INSIGHTS INTO TST AND IGRA DISCORDANCE

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OVERVIEW: TST/IGRA discordance

TST possible causes of variability

- BCG vaccination (effect in first 10 years)
- NTM exposures (more common in tropical areas)
- Operator dependence

IGRA possible causes of variability

- Reliability of the test (specially with low readouts)
- Lack of a clear cut off point
- TST induced IGRA response

SOURCES OF IGRA VARIABILITY

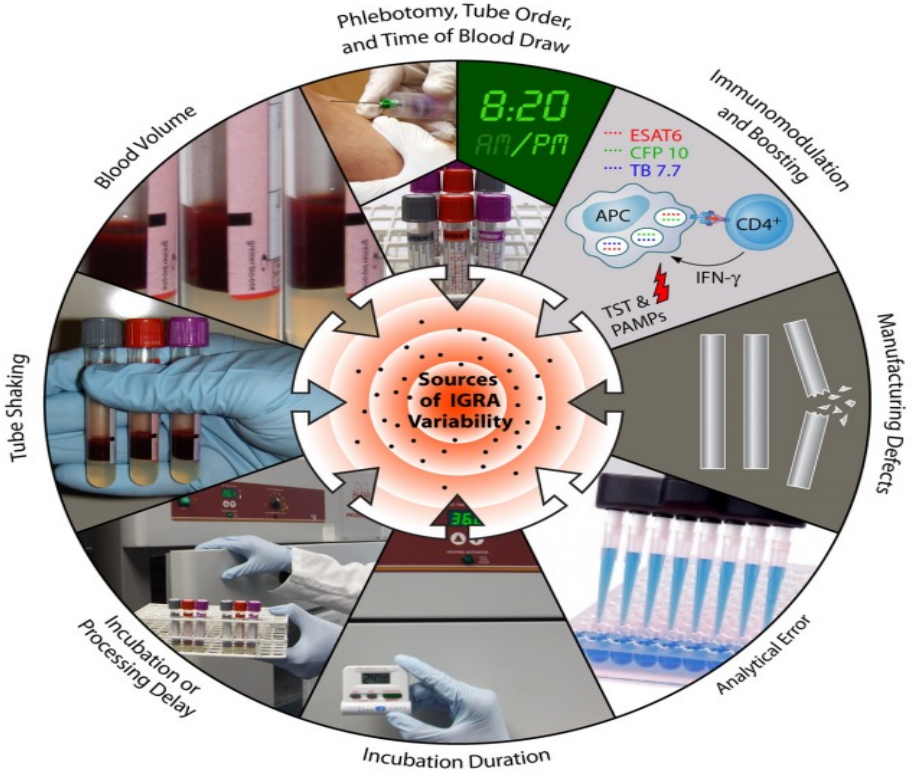
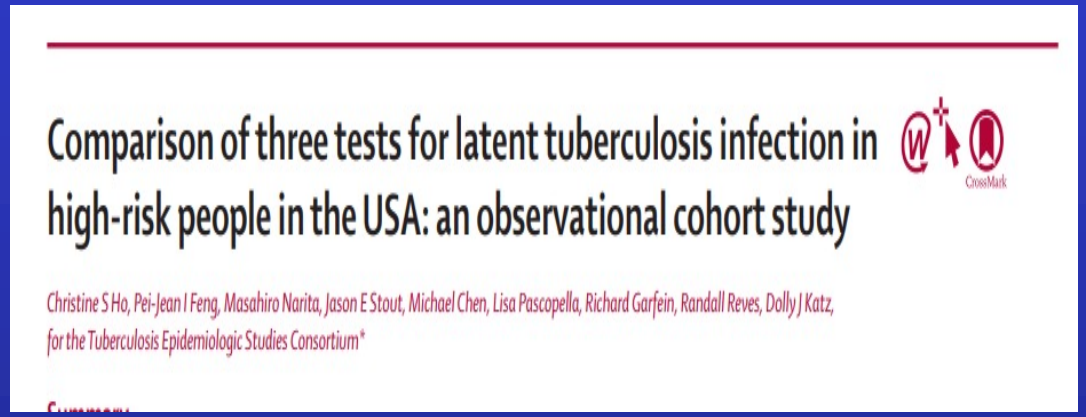


FIG 3 Sources of variability in the QuantiFERON-TB Gold In-Tube assay.

