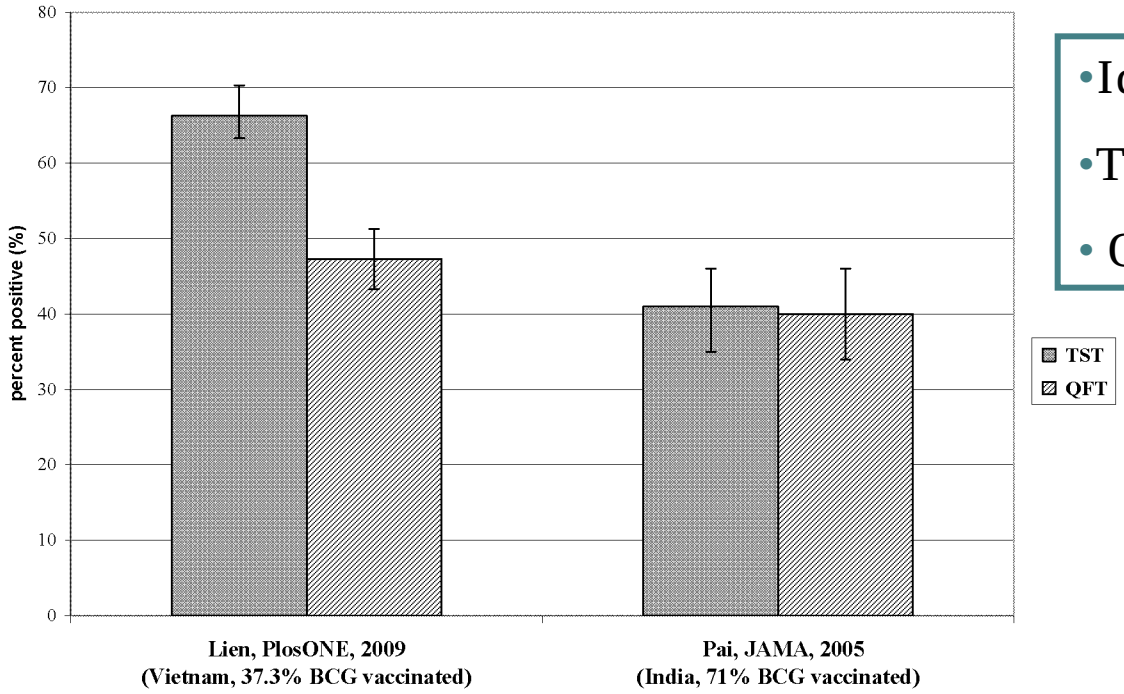
No. of Studies	**44 (with main outcome)**
Year study published	**2005-2010**
Cross-sectional design	**34 (77%)**
High TB Incidence	**3**
Low & Moderate Incidence	**31**
Serial testing studies	**10 (23%)**
High TB Incidence	**2**
Low & Moderate Incidence	**8**
Study participants	**11, 963 (Range: 12-1313)**
Proportion BCG vaccinated	**Range: 7-100%**

Study Characteristics

TST included in study	**38 (86%)**
TST Preparation (mode)	**2 TU (37%)** **(Range:1-5)**
IGRAs	**TSPOT.TB** **QFT-Gold** **QFT-Gold In Tube**
Index Tests	
Both IGRAs	**6 (14%)**
QFT	**35 (79%)**
TSPOT.TB	**3 (7%)**

Cross-Sectional Studies

LTBI Prevalence & test concordance: High Incidence Countries



†TST positivity was computed using a 10mm TST cut-point

- Identified 3 studies
- TST: 41-66% (n=2)
- QFT: 26.2-47.3% (n=3)

