

Reference standards – Tests for diagnosis of Latent TB Tuberculin Skin Tests (TST) vs Interferon Gamma Release Assays (IGRAs)

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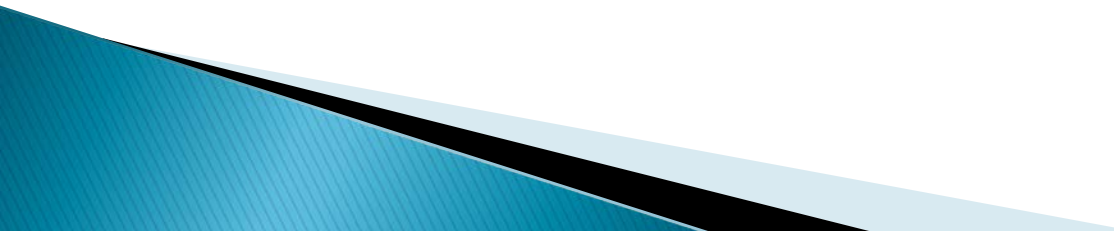
Disclaimer

- ▶ I have no financial conflicts of interest (sadly)

What is the reference (Gold) standard for latent TB infection?

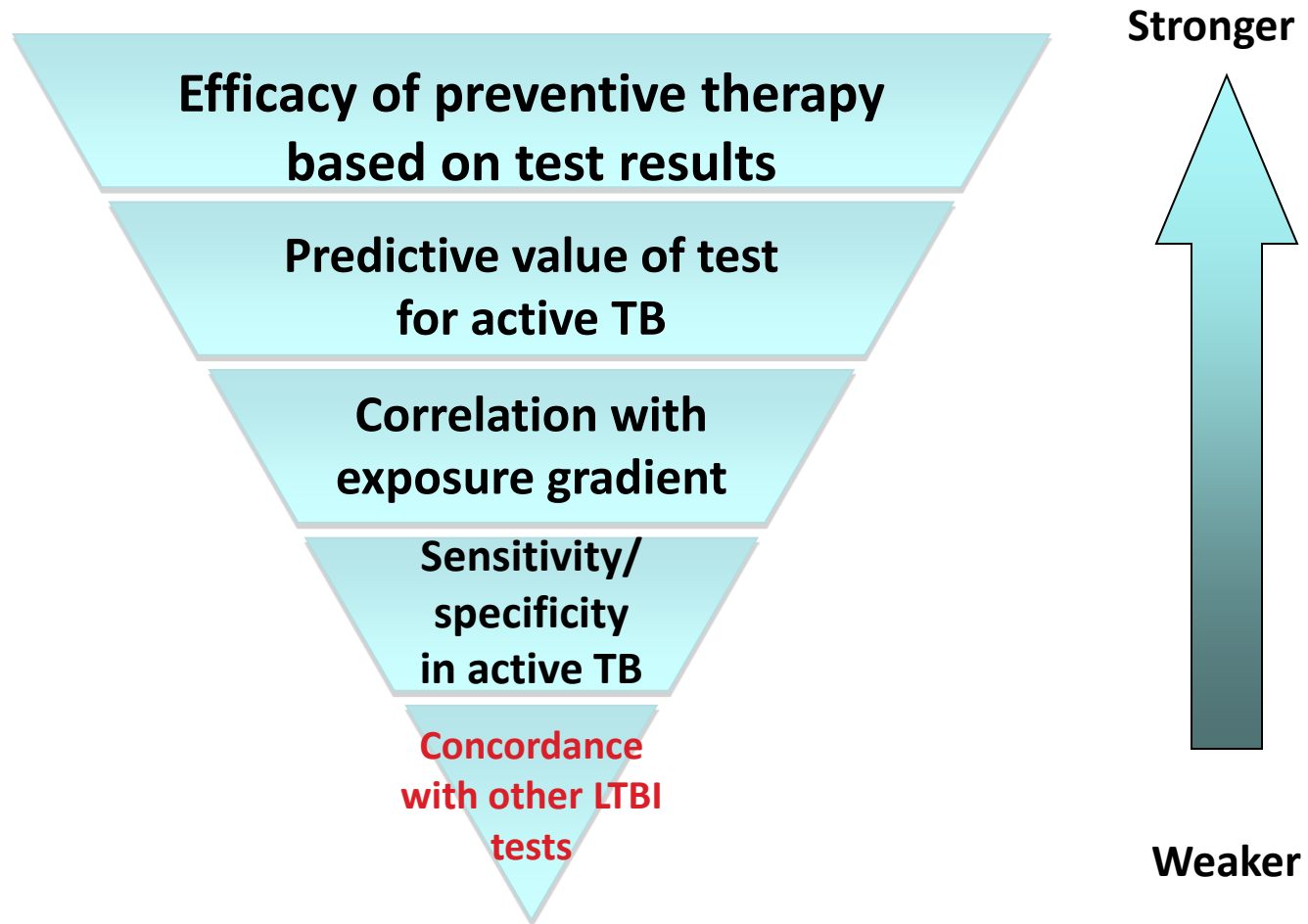
- ▶ Latent Tb infection (LTBI) is defined as the absence of active TB
 - No symptoms, normal exam
 - Normal tests – chest X-ray, blood tests
 - Negative smears and cultures
- ▶ In the past it was all above plus positive TST
 - Obviously not useful in evaluating LTBI tests

How to compare TST and IGRA, when there is no Gold standard?

- ▶ Concordance of tests
 - ▶ Sensitivity and specificity in active TB
 - ▶ Compare Positive rates in exposed/unexposed
 - Especially exposure gradients
 - ▶ Compare rates of disease in untreated cohorts
 - ▶ Compare benefit of INH in Test+ vs Test-
 - ▶ Spontaneous reversions (without treatment)
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Hierarchy of evidence for tests of LTBI