Pai et al, Clin Microbiol Rev January 2014

TST/IGRA discordance: Epidemiology



Comparison of three tests for latent tuberculosis infection in high-risk people in the USA: an observational cohort study

Christine S Ho, Pei-Jean I Feng, Masahiro Narita, Jason E Stout, Michael Chen, Lisa Pascopella, Richard Garfein, Randall Reves, Dolly J Katz, for the Tuberculosis Epidemiologic Studies Consortium*

- Large observational study in USA
- Foreign born, contacts
- TST, IGRA (Quantiferon, T-spot)
- 18 TB clinics: 26962 patients enrolled

Ho et al Lancet Infectious Diseases January 2022

TST/IGRA discordance: Epidemiology

	Tuberculin skin test		QuantiFERON		T-SPOT.TB	
	Tested	Positive	Tested	Positive	Tested	Positive
Birthplace						
All participants (n=21 846)	20 900	7870 (37·7%)	21 603	5184 (24·0%)	20 788	3995 (19·2%)
US-born participants	3575	391 (10·9%)	3693	445 (12·0%)	3638	295 (8·1%)
Non-US-born participants	17 306	7476 (43·2%)	17 882	4732 (26·5%)	17 118	3693 (21·6%)
RR (95% CI)	..	3·9 (3·6–4·3)	..	2·2 (2·0–2·4)	..	2·7 (2·4–3·0)

TST/IGRA discordance: Epidemiology

- TST positivity is more common than IGRA positivity
- Among IGRA, Quantiferon + more common than T-spot +
- Foreign born: TST+/IGRA- more common (significant)
- US born: TST-/IGRA+ more common (slight)

EFFECT OF AGE ON TST/IGRA EXPOSURE

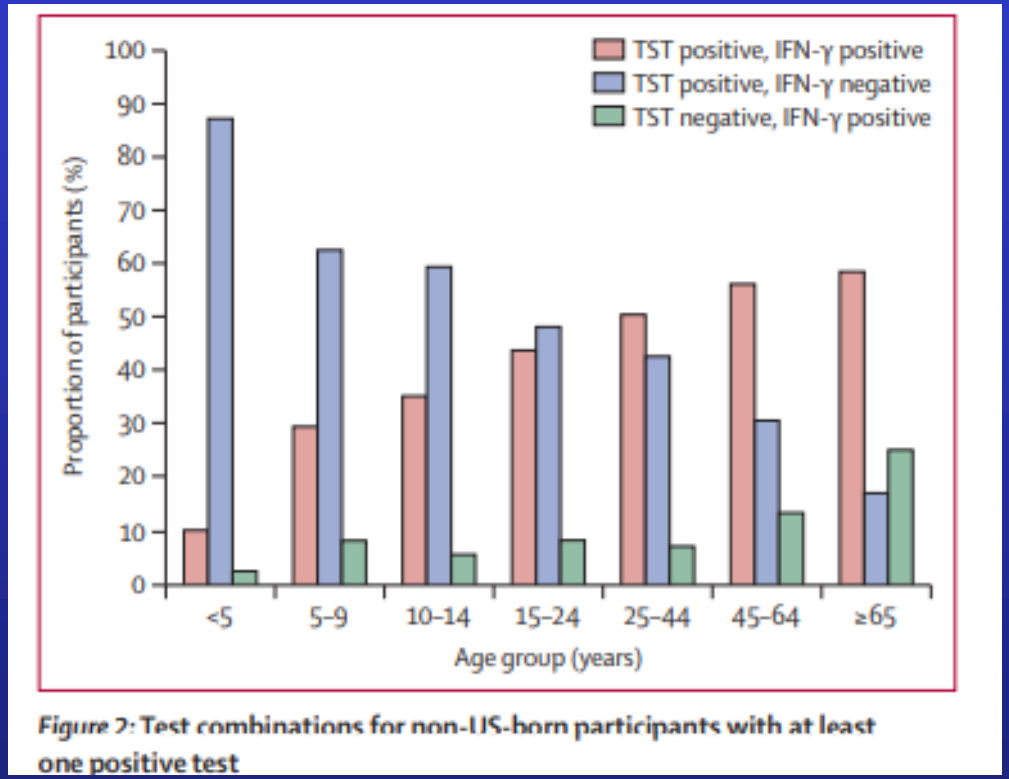


Figure 2: Test combinations for non-US-born participants with at least one positive test

- TST/IGRA discordance more common in younger ages
- Mainly driven by TST+/IGRA-
- Likely BCG related in younger ages
- Older: TST-/IGRA+ more common

Ho et al Lancet Infectious Diseases January 2022

SPECIAL CONSIDERATIONS ON TST/IGRA DISCORDANCE

- Effect of TST cut off
- Special populations: PLHIV, TST converters
- Effect of intensity of exposure
- TST or IGRA to predict progression

Does the TST cut off improve discordance

TABLE 5 Agreement and discordance between tuberculin skin test (TST) reactions and interferon-γ release assays (IGRAs) at baseline

	TST ⩾5 mm	TST ⩾10 mm	TST ⩾15 mm
QFT-GIT (n=482)			
Positive TST and positive IGRA	307 (66)	293 (61)	257 (53)
Negative TST and negative IGRA	39 (7)	53 (19)	77 (16)
Positive TST and Negative IGRA	126 (26)	112 (23)	88 (18)
Negative TST and positive IGRA	10 (2)	24 (5)	60 (12)
Agreement %	71.8	71.8	69.3
Kappa (95% CI)	0.25 (0.18–0.31)	0.28 (0.20–0.36)	0.29 (0.20–0.37)
T-SPOT.TB (n=450)			
Positive TST and positive IGRA	259 (58)	249 (55)	221 (49)
Negative TST and negative IGRA	40 (9)	55 (12)	84 (19)
Positive TST and Negative IGRA	141 (31)	126 (28)	97 (22)
Negative TST and positive IGRA	10 (2)	20 (4)	48 (11)
Agreement %	66.4	67.8	67.8
Kappa (95% CI)	0.21 (0.14–0.28)	0.25 (0.16–0.33)	0.30 (0.21–0.39)

Data are presented as n (%), unless otherwise stated. QFT-GIT: QuantiFERON-TB Gold-In-Tube.

