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)

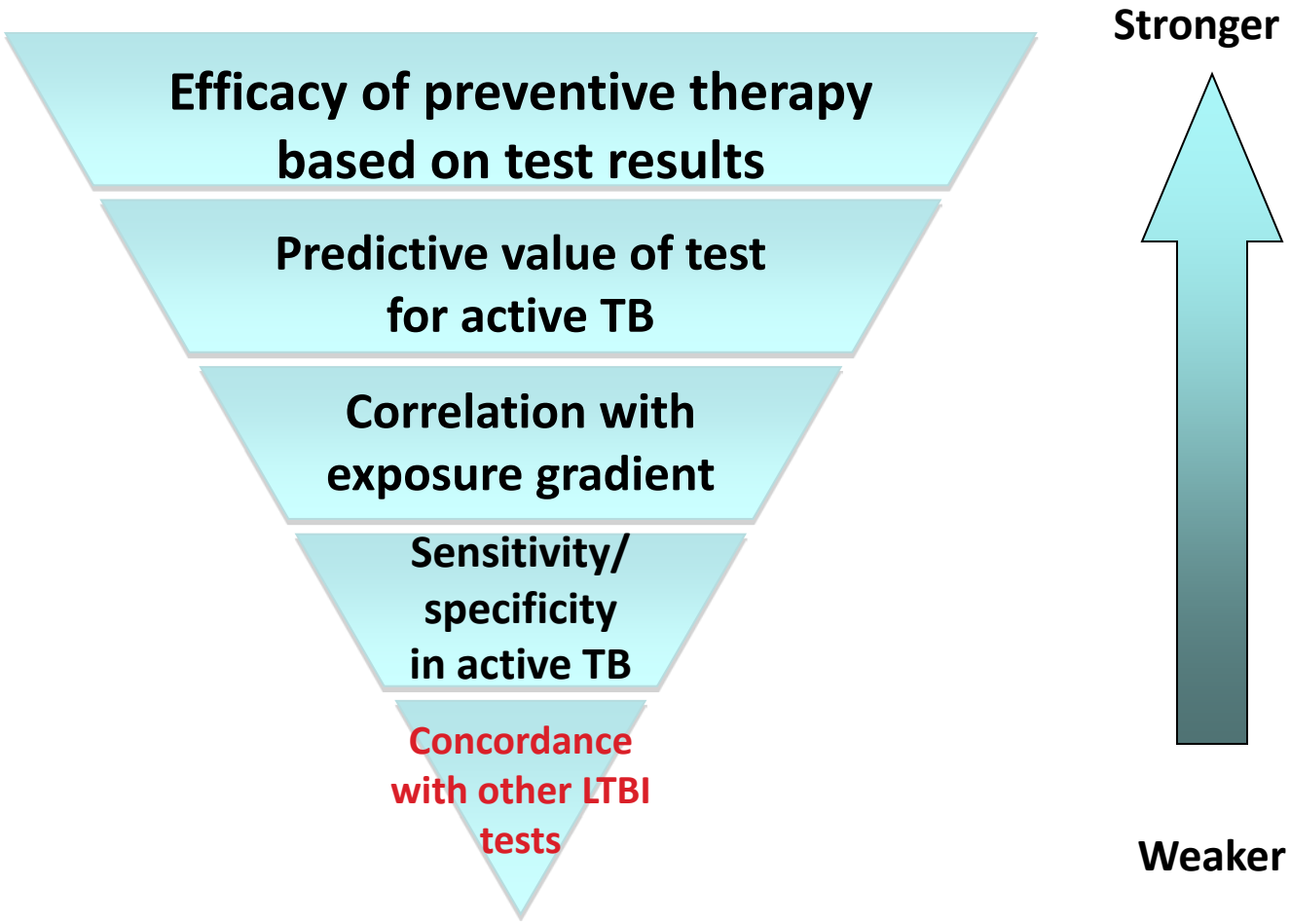
What is the reference (Gold) standard for latent TB infection?

- 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)