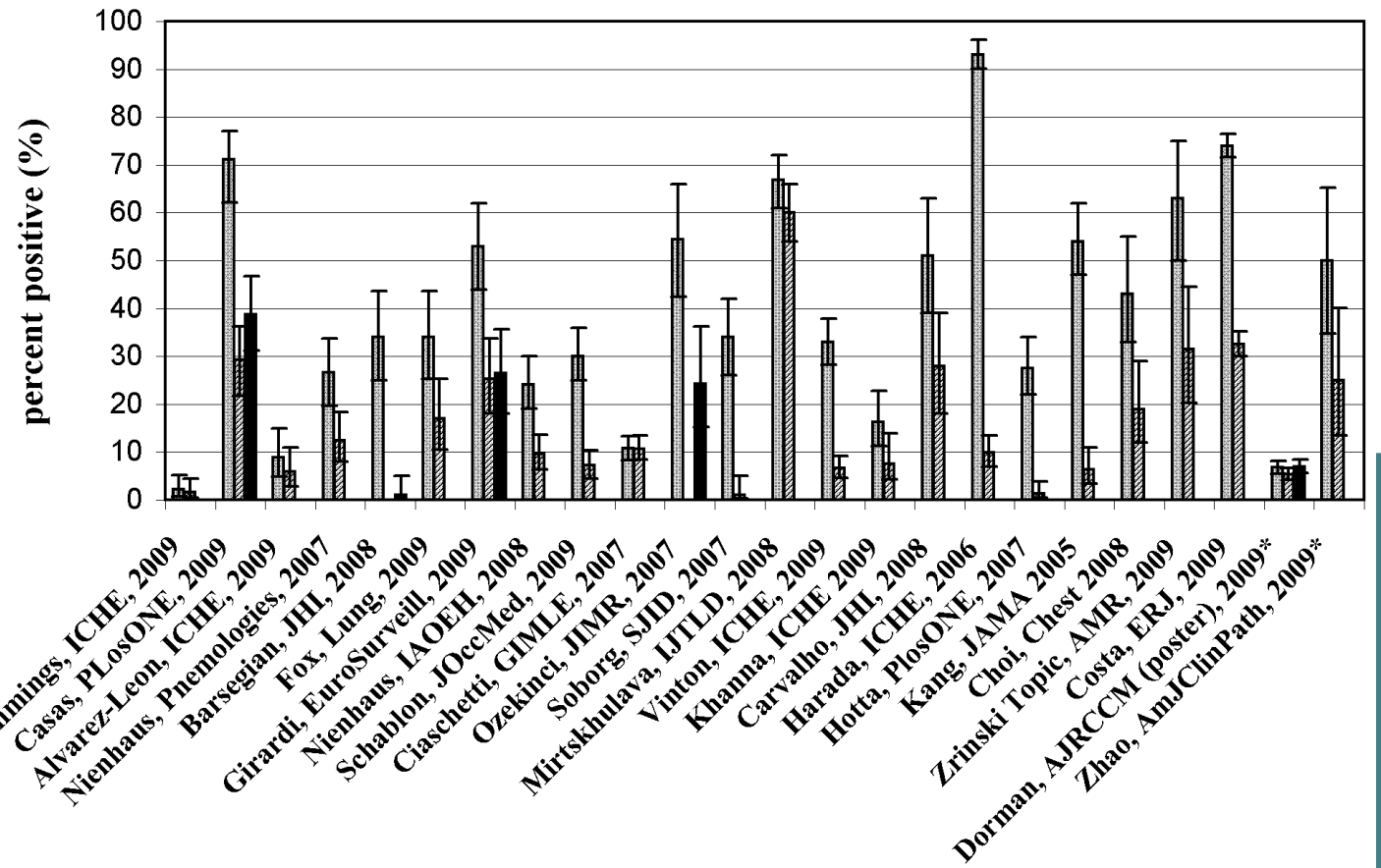
LTBI Prevalence & Test Concordance: High Incidence Countries

Secondary Outcomes	(# of studies reporting on outcome)	
Concordance Agreement kappa	2	 72.5-81.4% κ= 0.44-0.61
Predominant type of discordance	2	TST+/QFT-
Indeterminate rate	1	11.6%

LTBI Prevalence & test concordance: Low & Moderate Incidence Countries

- Identified 31 studies
- 25 studies included the TST
- 4 performed head to head comparisons TSPOT.TB & QFT
  - **Prevalence of + QFT : 1-66.8%**
  - **Prevalence of + TSPOT.TB: 1-60%**
  - **Prevalence of + TST: 2.2-93.1%**