WHO Expert Group on IGRAs

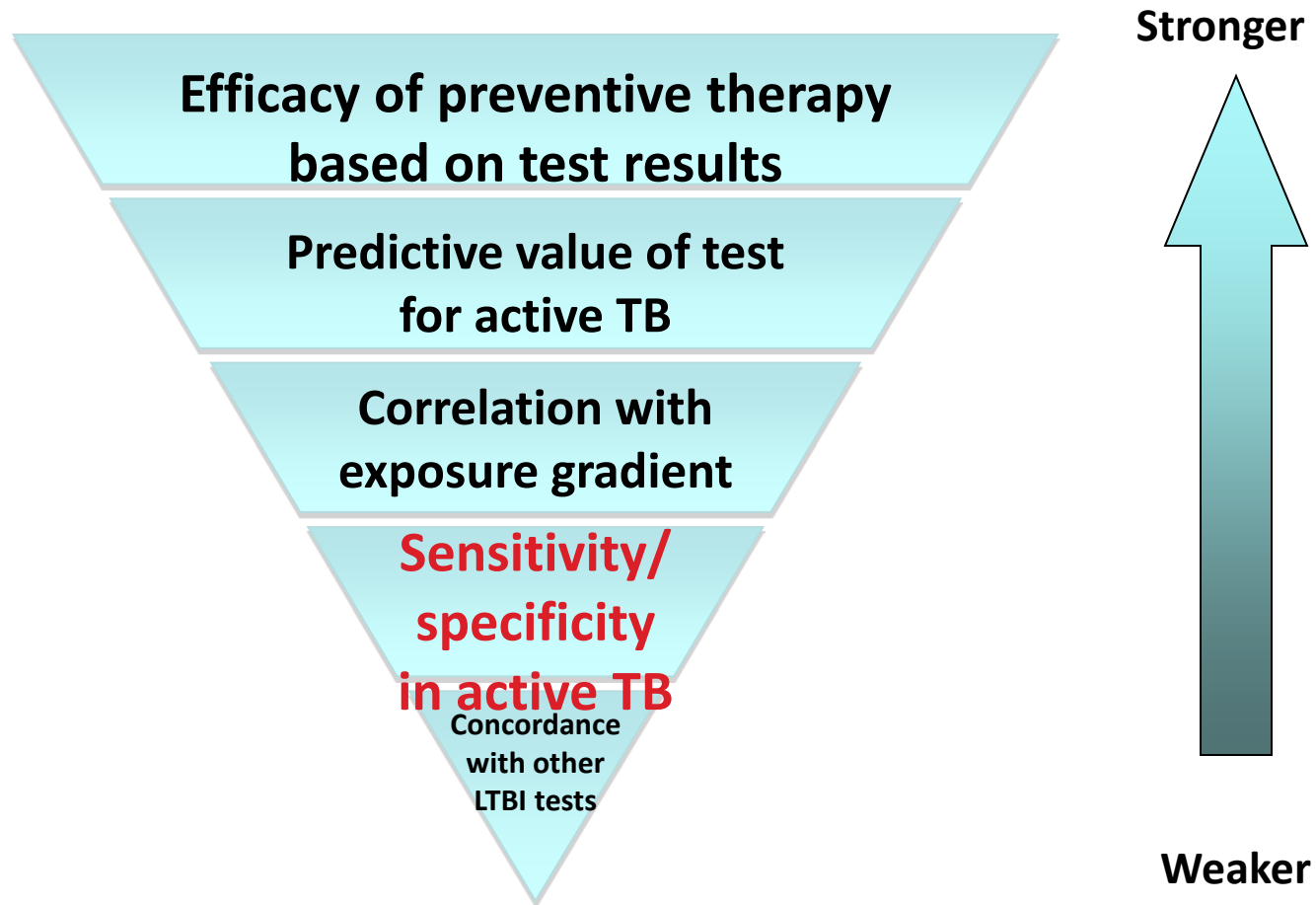


The least useful – concordance of tests

- ▶ Concordance of tests (agreement)
- ▶ Earliest studies assessed agreement between TST and QFT or T-Spot (or all 3)
- ▶ But – if there was complete agreement – there would be no point in using a new test
- ▶ Discordance is ‘good’
 - If TST is not 100% sensitive or specific
 - TST- and IGRA+ = more sensitive
 - TST+ and IGRA- = more specific

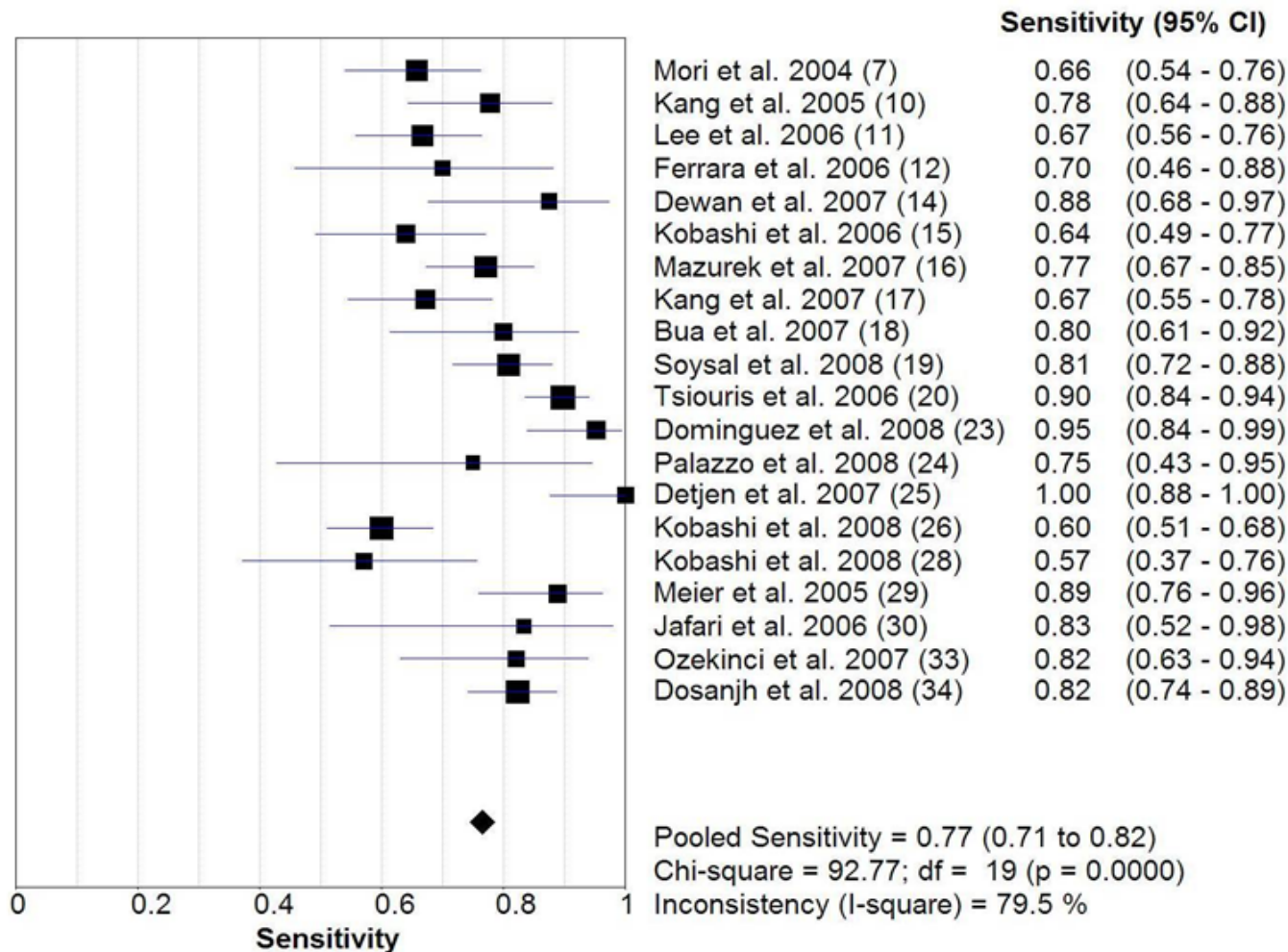
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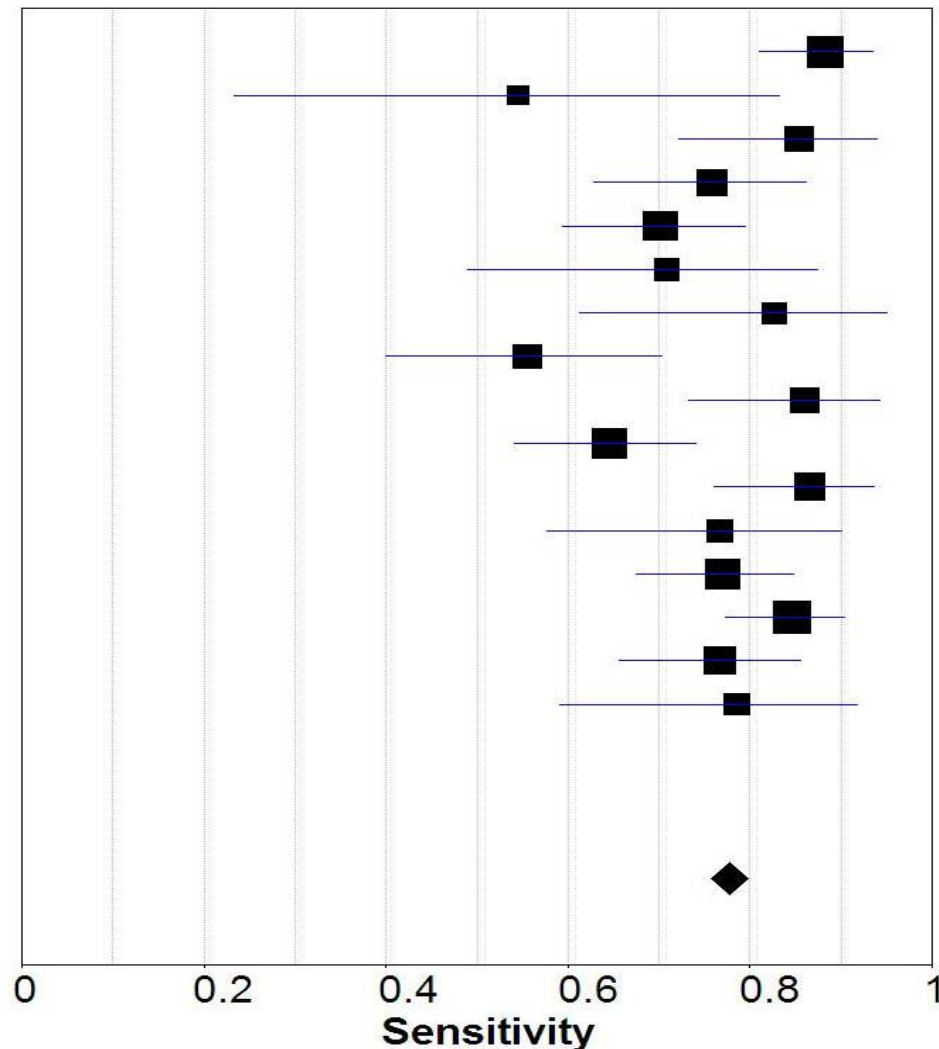
Sensitivity of TST in Active TB [all settings]