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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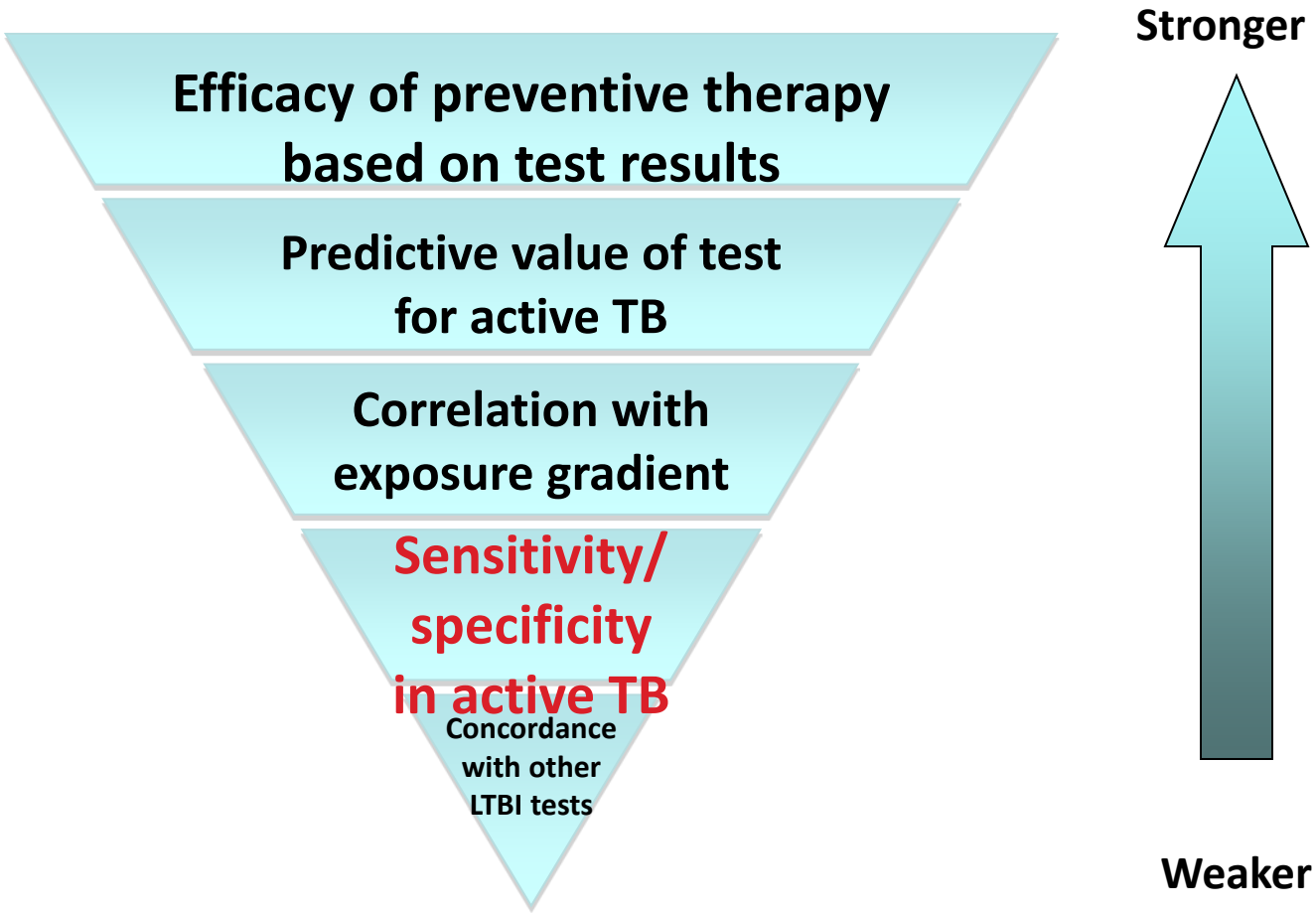
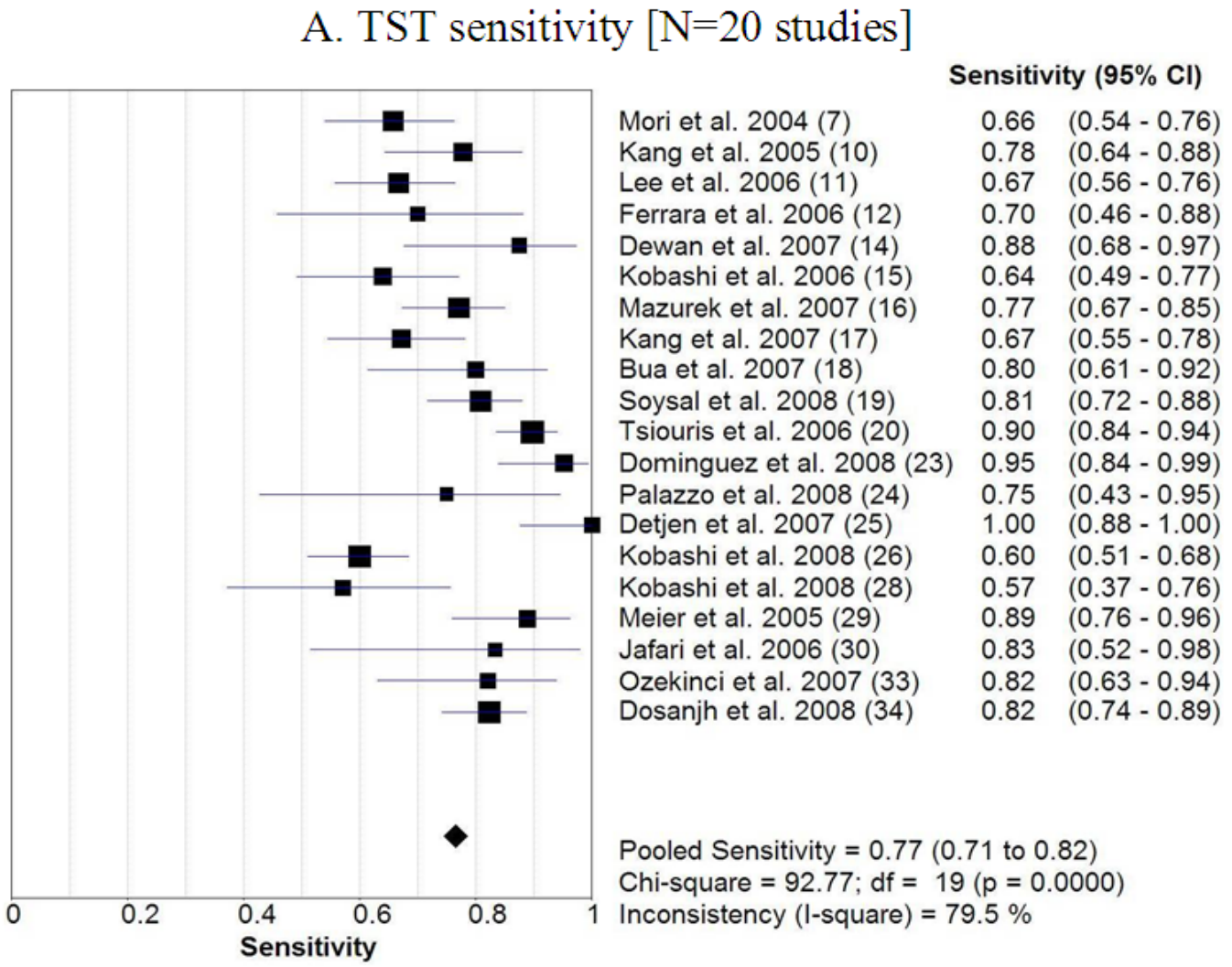
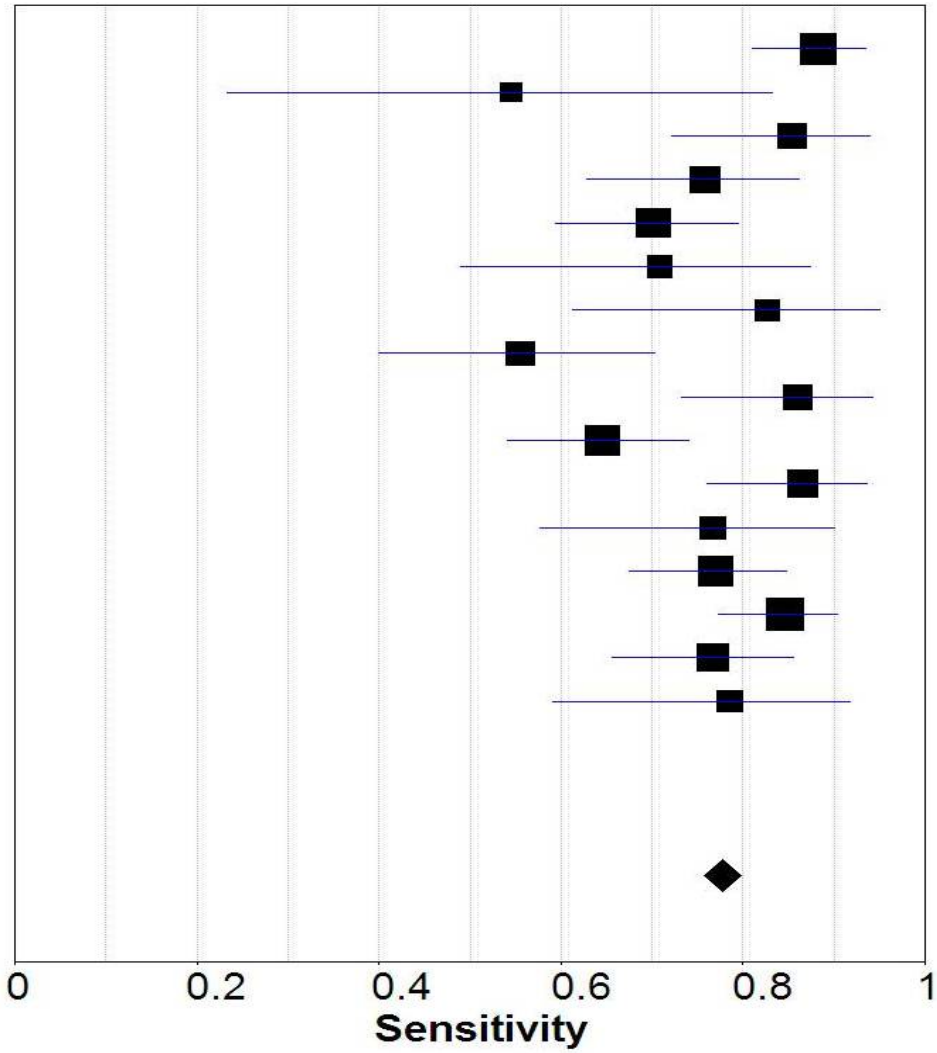


Sensitivity of TST in Active TB [all settings]