LTBI Prevalence & test concordance: Low & Moderate Incidence Countries

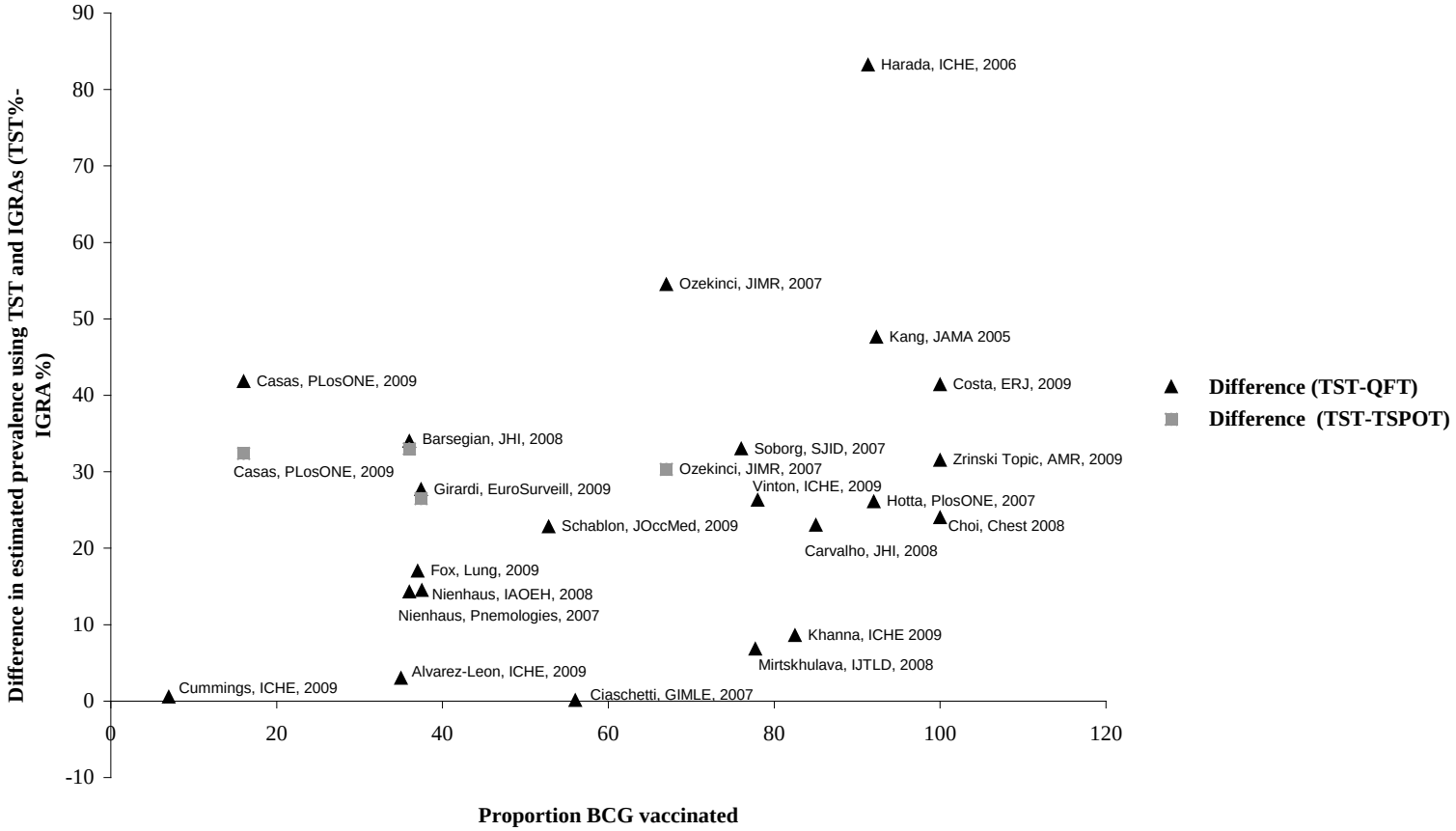


- 24/25 studies reported a lower positivity rate with IGRA than TST
- 17/24 difference was statistically significant
- BCG vaccine?

*proportion BCG vaccinated was not reported for these studies

**TST positivity was computed using the TST cut-point used by authors of the primary studies. When results for multiple cut-points were presented, data for TST cut-point 10mm was displayed

Summary Differences in Prevalence of Positive tests in Low and Moderate incidence settings [N=25]