A. TST sensitivity [N=20 studies]



20 Studies Pooled sensitivity = 77%

Sensitivity of QuantiFERON-TB Gold in active TB



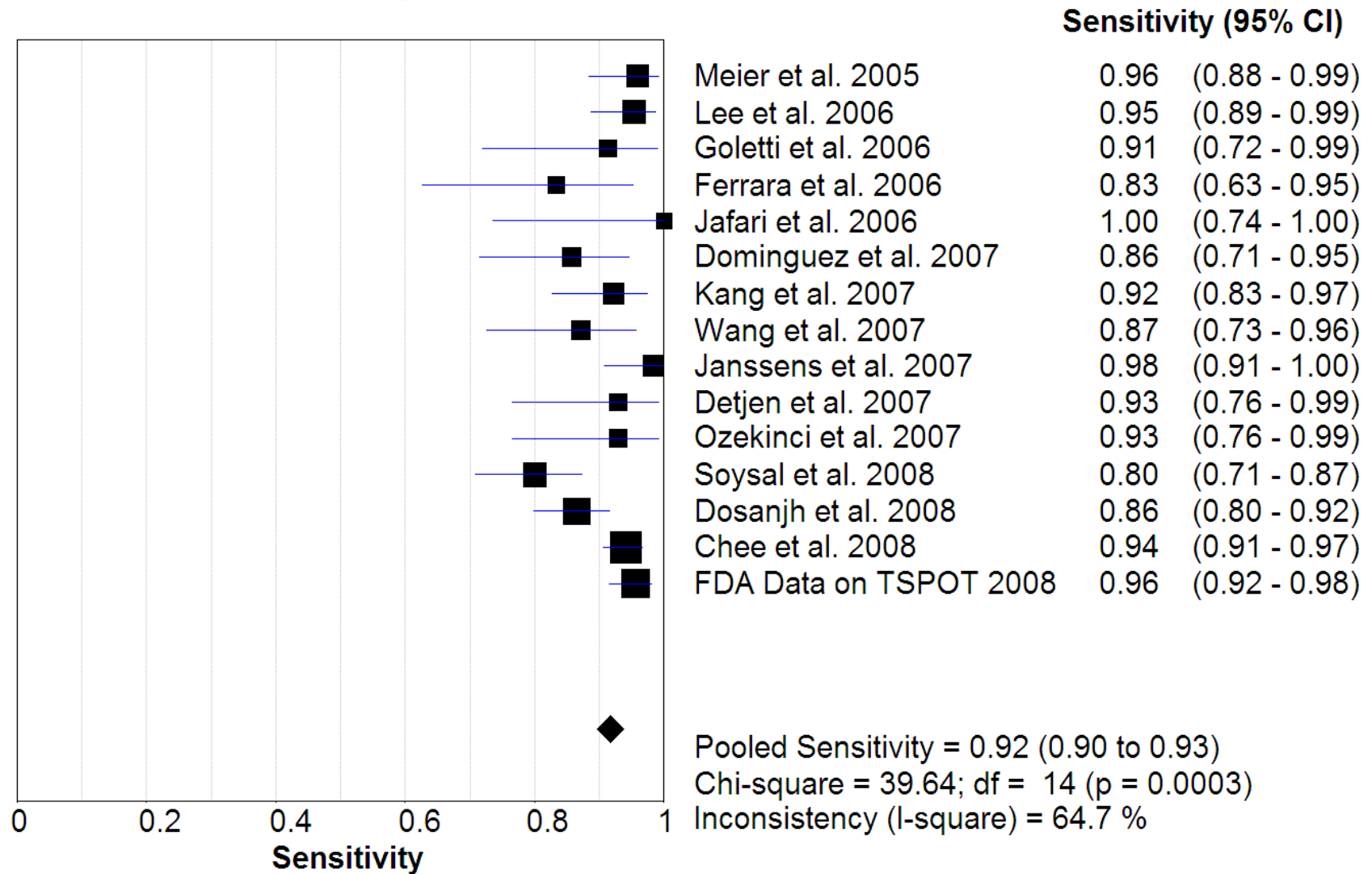
Sensitivity (95% CI)

Mori et al. 2004 (7)	0.88	(0.81 - 0.93)
Ferrara et al. 2005 (8)	0.55	(0.23 - 0.83)
Ravn et al. 2005 (9)	0.85	(0.72 - 0.94)
Kang et al. 2005 (10)	0.76	(0.63 - 0.86)
Lee et al. 2006 (11)	0.70	(0.59 - 0.79)
Ferrara et al. 2006 (12)	0.71	(0.49 - 0.87)
Goletti et al. 2006 (13)	0.83	(0.61 - 0.95)
Dewan et al. 2007 (14)	0.56	(0.40 - 0.70)
Kobashi et al. 2006 (15)	0.86	(0.73 - 0.94)
Mazurek et al. 2007 (16)	0.65	(0.54 - 0.74)
Kang et al. 2007 (17)	0.87	(0.76 - 0.94)
Bua et al. 2007 (18)	0.77	(0.58 - 0.90)
Soysal et al. 2008 (19)	0.77	(0.68 - 0.85)
Kobashi et al. 2008 (26)	0.85	(0.77 - 0.90)
Nishimura et al. 2008 (27)	0.77	(0.66 - 0.86)
Kobashi et al. 2008 (28)	0.79	(0.59 - 0.92)

Pooled Sensitivity = 0.78 (0.73 to 0.82)
 Chi-square = 46.23; df = 15 (p = 0.0000)
 Inconsistency (I-square) = 67.6 %

16 Studies Pooled sensitivity = 78%

Sensitivity of T-SPOT.TB in active TB



13 Studies Pooled sensitivity = 92%

Accuracy of Interferon-Gamma Release Assays for Active Pulmonary TB Diagnosis in ADULTS in Low and Middle-Income Countries: Systematic Review and Meta-Analysis. *(Metcalfe et al JID, 2011 in press)*