20 Studies Pooled sensitivity = 77%

Sensitivity of QuantiFERON-TB Gold in active TB

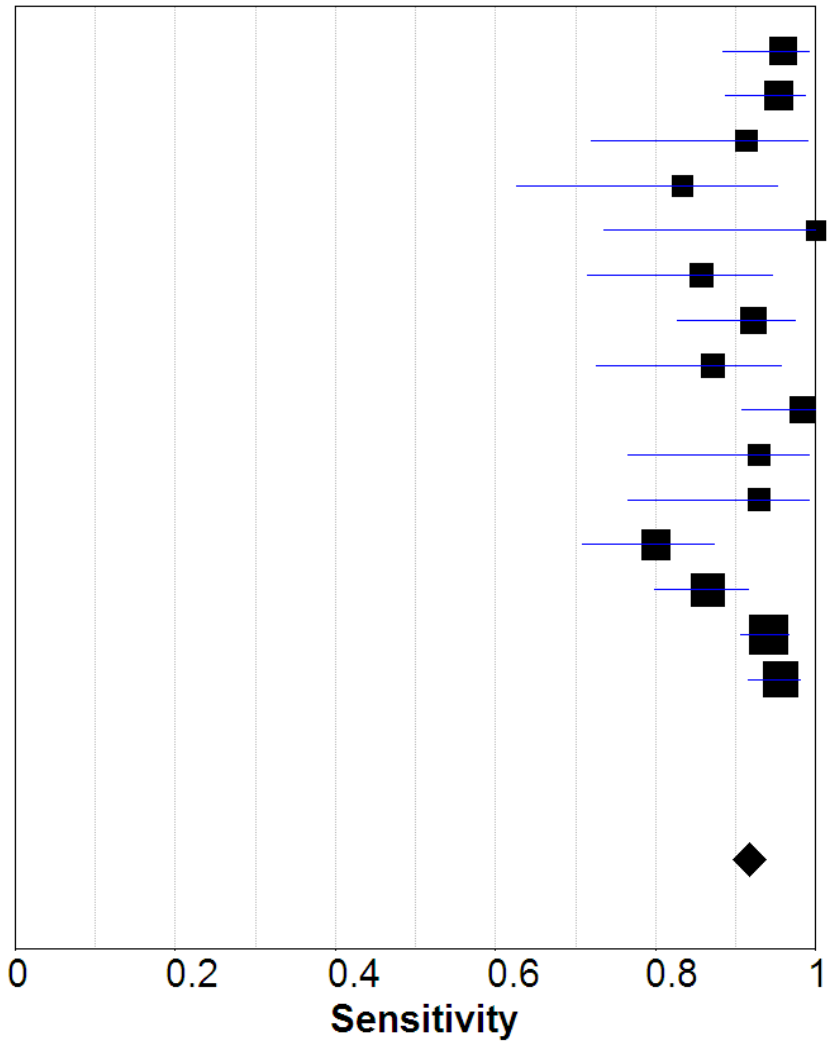


	Sensitivity	(95% CI)
Mori et al. 2004 (7)	0.88	(0.81 - 0.93)
Ferrara et al. 2005 (8)	0.55	(0.23 - 0.83)
Ravn et al. 2005 (9)	0.85	(0.72 - 0.94)
Kang et al. 2005 (10)	0.76	(0.63 - 0.86)
Lee et al. 2006 (11)	0.70	(0.59 - 0.79)
Ferrara et al. 2006 (12)	0.71	(0.49 - 0.87)
Goletti et al. 2006 (13)	0.83	(0.61 - 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



	Sensitivity (95% CI)	
Meier et al. 2005	0.96	(0.88 - 0.99)
Lee et al. 2006	0.95	(0.89 - 0.99)
Goletti et al. 2006	0.91	(0.72 - 0.99)
Ferrara et al. 2006	0.83	(0.63 - 0.95)
Jafari et al. 2006	1.00	(0.74 - 1.00)
Dominguez et al. 2007	0.86	(0.71 - 0.95)
Kang et al. 2007	0.92	(0.83 - 0.97)
Wang et al. 2007	0.87	(0.73 - 0.96)
Janssens et al. 2007	0.98	(0.91 - 1.00)
Detjen et al. 2007	0.93	(0.76 - 0.99)
Ozekinci et al. 2007	0.93	(0.76 - 0.99)
Soysal et al. 2008	0.80	(0.71 - 0.87)
Dosanjh et al. 2008	0.86	(0.80 - 0.92)
Chee et al. 2008	0.94	(0.91 - 0.97)
FDA Data on TSPOT 2008	0.96	(0.92 - 0.98)

Pooled Sensitivity = 0.92 (0.90 to 0.93)
Chi-square = 39.64; df = 14 (p = 0.0003)
Inconsistency (I-square) = 64.7 %