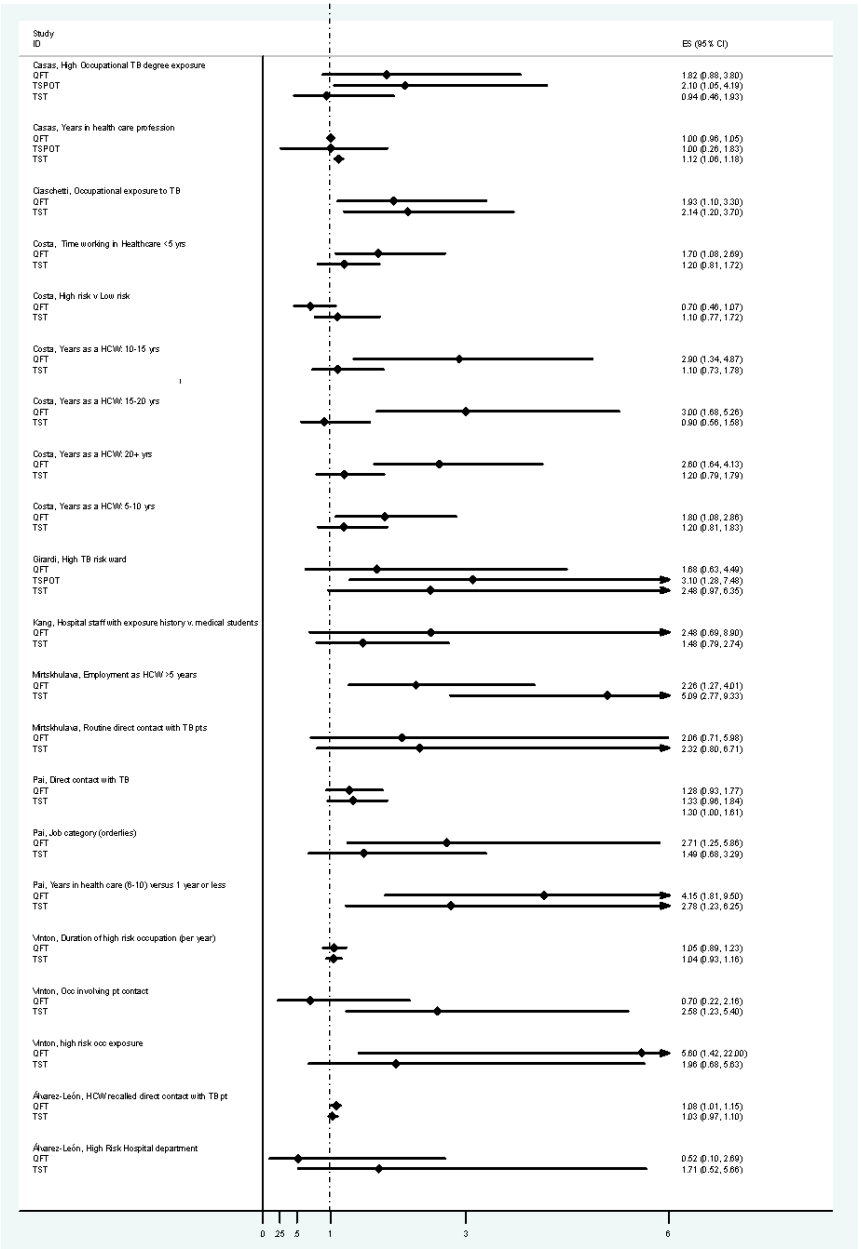


LTBI Prevalence & Test Concordance: Low & Moderate Incidence Countries

Secondary Outcomes	(# of studies reporting on outcome)	
Concordance (kappa)	19	0.05-0.56
Predominant type of discordance	19	TST+/QFT-
Indeterminate rate	12	0-9%

IGRAs & occupational TB exposure

- 9 cross-sectional studies evaluating 21 different characterizations of occupational exposure (N=3,847)
- 1/9 study from high incidence country
- 2 studies evaluated both IGRAs



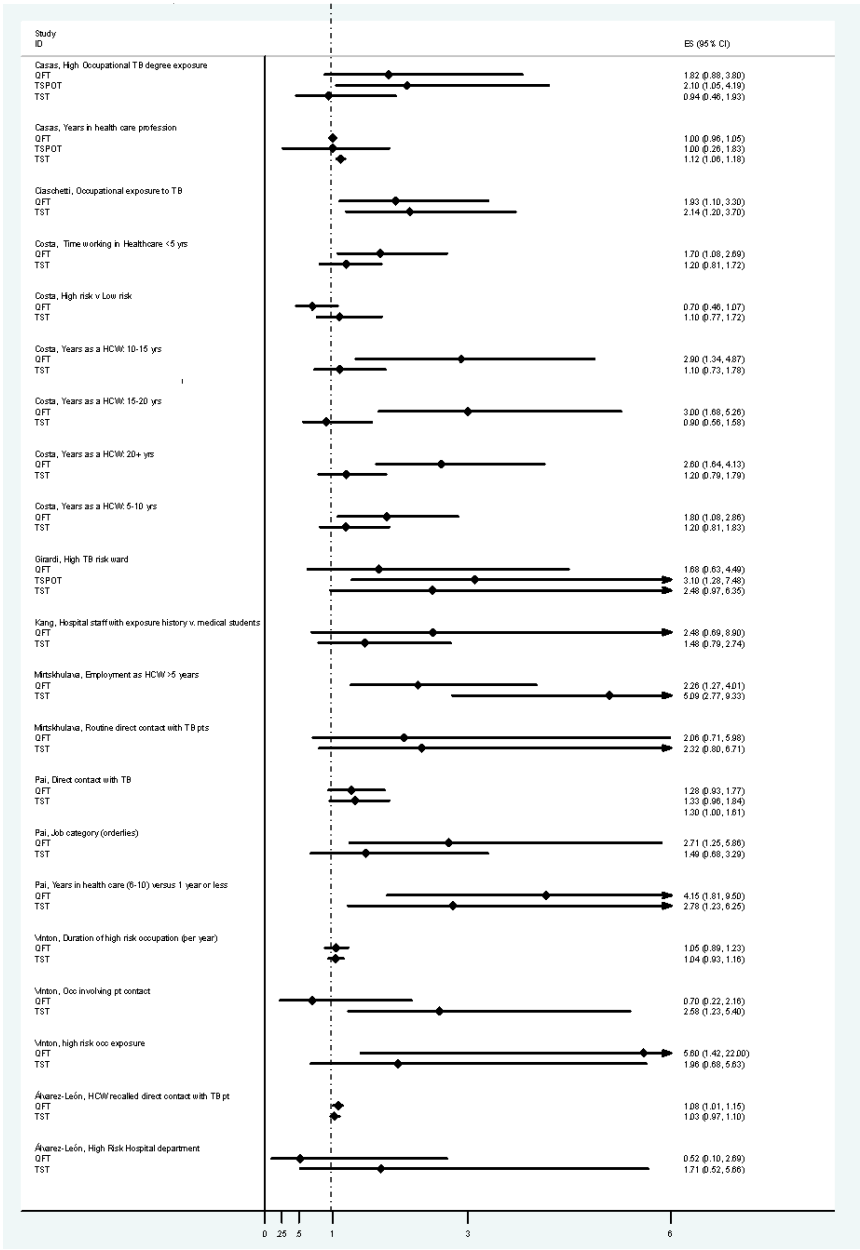
IGRAs & occupational TB exposure

QFT:

- 18/21 (86%) comparisons estimate a positive association between occupational exposure and test positivity.
- 12/18 (66%) reached statistical significance

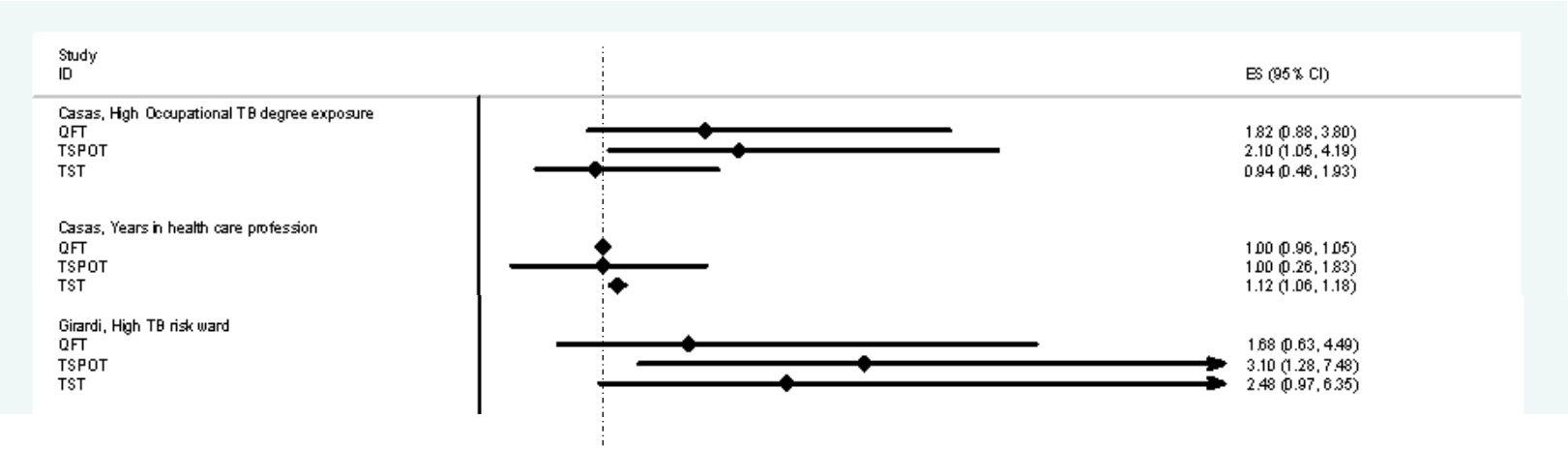
TST:

- 19/21 (90%) estimated a positive association, but only 5/19 (26%) reached statistical significance



IGRAs & occupational TB exposure

TSPOT.TB:



Serial Testing Studies

Rates of Conversions & Reversions

Table 3 Summary of rates of conversions and reversions in serial testing studies (N=8)

Study	Duration between testing	TST converters, n/N (%)	IGRA converters, n/N (%)	IGRA reverters, n/N (%)
High TB incidence countries				
Pai, 2008[15]	18 months	6/147 (4.1%)	17/147 (11.6%)	7/38 (18.4%)
Joshi, 2009[58]	6 months	–	11/57 (19%)	6/22 (27%)
	6 months (6–12 months)	–	11/52* (21%)	11/27† (40%)
Moderate and low TB incidence countries				
Pollock, 2009[64]	1–7 months	–	2/43‡ (4.6%)	–
Zwerling, 2009[59]	1 year	0/57 (0%)	4/56 (7.14%)	4/5 (80%)
Yoshiyama, 2009[63]	2 and 4 years	–	5/277 (1.8%)	13/32 (41%)
Chee, 2009[61]	1 year	0/18‡	9/182 (4.9%)	–
Lee, 2009[62]	1 year	16/75 (21.3%)	21/146 (14.4%)	–
Belknap, 2010[60]	6 months	4/1202 (0.3%)	TSPOT 44/1117 (3.9%) QFT-GIT 44/1169 (3.8%)	TSPOT 36/68 (52.9%) QFT-GIT 20/50 (40%)
Costa, 2010[20]	1–2.5 years	98/199 (49.2%)	51/462 (11%)	46/208 (22.1%)
Ringshausen, 2010[21]	18 weeks	(baseline only)	3/162 (1.9%)	6/18 (33.3%)

All conversions/reversions using simple negative/positive definition.
*Denominator includes only participants negative at 6 months.
†Denominator includes only participants positive at 6 months.
‡Denominator includes only baseline concordant negatives.
IGRA, interferon-gamma release assay; PPD, purified protein derivative; TB, tuberculosis; TST, tuberculin skin test.