17 studies with 1334 patients

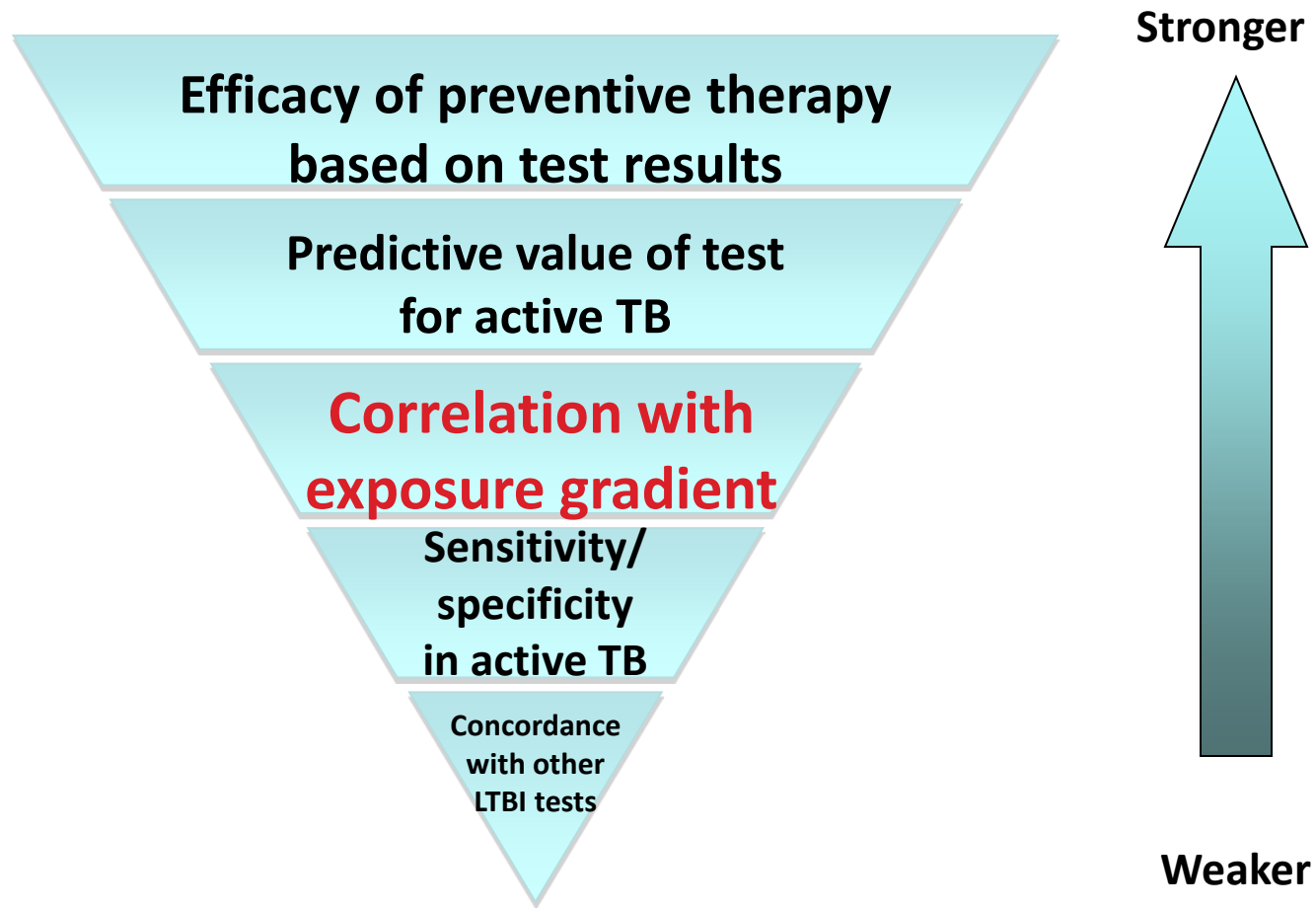
HIV Negative	Sensitivity	Specificity
QFT	85%	42%
TSPOT	87%	NA
HIV Infected		
QFT	65%	51%
TSPOT	70%	55%

Summary – IGRA vs TST in active TB

- ▶ Sensitivity for active TB:
 - TST = QFT
 - Elispot/T. Spot \geq TST or QFT.
 - None are 100% sensitive – because people with active TB are *sick*
 - May be anergic, or have specific anergy to TB
 - It's why they got TB!!
- ▶ Specificity for active TB:
 - Specificity in adults <50%
 - Because these tests do NOT distinguish latent from active TB