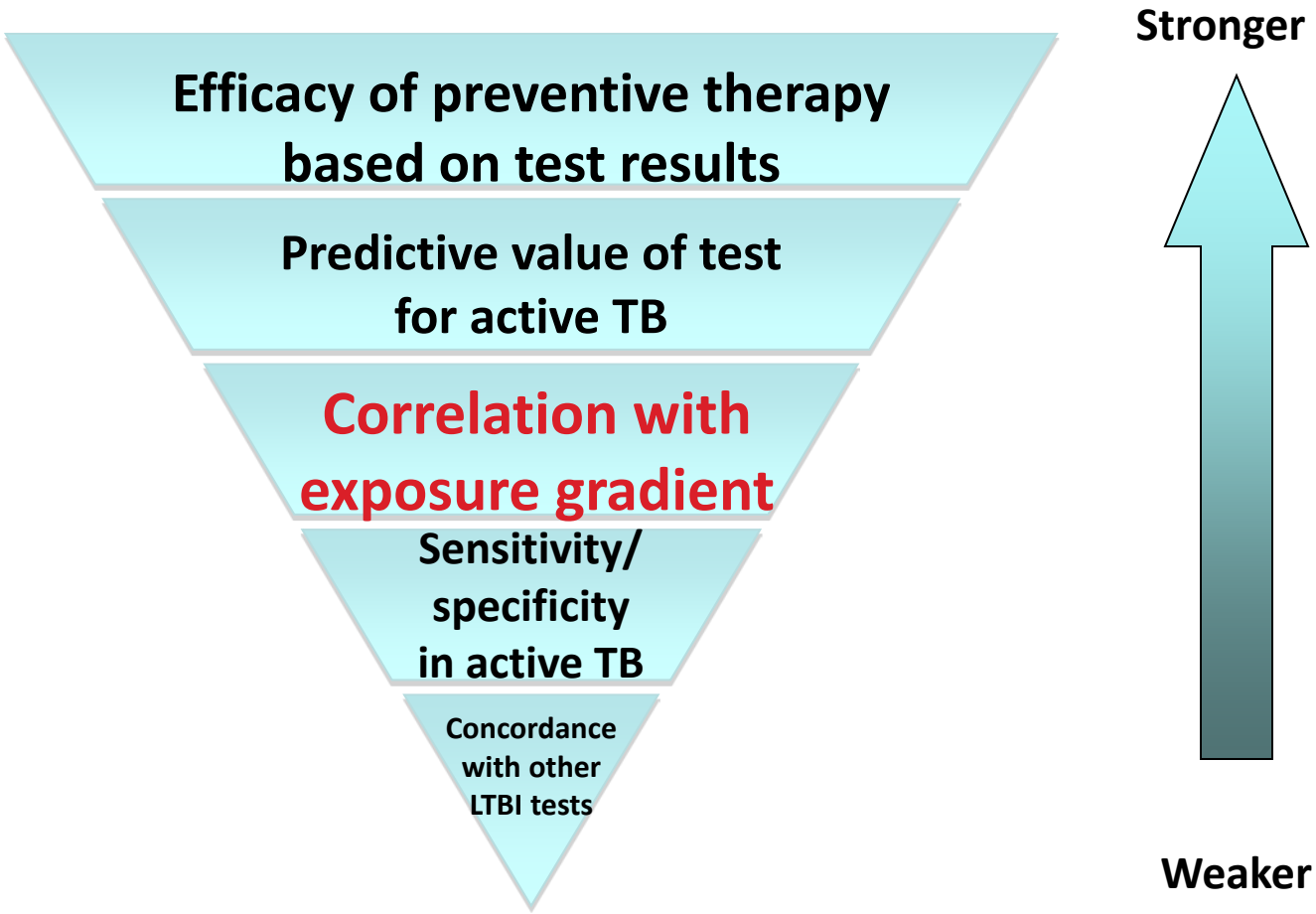
13 Studies Pooled sensitivity = 92%

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%**

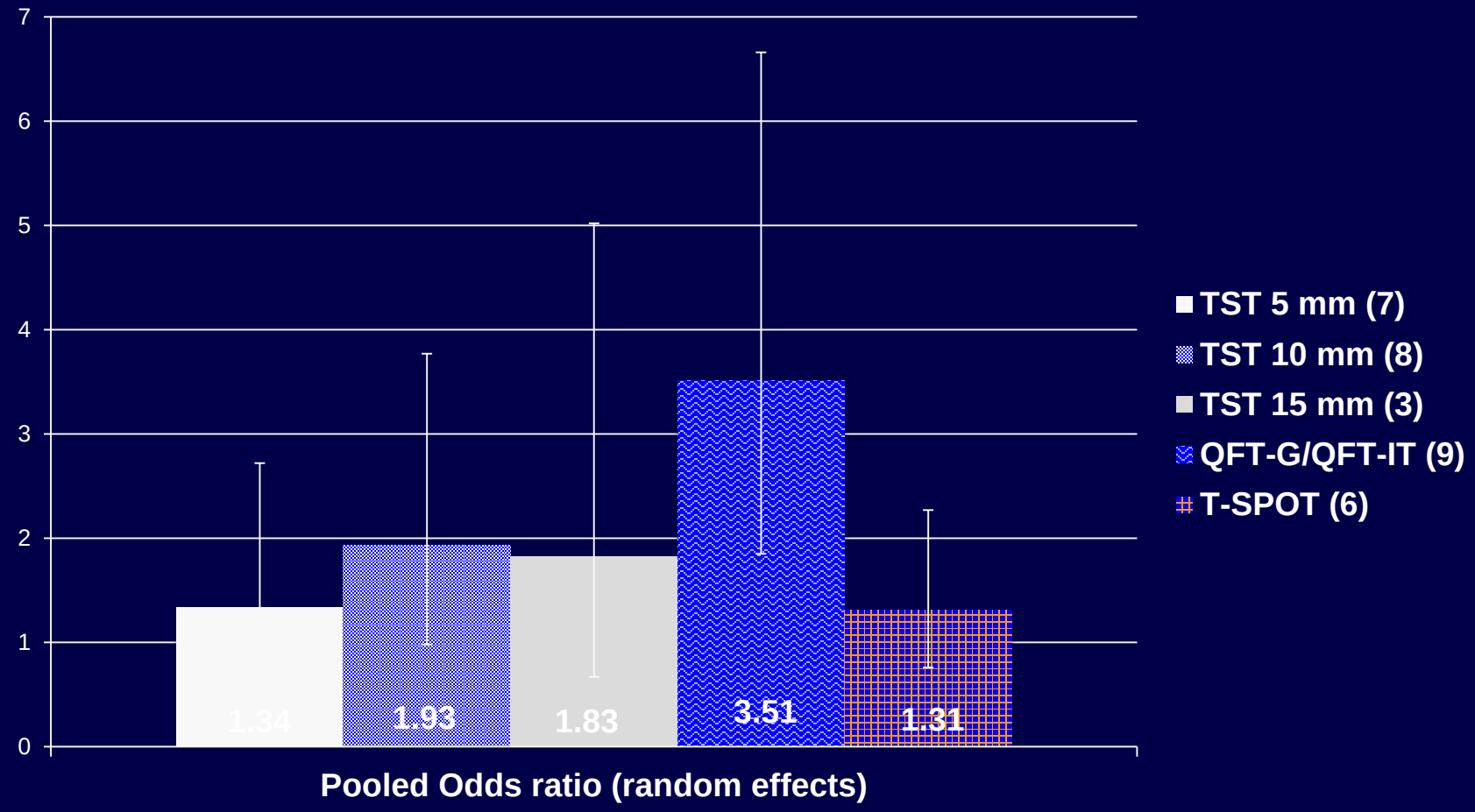
Hierarchy of evidence for tests of LTBI
WHO Expert Group on IGRAs