Concordance: IGRA and TST Conversions

- Pai, AJRCCM, 2009, India (middle income country) n=216
  - 96% Agreement, kappa=0.7
- Lee et al., ICHE, 2009, Korea (high income country) n=196
  - 84% Agreement, kappa=0.417

IGRA conversions & occupational TB exposure

- 3 longitudinal studies evaluated IGRA conversions and their association with occupational exposure to TB
- Total N=550
- 1 study evaluated both IGRAs & 2 evaluated QFT only

IGRA conversions & occupational TB exposure

- Yoshiyama et al., Epi&Inf, 2009
- Japan, N=311
- Only factor to reach statistical significance : working in TB Ward OR=8.6 (95%CI: 1.4-54)

- Pollock, ICHE, 2008 & Lee, ICHE 2009: neither study found an association between occupational exposure and conversion status

Other Outcomes

- **Cost-Effectiveness (3 studies):**
  - 3 studies assessed cost-effectiveness of IGRAs for screening HCWs
  - Two studies showed IGRAs could be less costly, one using a dual testing strategy
  - One study found in costs for IGRAS and TST to be quite comparable.
  - No studies accounted for serial testing of HCWs

- **Feasibility & Improved Uptake (3 studies):**
  - Sahni et al., ICHE, 2009: Evaluated improved uptake of LTBI therapy using IGRA
    - OR=3.3 for accepting LTBI therapy (95%CI: 1.3-8)
  - Miranda et al., and Budnick et al. both evaluated indeterminate rates in HCWs
    - Both found indeterminate rates could be reduced with successful intervention such as standardizing sample processing

Summary: TST and IGRA Prevalence

- Across 34 cross-sectional studies, the prevalence of positive IGRA was lower than positive TST
- The difference is prevalence was statistically significant in low & moderate incidence settings but not in high TB incidence countries
- Concordance was poor in low and moderate inc. countries, but was improved in high incidence countries

Summary: Association with Exposure

- In low and moderate incidence countries, QFT and TST are both correlated with occupational exposures
- Data are limited in high incidence countries
- Data are limited for TSPOT.TB in HCWs
- There is no strong evidence IGRAs are more strongly associated with occupational exposure than TST

Summary: Conversions & Reversions

- Upon serial testing, IGRAs had frequent reversions & conversions
- IGRAs may estimate a higher conversion rate than the TST
- IGRA and TST conversions show moderate concordance based on 2 studies
- 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.
- No strong evidence to suggest that IGRAs are superior at identifying incident cases of LTBI in HCWs

Strengths & Limitations

- Strengths
  - Comprehensive search strategy & standardized systematic review protocol
- Limitations
  - Considerable heterogeneity in study methods and exposure gradients analyzed, therefore, could not pool estimates
  - Lack of evidence at the highest level of the hierarchy of reference standards
  - Primarily cross-sectional studies from high income countries

Table 1. GRADE Evidence Profile: Interferon-γ release assays for tuberculosis screening of healthcare workers: a systematic review

No of Participants (Studies)	Study design	Limitations	Indirectness	Inconsistency	Imprecision	Publication Bias	Quality of Evidence (GRADE)[1]	Importance
A. Efficacy of preventive therapy based on IGRA test results								
No Studies in	HCWs							Critical (7-9)
B. Predictive value of IGRA for active TB								
No Studies in	HCWs							Critical (7-9)
C. Outcome: Correlation of IGRA results with occupational TB exposure								
3,847 (9)[A1]	Cross-sectional	No Serious limitations[A2]	Serious[A3] (-1)	Serious[A4] (-1)	Serious[A5] (-1)	Likely[A6]	Very Low ⊕OOO	Critical (7-9)
D. Outcome: Correlation between IGRA conversions and occupational TB exposure								
550 (3)[B1]	Longitudinal	No serious limitations[B2]	Serious[B3] (-1)	Serious[B4] (-1)	Serious[B5] (-1)	Likely[B6]	Very Low ⊕OOO	Critical (7-9)
E. Outcome: Sensitivity for active TB (as a surrogate reference standard for LTBI)								
No Studies in	HCWs							Important (4-6)
F. Outcome: Concordance between IGRAs and TST (cross-sectional)								
5,081 (21)[C1]	Cross-sectional	No serious limitations[C2]	Very Serious[C3] (-2)	Serious[C4] (-1)	Serious[C5] (-1)	Likely[C6]	Very Low ⊕OOO	Important (4-6)
G. Outcome: Concordance between IGRA and TST conversions (longitudinal)								
421 (2)[D1]	Longitudinal	No serious limitations[D2]	Very Serious[D3] (-2)	No serious inconsistency[D4]	Serious[D5] (-1)	Likely[D6]	Very Low ⊕OOO	Important (4-6)

Serial Testing update

- Park et al. Scan JID, 2010
  - n=275, Korea, 1 year serial testing
  - 4 conversion definitions:
    - 1) manufacturer's cut-off
    - 2) cut-off plus 30% increase over baseline
    - 3) cut-off plus ≥0.35
    - 4) <0.35 to ≥0.70