Hierarchy of evidence for tests of LTBI

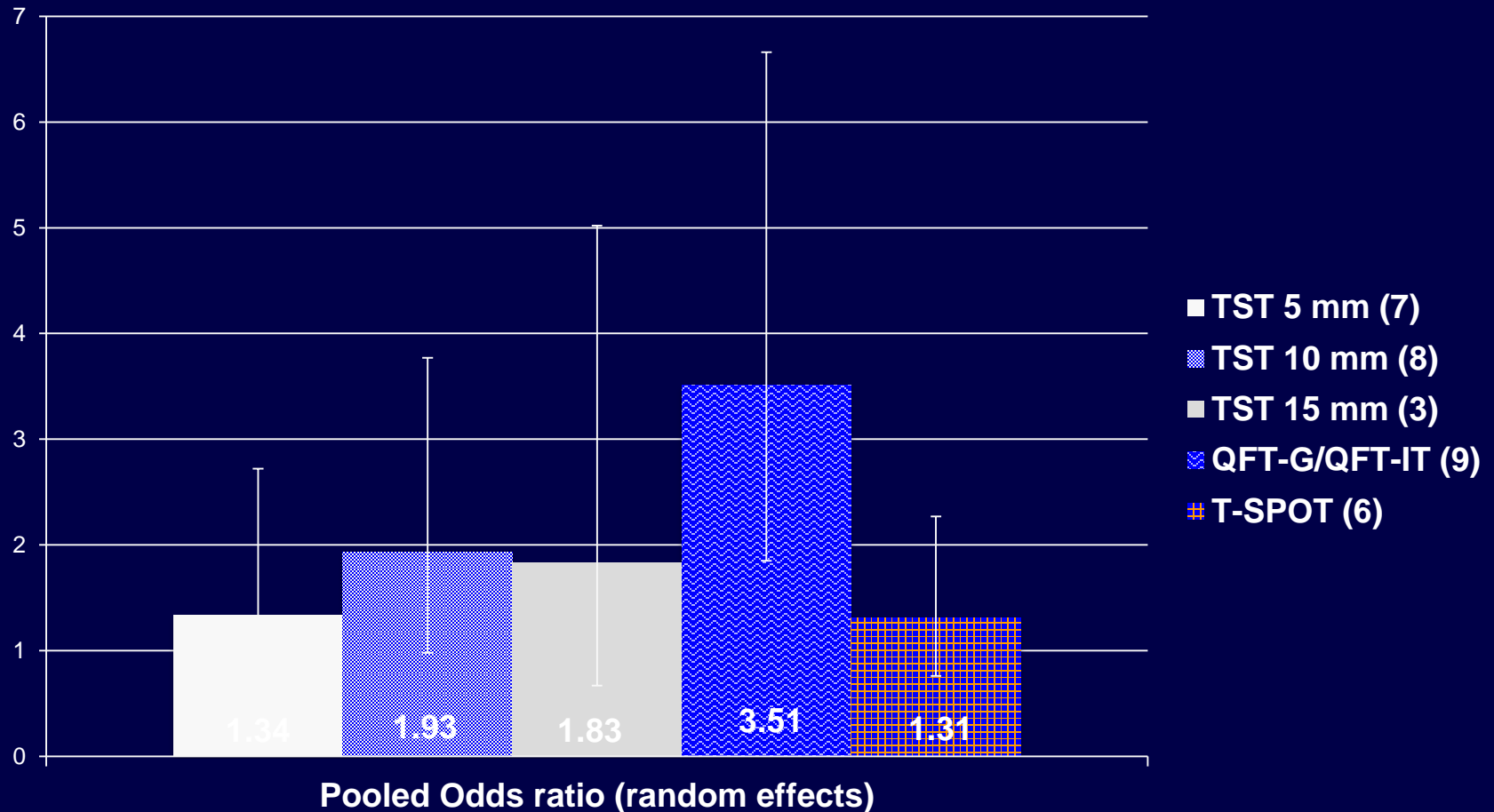
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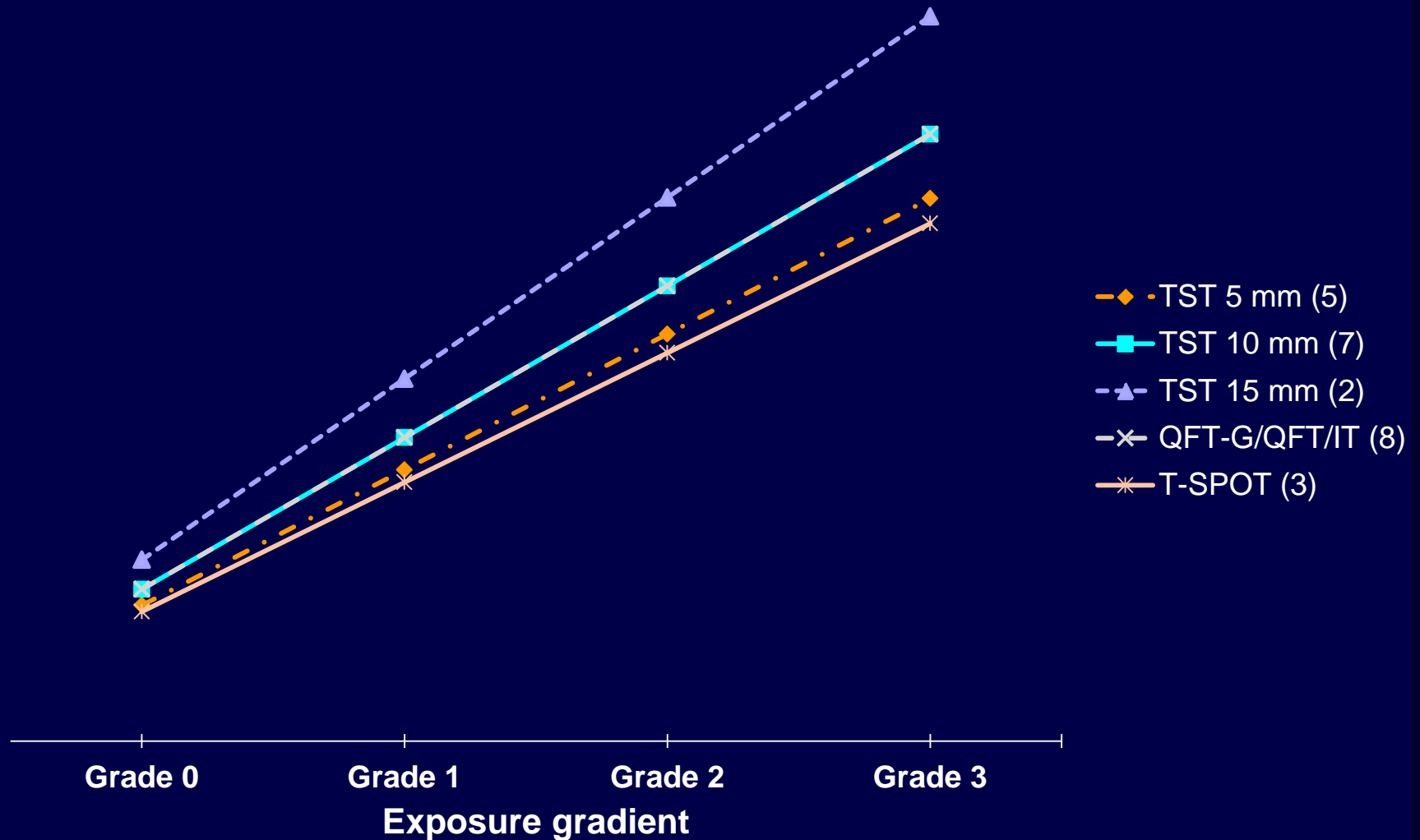
Exposure / gradient studies

- ▶ Exposed/unexposed studies
 - If test indicates true LTBI infection then more likely positive in exposed (contacts) than unexposed
 - Better test – will show greatest and consistent differences between exposed / unexposed
- ▶ Exposure gradient studies
 - Assign contacts to 3, or 4, or more categories
 - Most to least exposed
 - Tests should show parallel gradient of proportion of positive tests.
 - Best test – closest correlation to gradient