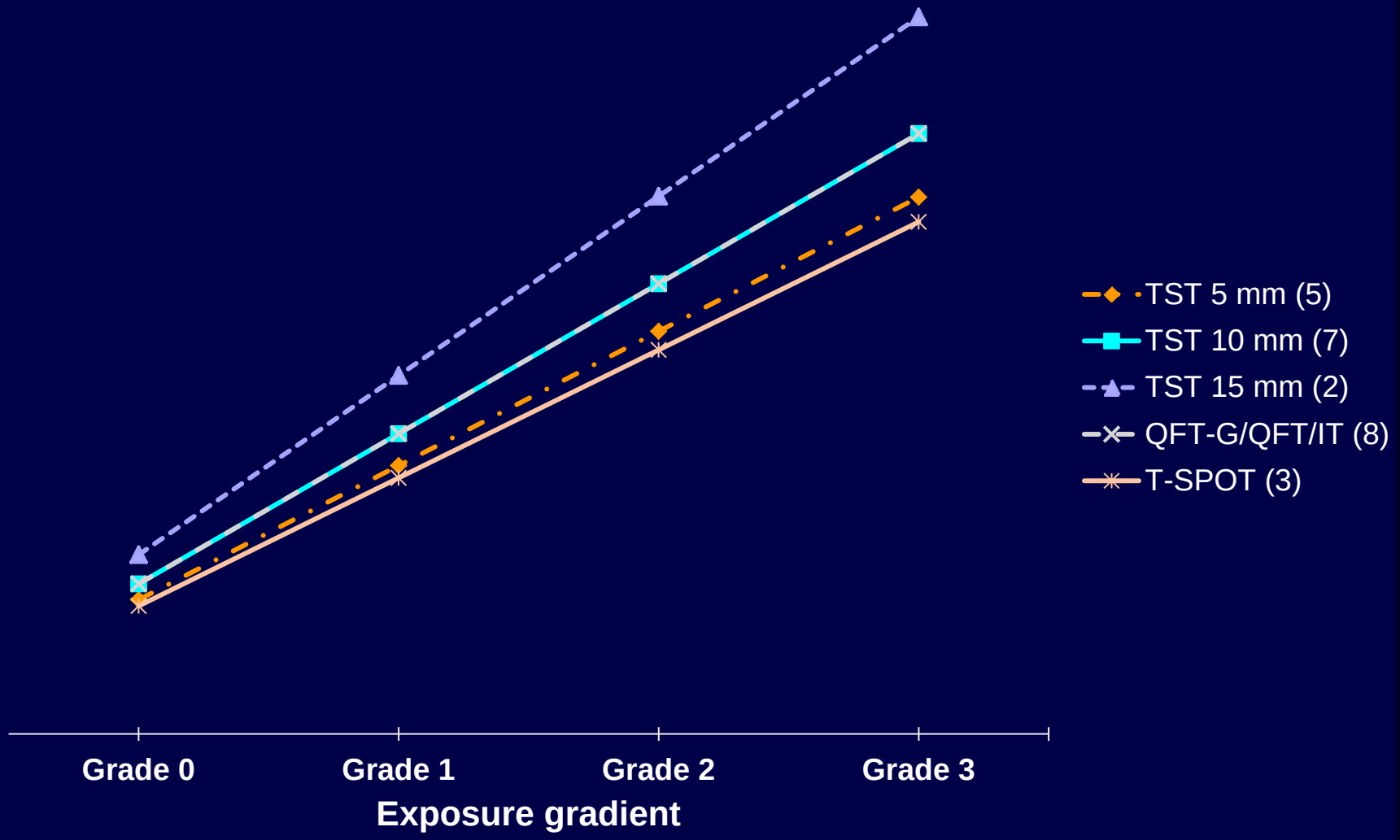
Exposure / gradient studies

- 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



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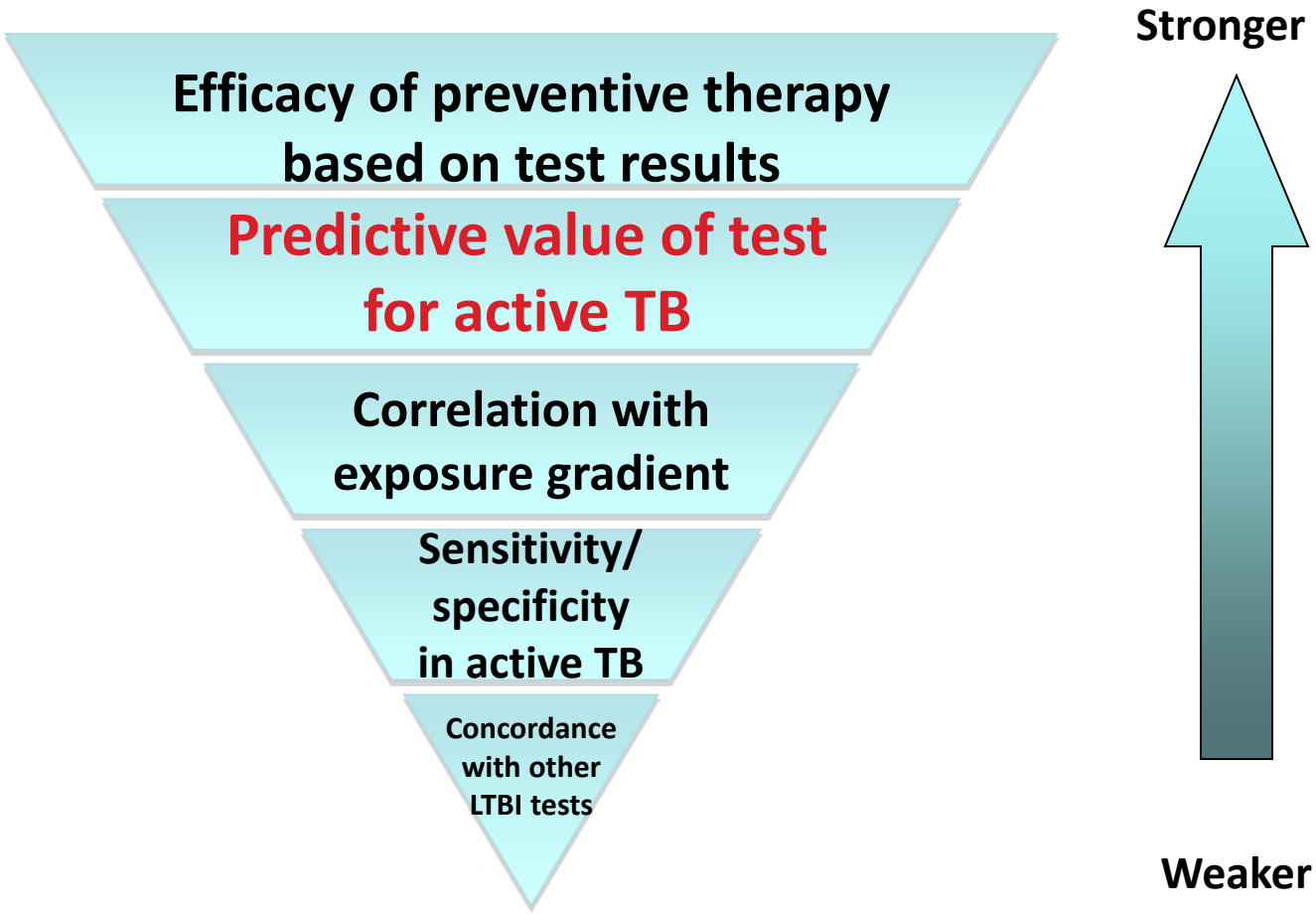
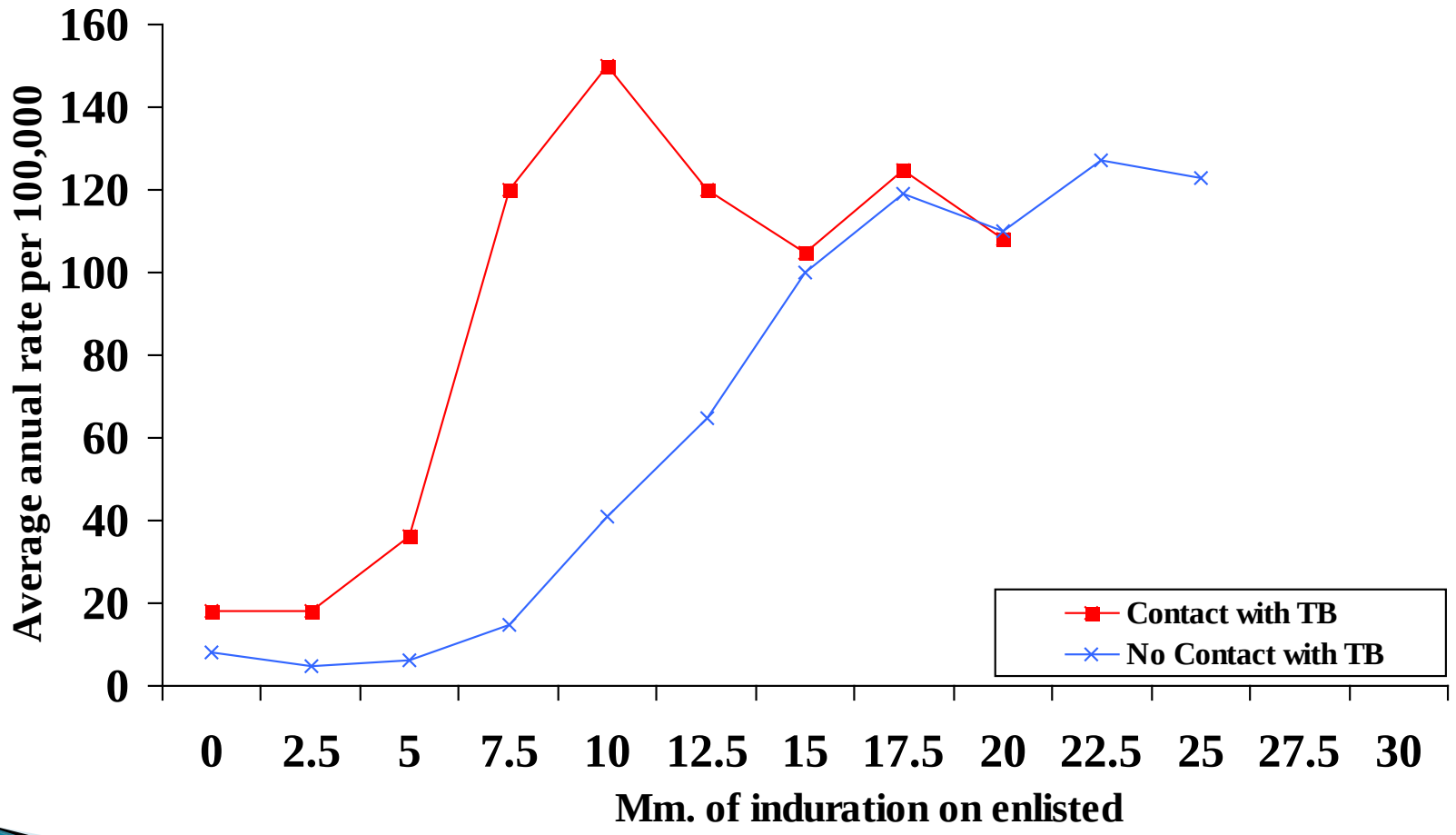