    - Conversions ranged from 3.3%-5.7%

Serial Testing update

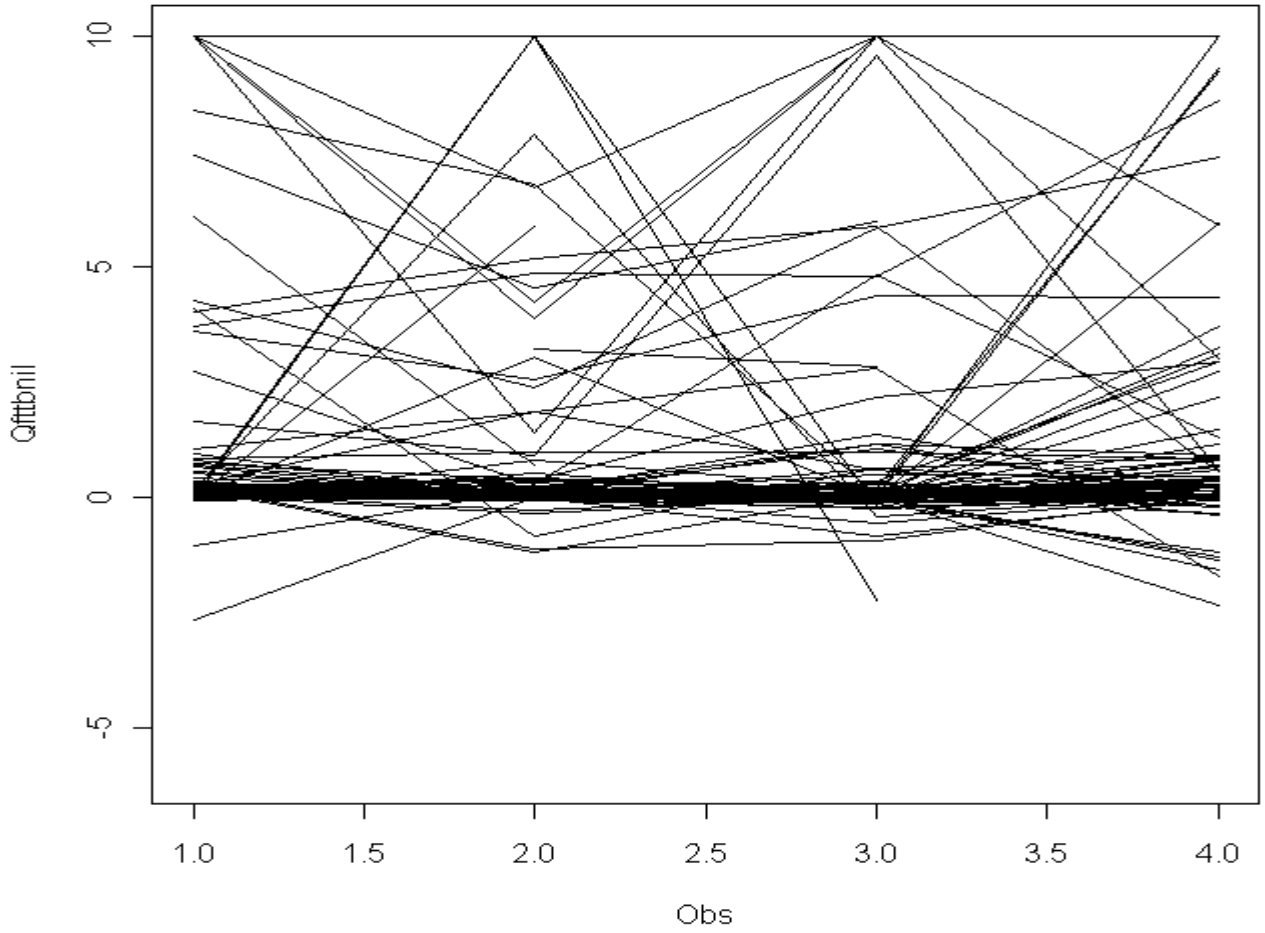
- Schablon et al. GMS KI, 2010
  - n=287 HCWs, Germany, 1 year serial testing
  - 4 conversion/reversion definitions
    - 1) <0.35 to ≥0.35 (manufacturer's cut-off)
    - 2)<0.2 to ≥0.7 (or decrease for reversion) "uncertainty zone"
    - 3) cut-off plus increase/decrease ≥0.5
    - 4) cut-off plus increase/decrease ≥0.7

    - Least stringent: 6.1% converters 32.6% reverters
    - Most stringent: 2.5% converters, 14% reverters

Serial Testing update (sort of)

- Ringhaussen et al. , CVI, 2011: 4 week reproducibility
- Costa et al. JOccMed, 2011, predictive study
- Joshi R et al. ERJ 2011 (in press) – predictive value study
- 3 new cost effectiveness papers, start to address serial testing

Serial Testing Data from Indian Medical Students (sneak peak)



n=170 students, tested at 4 time points

Patterns of Change???