Concordance of tests with dichotomous exposure – Pediatric contacts

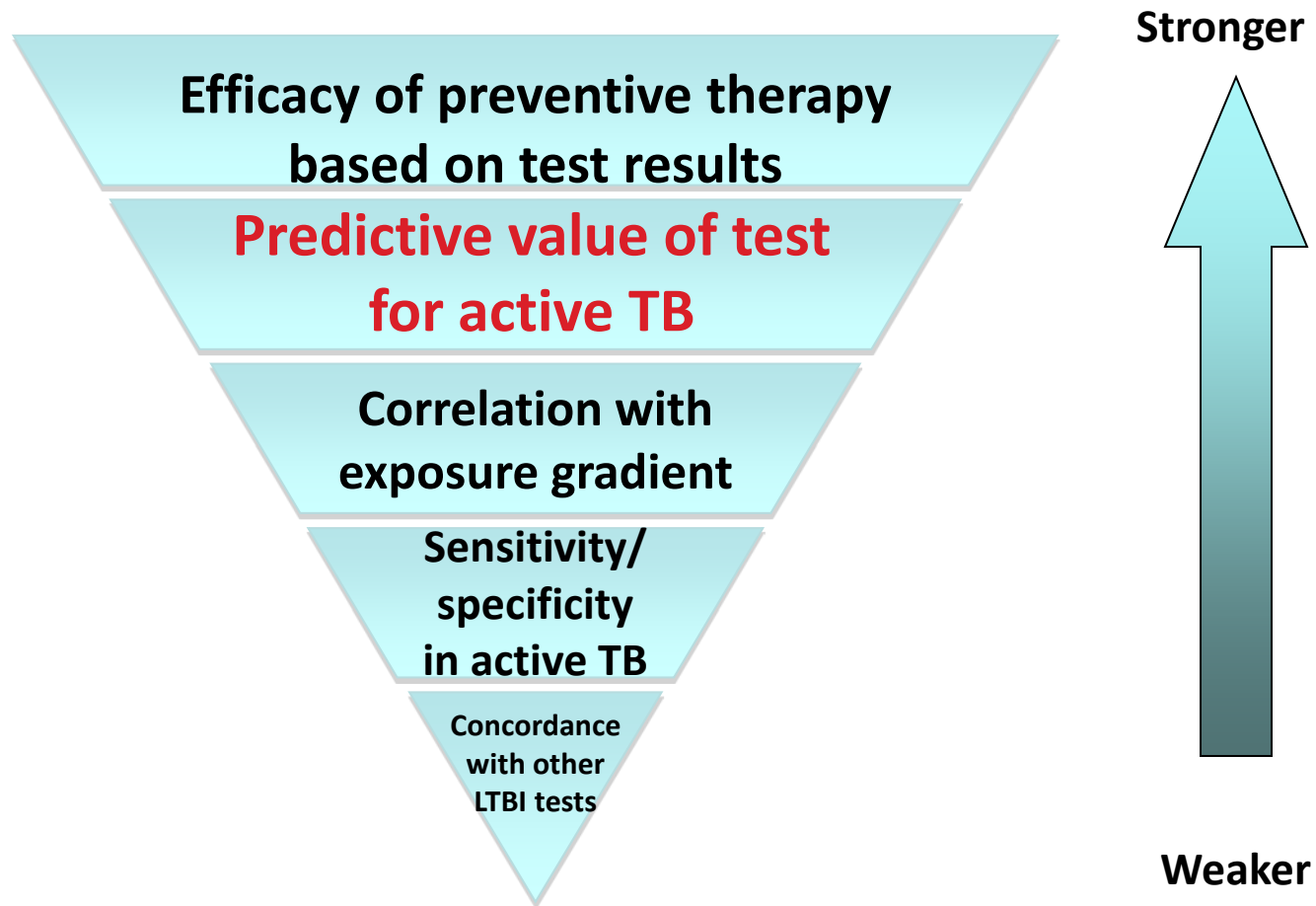


Correlation of tests with Gradient of exposure – Pediatric contacts

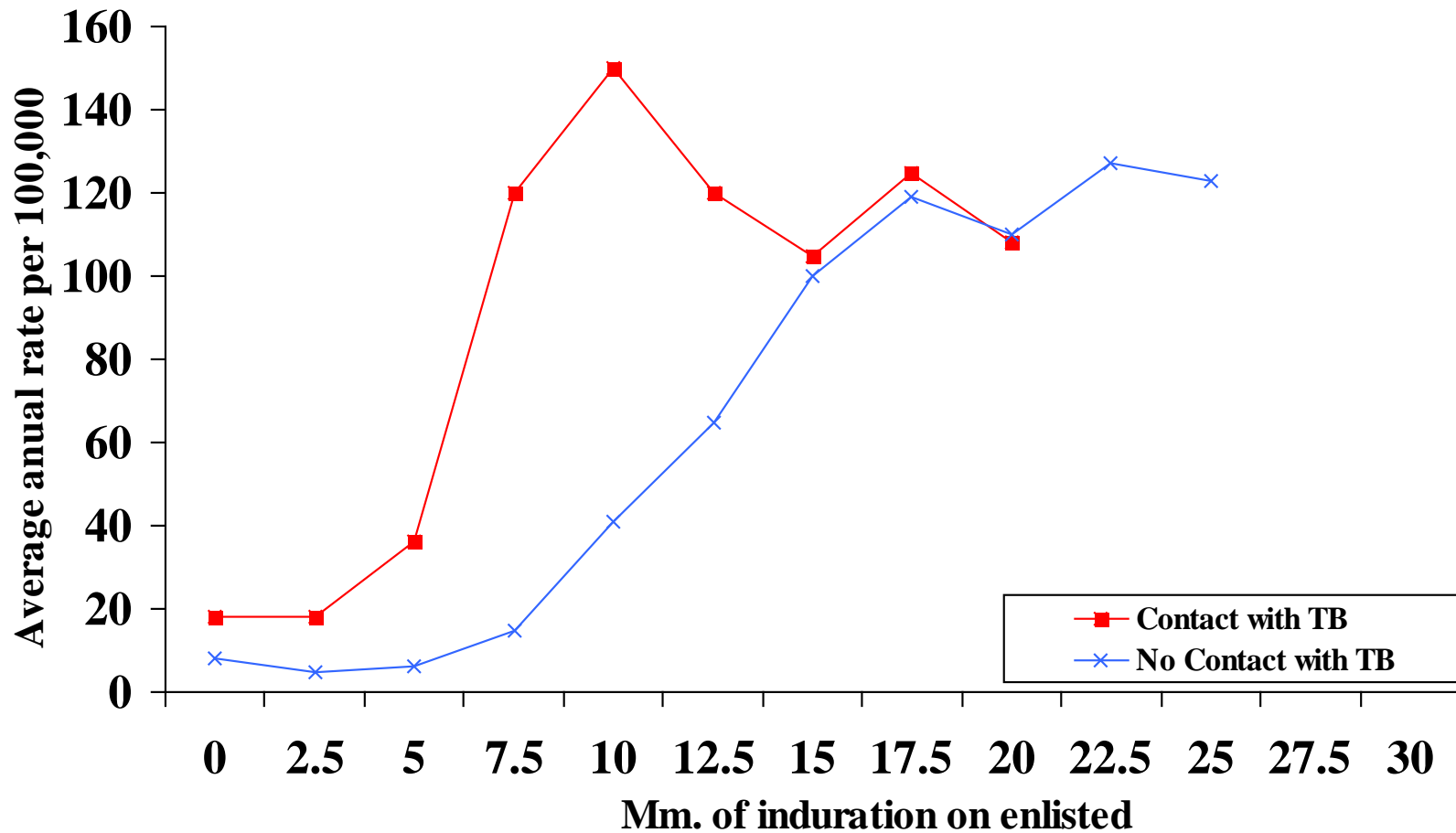


Hierarchy of evidence for tests of LTBI

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Average Annual Incidence of Tuberculosis Among Navy Recruits – By History of Household Contact



Predictive Value of interferon-gamma release assays for incident active TB disease in low, middle and high-income countries: A systematic review. (RM Rangaka et al. under review)

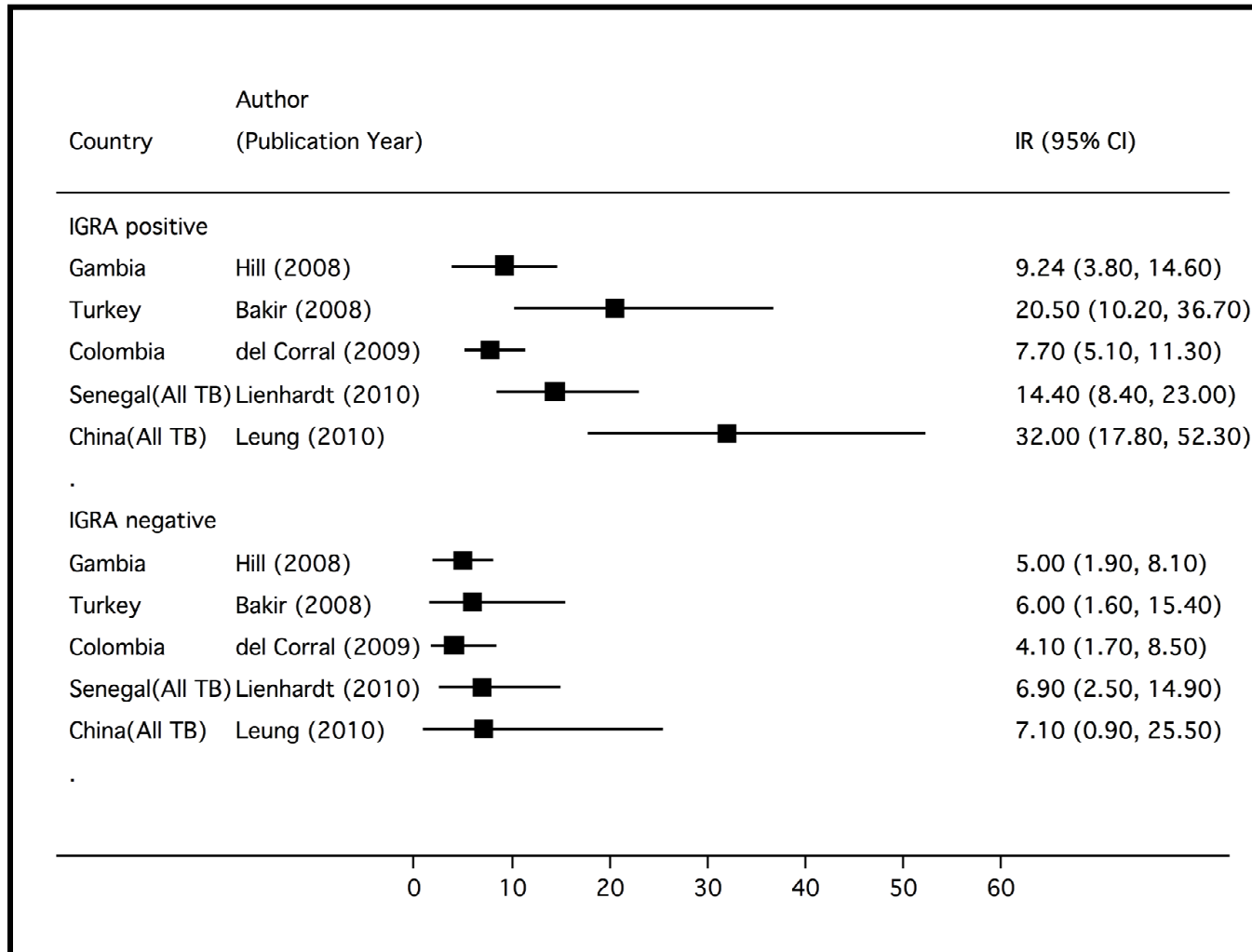
- 11 studies identified with 17,000 subjects in all
- 3 Low income countries (Ethiopia, Gambia, Senegal)
- 3 Middle income countries (Turkey, Colombia, China)
- 5 High income countries (Austria, Netherlands, Japan, Norway, Germany).