Average Annual Incidence of Tuberculosis Among Navy Recruits – By History of Household Contact



Comstock, Edwards, and Livesay; Am Rev Respir Dis 1974; 110:576

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. Lancet Inf Dis, 2012)*

11 studies identified with 17,000 subjects in all

3 Low income countries (Ethiopia, Gambia, Senegal)

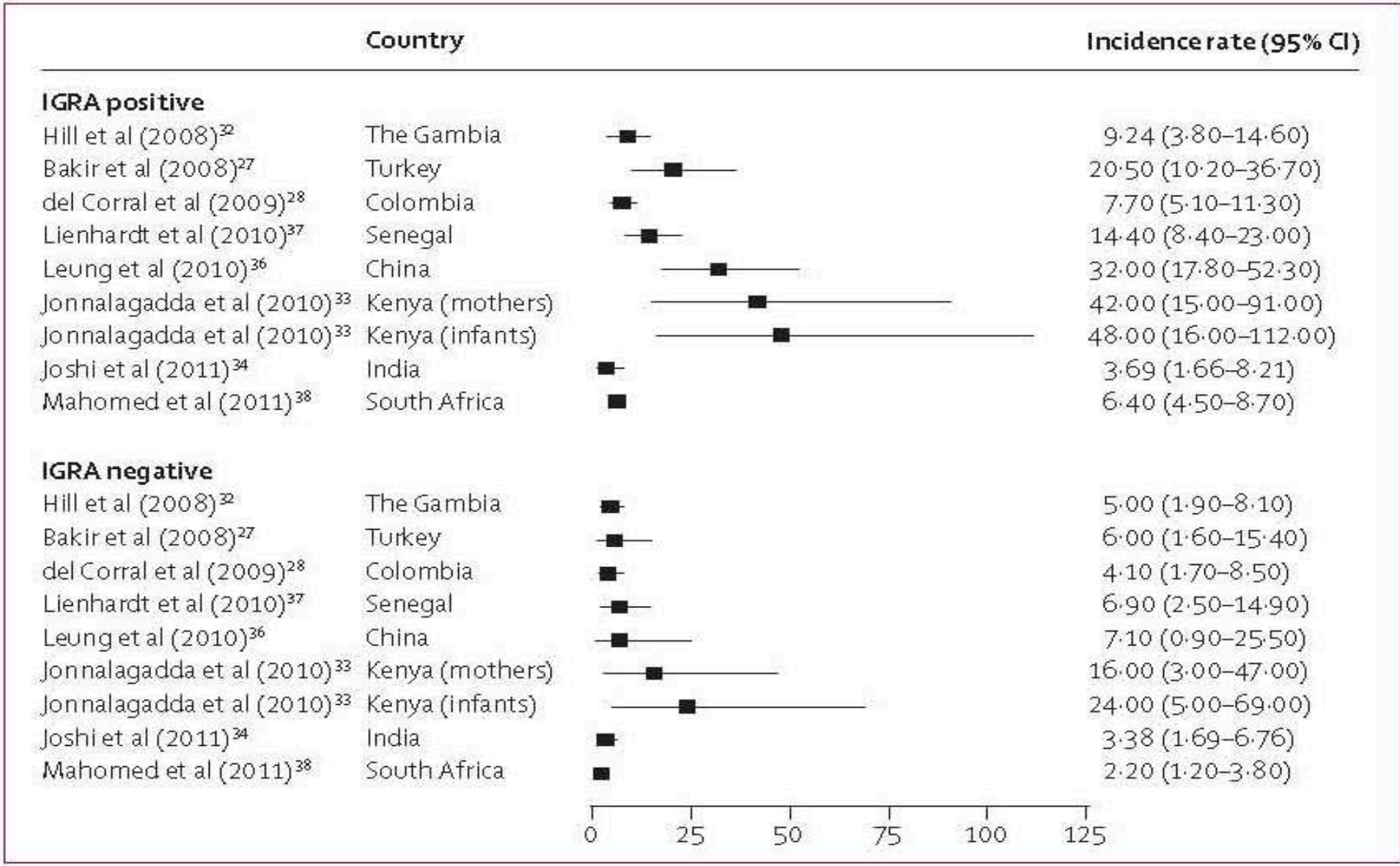
3 Middle income countries (Turkey, Colombia, China)

5 High income countries (Austria, Netherlands, Japan, Norway, Germany).

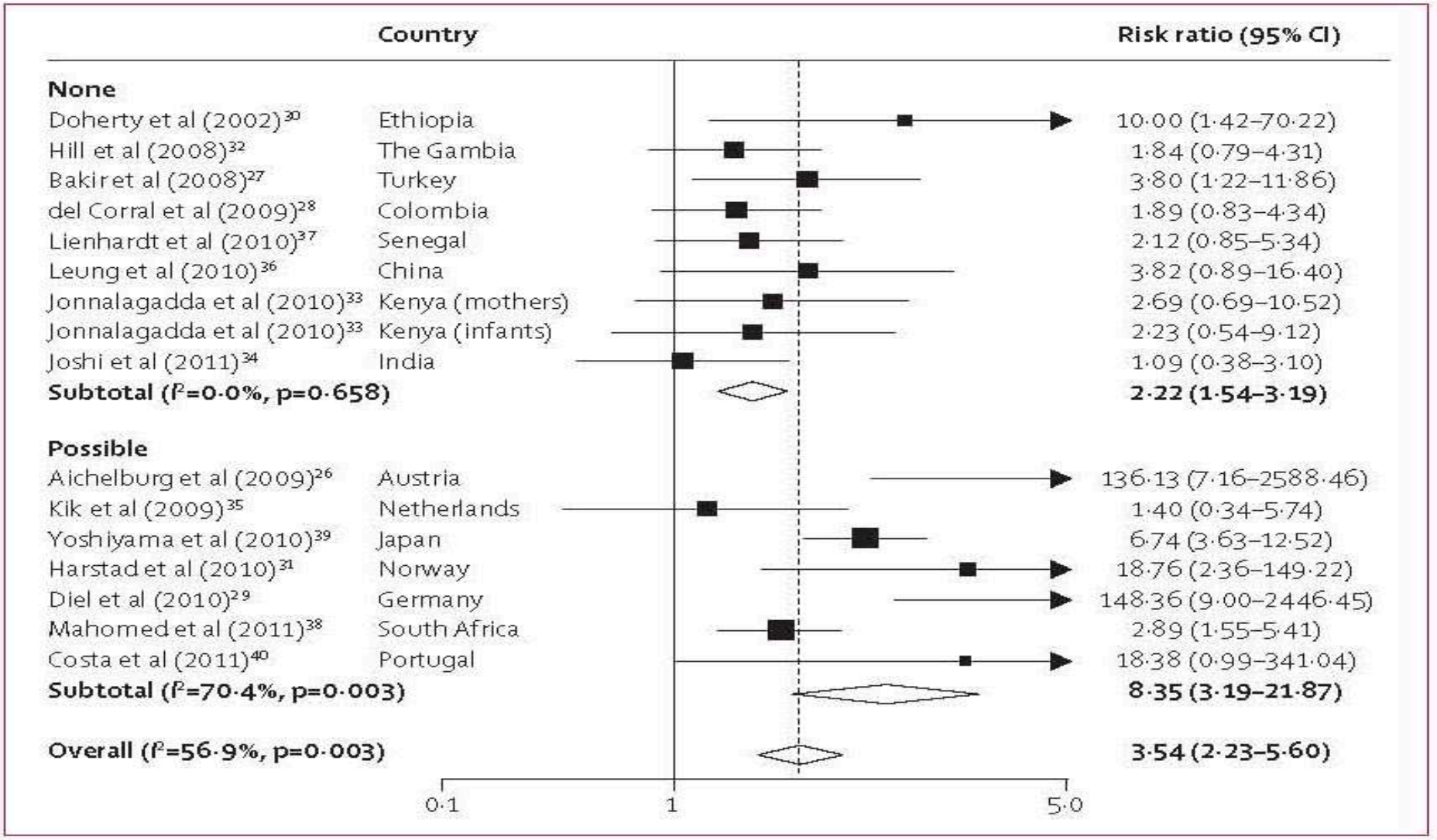
Incidence of active TB after a positive IGRA
The 5 largest studies from high burden countries