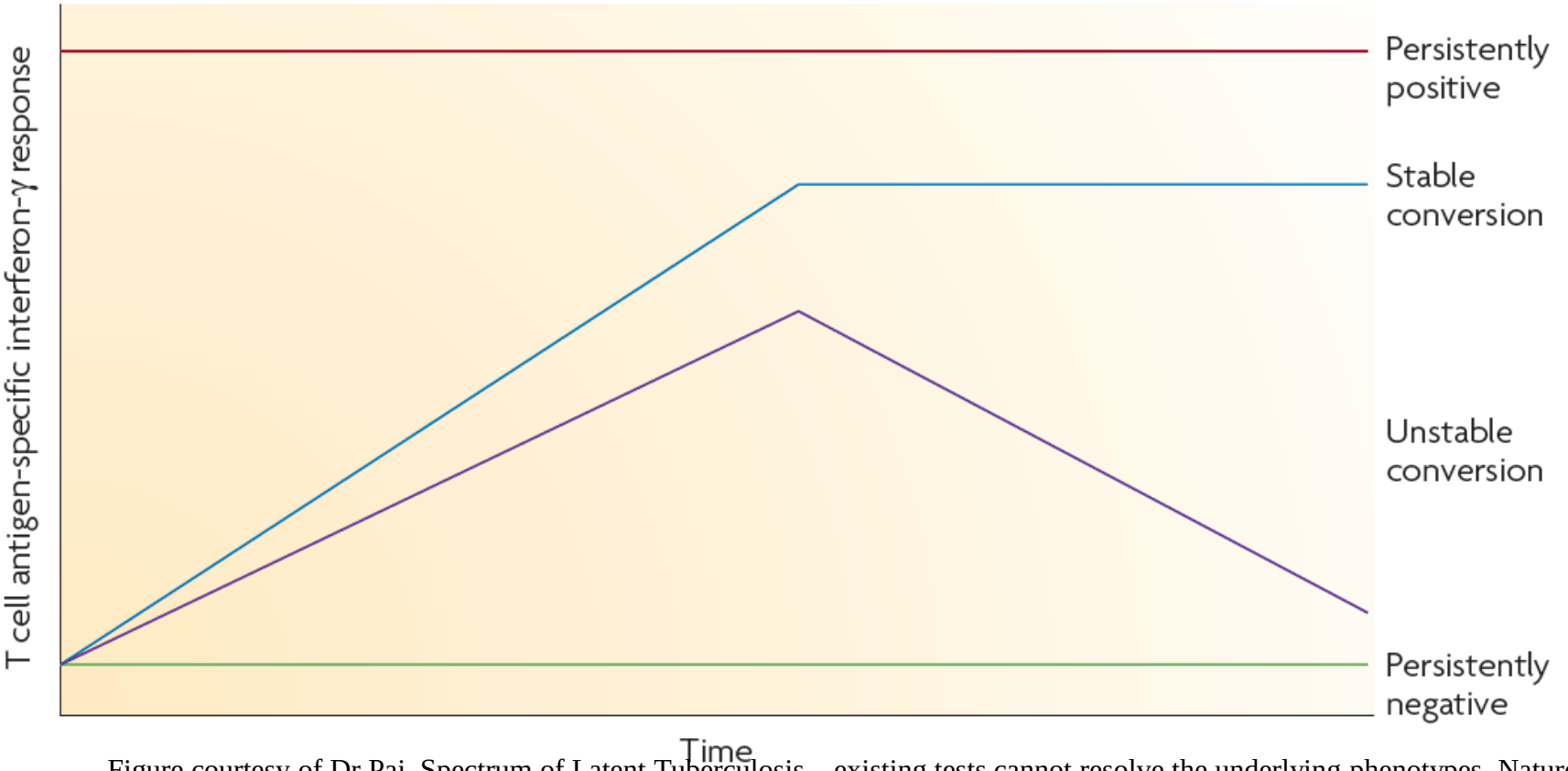


Figure courtesy of Dr Pai, Spectrum of Latent Tuberculosis – existing tests cannot resolve the underlying phenotypes, Nature Reviews, 2010

Serial Testing

- High Rates of Reversions & Conversions across both high and low & moderate TB incidence settings

- No consensus on how to define a conversion or reversion, and who should be treated, especially among low risk HCWs?

Serial Testing...what's next

- While IGRAS may estimate a lower LTBI prevalence than TST, upon subsequent annual screening with IGRAs, TBIC programmes may observe higher conversion numbers with IGRAs than TST
- Given high rates of reversion, what is the prognosis of IGRA converters HCWs?
- Need to be cautious in terms of avoiding excessive treatment in low risk groups
- Many guidelines are hesitant to recommend IGRAs for serial testing
- Need to be cautious about conversion/reversion definitions!!
- Need new conversion and reversion cut-points, uncertainty zone, etc

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