Incidence of active TB after a positive IGRA

The 5 largest studies from high burden countries

Country	N	Test	Incidence of active TB in IGRA+ groups
The Gambia [Hill et al. 2008]	2348	ELISPOT (in-house)	9/1000 person-yr
Turkey [Bakir et al. 2008]	908	ELISPOT (T-SPOT.TB)	21/1000 person-yr
S Africa [Mahomed et al. 2009 (abstract)]	5248	QFT	6/1000 person-yr
Colombia [del Corral et al. 2009]	2060	In-house whole-blood CFP-10 assay	11/1000 person-yr
Senegal [Lienhardt et al. PLoS One 2010]	2679	ELISPOT (in-house)	14/1000 person-yr

Results: Incidence rates of TB by IGRA status



Incidence rate per 1000 person-years

Incidence of active TB after close TB contact – per 1000 person-years

Setting	Incidence IGRA Pos	Incidence IGRA Neg	Risk Ratio
Gambia	9.2	5.0	1.8
Turkey	20.5	6.0	3.8
Colombia	7.7	4.1	1.9
Senegal	14.4	6.9	2.1
China	32.0	7.1	3.8
Pooled	15.6	5.5	2.4

Incidence rates ratios - Active TB after close TB contact – IGRA vs TST

Setting	IRR: IGRA Pos/Neg	IRR: TST Pos/Neg
Gambia	1.9	2.1
Turkey	3.4	2.7
Senegal	2.0	1.4
China	4.5	1.6
Pooled (95% CI)	3.0 (0.1, 5.9)	1.8 (0.5, 3.0)

Influence of discordant or concordant TST/IGRA results on risk of TB

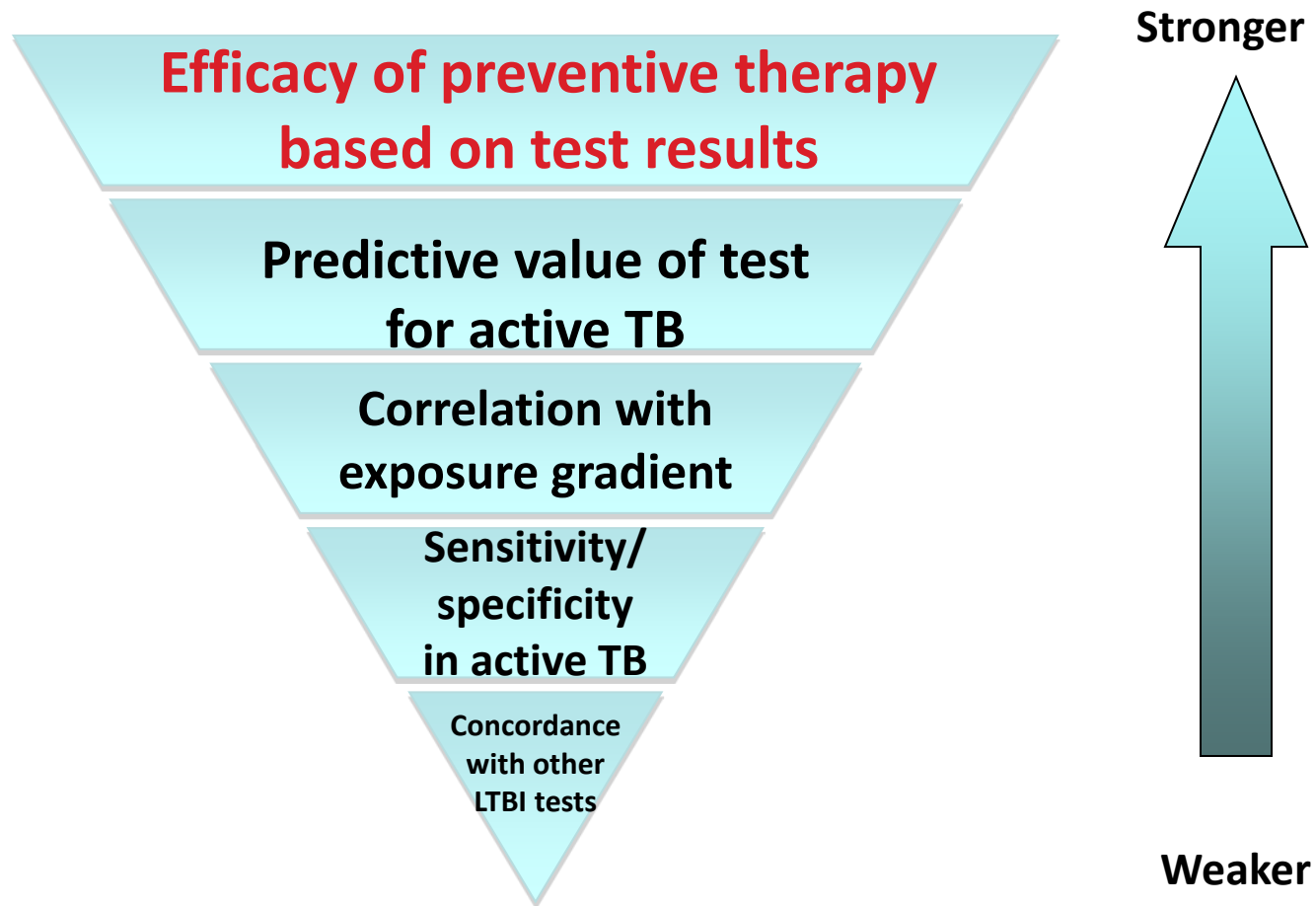
TST/IGRA	The Gambia (Hill et al)	Turkey (Bakir et al)	Senegal (Lienhardt et al)
TST + / IGRA +	8.9	22.2	14.7
TST + / IGRA -	9.6	7.4	4.9
TST - / IGRA +	12.4	11.7	5.9
TST - / IGRA -	4.0	5.1	9.9

Predictive ability of IGRAs – summary

- Several large scale studies now completed
- Predictive ability of IGRA somewhat better than TST
 - But not significantly better
- **Key point: No test accurately predicts who should be treated for LTBI (not yet)**

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The ultimate gold standard: Benefit from treatment of persons with positive vs negative tests

Particularly in immune-compromised – who
may have false negative tests

Meta-Analysis: INH protects against TB In HIV (+) who are TST (+) (Pooled estimates: 0.4 (0.24-0.65))