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

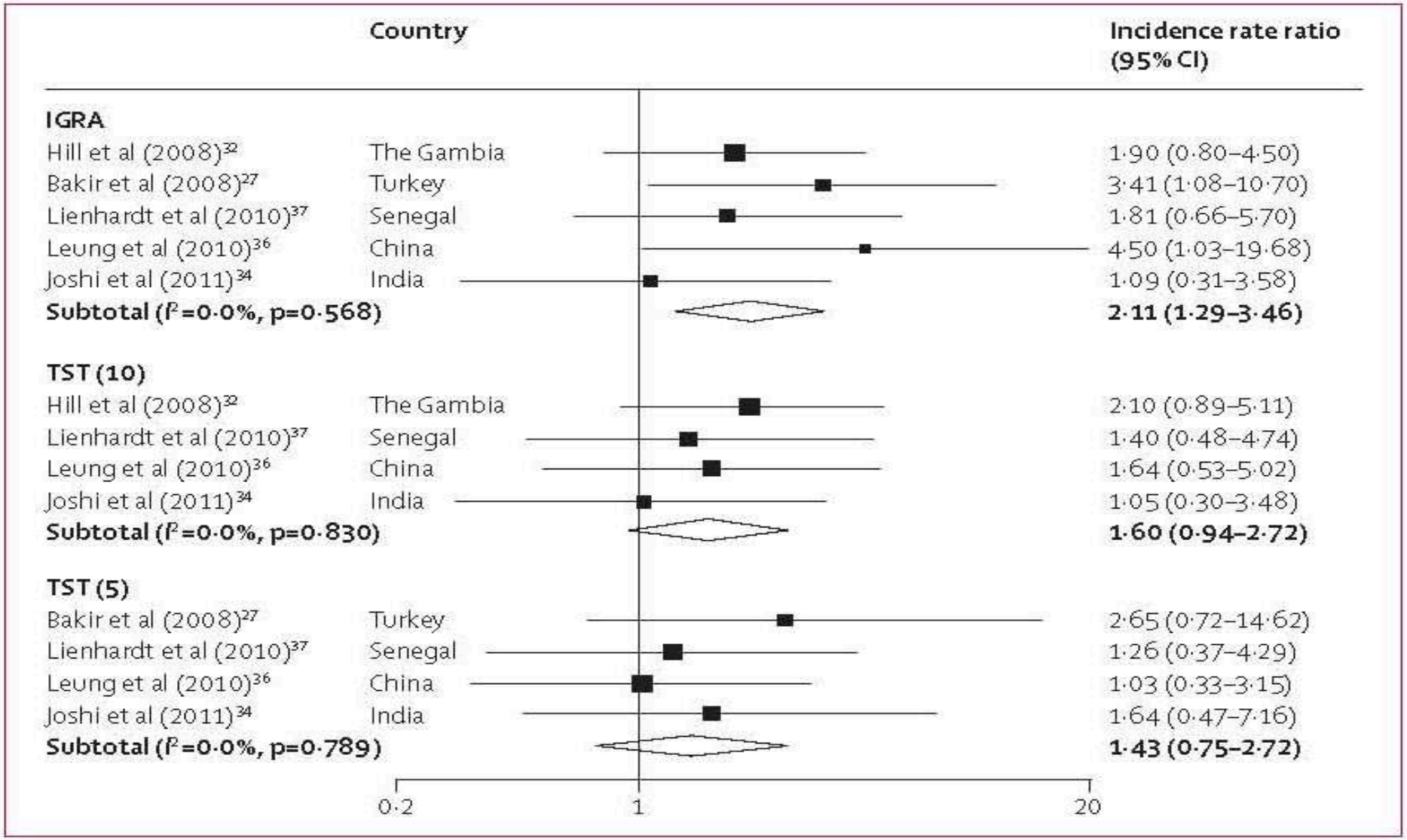
Crude incidence – IGRA+ vs IGRA–



Risk ratios for disease IGRA+ vs IGRA– By possible incorporation bias



Risk ratios for disease: Test+ vs Test−



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

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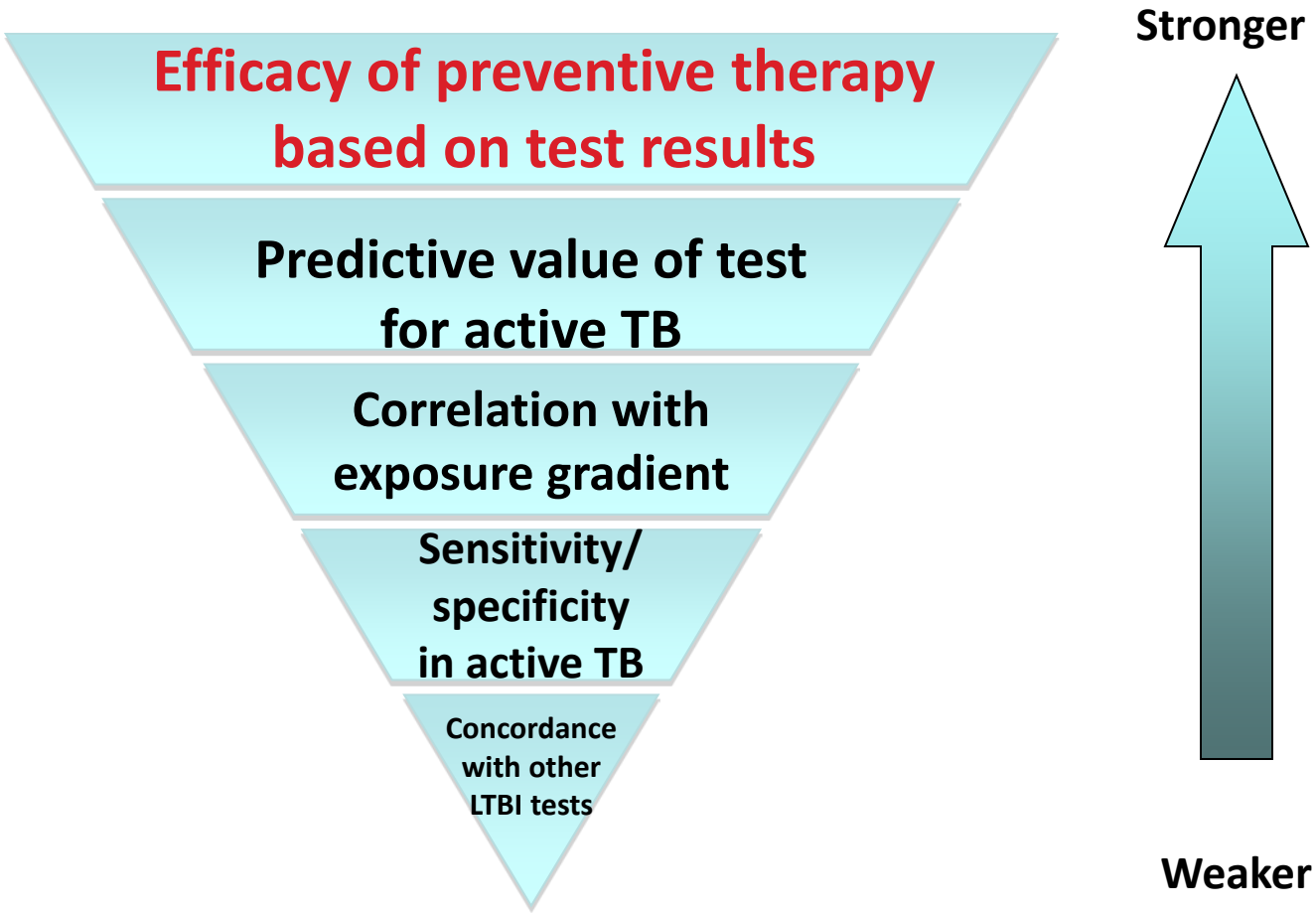


The ultimate gold standard: Benefit from treatment of persons with positive vs negative tests

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))

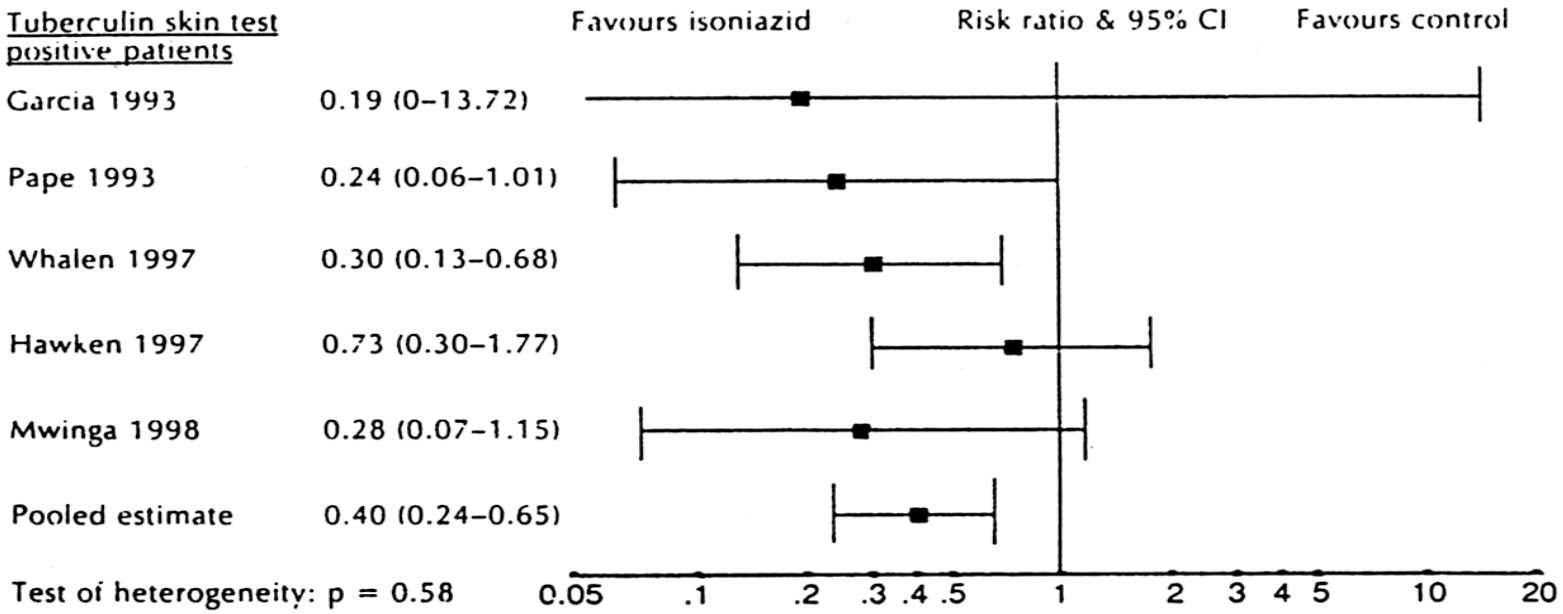


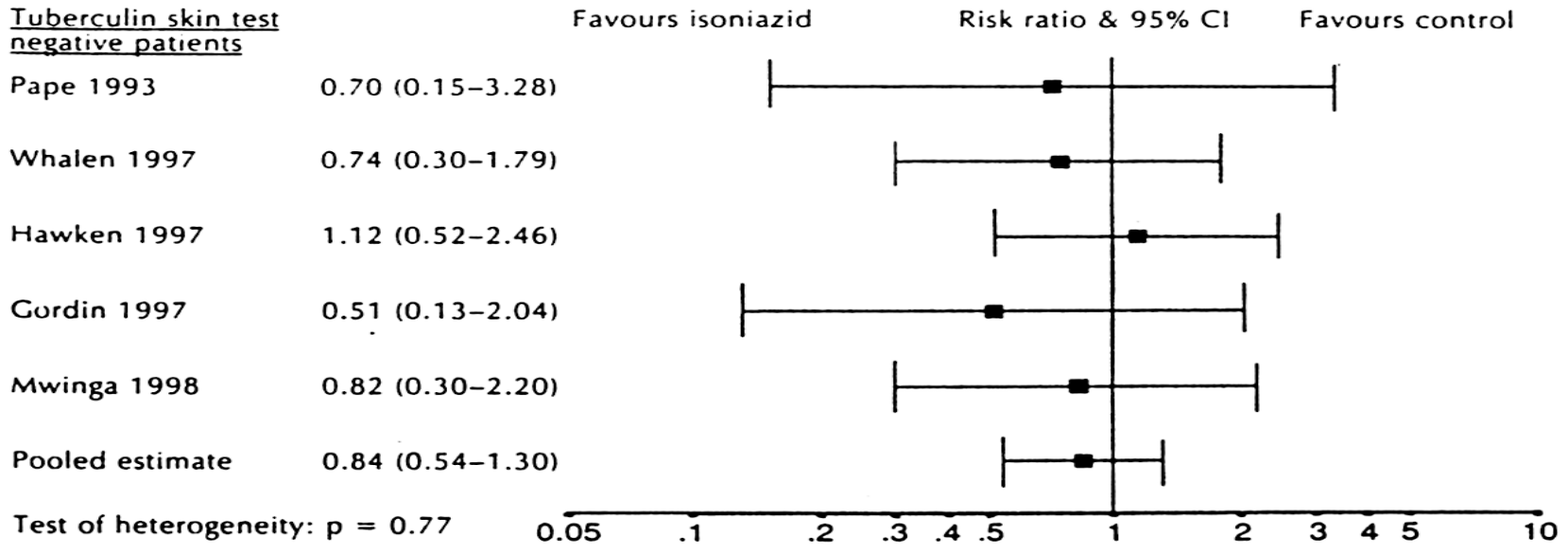
Fig. 1. RR and 95% CI of TB for INH versus placebo or control regimens in randomized controlled trials for prevention of TB in HIV infection. See Table 1 for study references.

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

AIDS 1999;13:501-7

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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AIDS 1999;13:501-7

Influence of TST on the TB prevention effect

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

* Significant <0.05

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)

Merci

Thanks

Gracias

Obrigado

- Thanks also to Madhu (Pai) for several slides