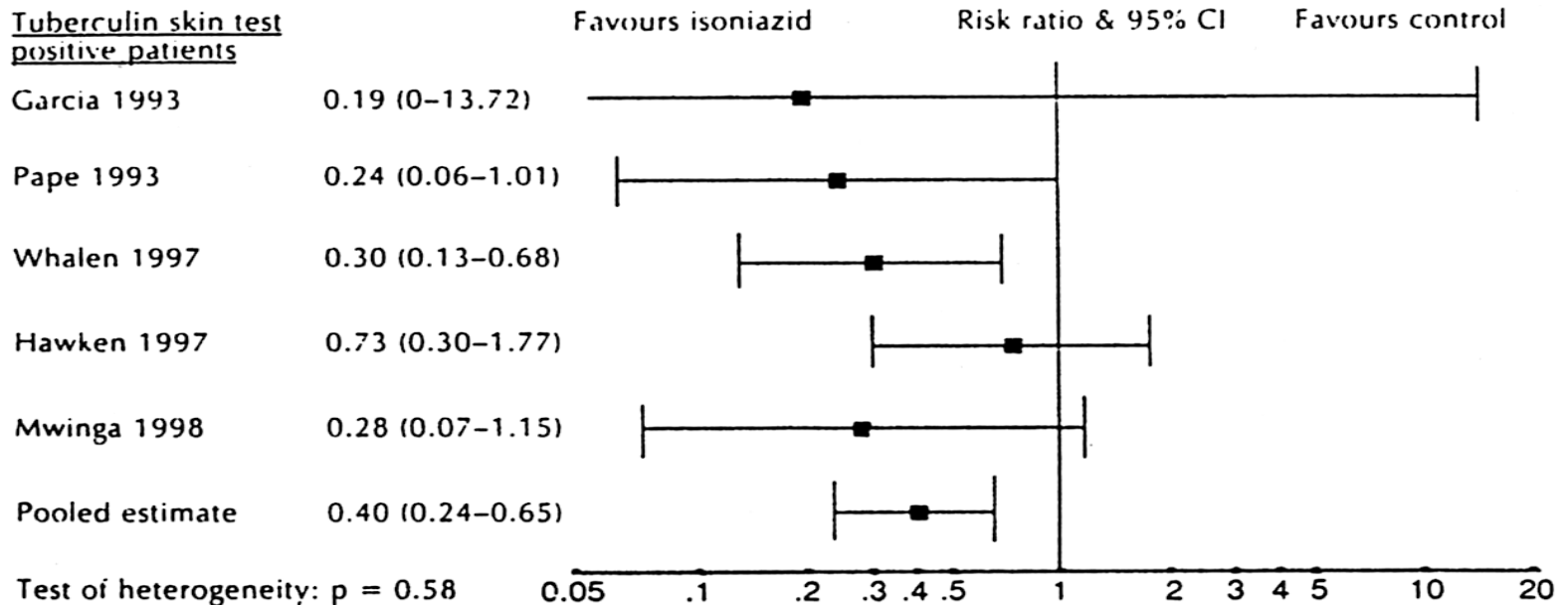


Fig. 1. RR and 95% CI of TB for INH versus placebo or control regimens in randomized controlled trials for prevention of TB in HIV infection. See Table 1 for study references.

Heiner BC, Lauren GE, Gordon GH, et al. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled

Meta-Analysis: INH does not protect against TB in HIV (+) who are TST (-) (Pooled estimates: 0.84 (0.54-1.30))

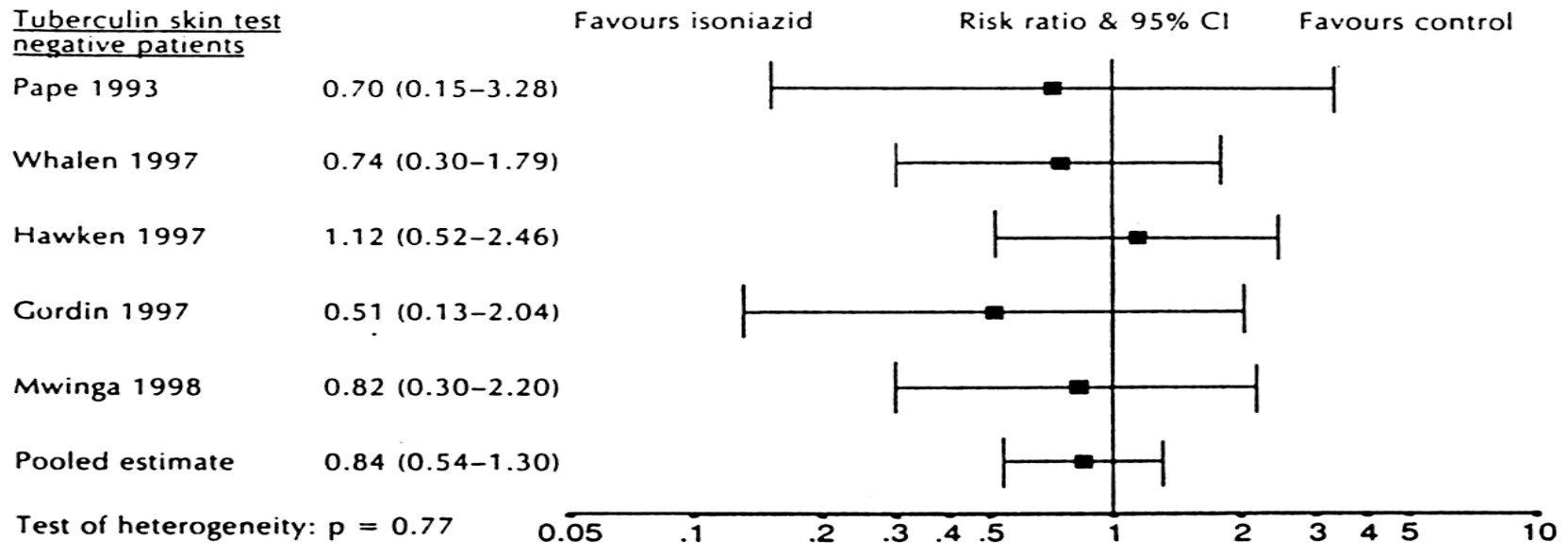


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Influence of TST on the TB prevention effect

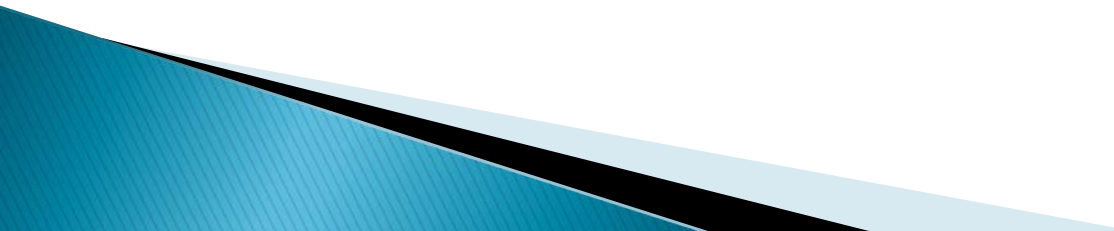
		TB Rate per 100 p.y.		HR	P-value
		6H	36H		
TST	Positive n=400	2.53	0.19	0.08	0.015*
				92% reduction	
TST	Negative n=1194	0.92	0.78	0.86	0.69
				14% reduction	

* Significant <0.05

Ability of TST to predict benefit of LTBI treatment – summary

- TST appears to predict benefit of INH therapy
 - Several RCT have shown this
 - Recent Botswana study confirmed this
- Remains useful even in advanced HIV
 - When many HIV infected are anergic
 - And for several years (up to 36 months in Botswana trial)

Ability of IGRAs to predict benefit of LTBI treatment – summary

- So far – no studies
 - Given similarity of TST and IGRAs in cohort studies – IGRAs should predict benefit at least as well as TST (or somewhat better)
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Merci

Thanks

Gracias

Obrigado

- ▶ Thanks also to Madhu (Pai) for several slides