- HCW in South Africa
- TST/IGRA discordance unchanged when TST cut off > 5 mm or 15 mm
- No major change on % agreement
- Trade between sens/specificity

Adams et al, Eur Resp Journal, Feb 2015

EFFECT OF HIV IN DISCORDANCE

Table 2 Results of multinomial regression models for discordant TSPOT.TB and tuberculin skin test at baseline

Risk Factor	Positive TST and negative TSPOT.TB test result		Negative TST and positive TSPOT.TB test result	
	OR (95% CI) $N = 126$	Adjusted	OR (95% CI) $N = 20$	Adjusted
Older age, per each additional year	0.97 (0.95–0.99) **	0.97 (0.94–0.99)*	1.00 (0.96–1.04)	1.07 (1.01–1.13)*
Male gender	0.93 (0.58–1.50)	0.72 (0.43–1.21)	1.22 (0.45–3.29)	1.46 (0.45–4.75)
BCG Vaccination scar	1.42 (0.82–2.46)	1.92 (1.02–3.63) *	1.07 (0.34–3.32)	1.04 (0.26–4.17)
HIV Positive/reported as positive	1.03 (0.50–2.11)	0.88 (0.37–2.05)	4.72 (1.64–13.59) **	4.44 (1.14–17.27)*
Previous TB Treatment	0.88 (0.46–1.68)	1.02 (0.48–2.17)	3.00 (1.09–8.28)*	1.33 (0.35–5.10)
Symptom screen positive	1.05 (0.65–1.68)	1.03 (0.60–1.75)	2.95 (1.18–7.35) *	1.94 (0.64–5.86)
Years in healthcare	0.98 (0.96–1.0)	1.00 (0.97–1.03)	CI (0.88 - 0.99)*	0.92 (0.85–0.99)*
Home-care	0.32 (0.11–0.94) *	0.32 (0.10–0.95) *	1.74 (0.48–6.30)	0.63 (0.11–3.56)
Daily contact with TB patient	0.88 (0.45–1.71)	0.94 (0.45–1.98)	2.08 (0.27–16.09)	NC

- HCW in South Africa (N=595)
- TST/IGRA (Quantiferon, T spot)
- HIV independently associated with discordance
- TST-/Tspot positive

Adams et al, Eur Resp Journal, Feb 2015

EFFECT OF EXPOSURE ON TST IGRA DISCORDANCE

TABLE 2 Modified Mandalakas score, tuberculin skin test (TST)/interferon-γ release assay (IGRA) positivity and secondary tuberculosis (TB) cases among household contacts

Score	Household contacts	TST+	TST# diameter (mm)	QFT ≥0.35 UI·mL^{-1}	TB antigen nil	TB secondary cases (total)	TB incident cases
3	43 (5)	16/33 (48)	10 (0–14) 8.6±7.4 0–30	10/33 (30)	0.03 (0–0.4) 2.1±4.7 0–22	0	0
4	209 (23)	93/158 (59)	13 (2–16) 10.5±7.2 0–25	69/158 (44)	0.1 (0.0–2.13) 3.0±6.2 0–34	5 (2.4)	2 (1.0)
5	323 (36)	169/263 (64)	14 (5–17) 11.7±7.5 0–25	155/263 (60)	1.2 (0.0–8.9) 5.5±8.2 0–43	11 (3.5)	6 (1.9)
6	138 (15)	76/113 (67)	14 (6–18) 12.1±7.2 0–25	74/113 (65)	3.2 (0.1–10.0) 5.9±7.3 0–35	5 (3.7)	3 (2.2)
7	61 (7)	35/51 (69)	15 (6–18) 12.5±7.5 0–25	36/51 (71)	2.8 (0.1–10) 6.0±8.1 0–34	5 (8.3)	3 (4.9)
8	101 (11)	60/76 (80)	15 (11–19) 14.0±6.6 0–28	57/76 (75)	4.3 (0.3–9.7) 5.9±6.4 0–22	7 (7.1)	7 (7.0)
9	20 (2)	15/16 (94)	14 (12–18) 14.3±4.5 4–20	14/16 (88)	2.8 (0.8–9.1) 5.7±6.5 0–23	3 (15)	2 (10)
Total	894	492/710 (69)	14 (5–18) 11.7±7.3 0–30	418/710 (59)	1.02 (0.03–8.26) 4.9±7.3	36 (4)	23 (2.7)

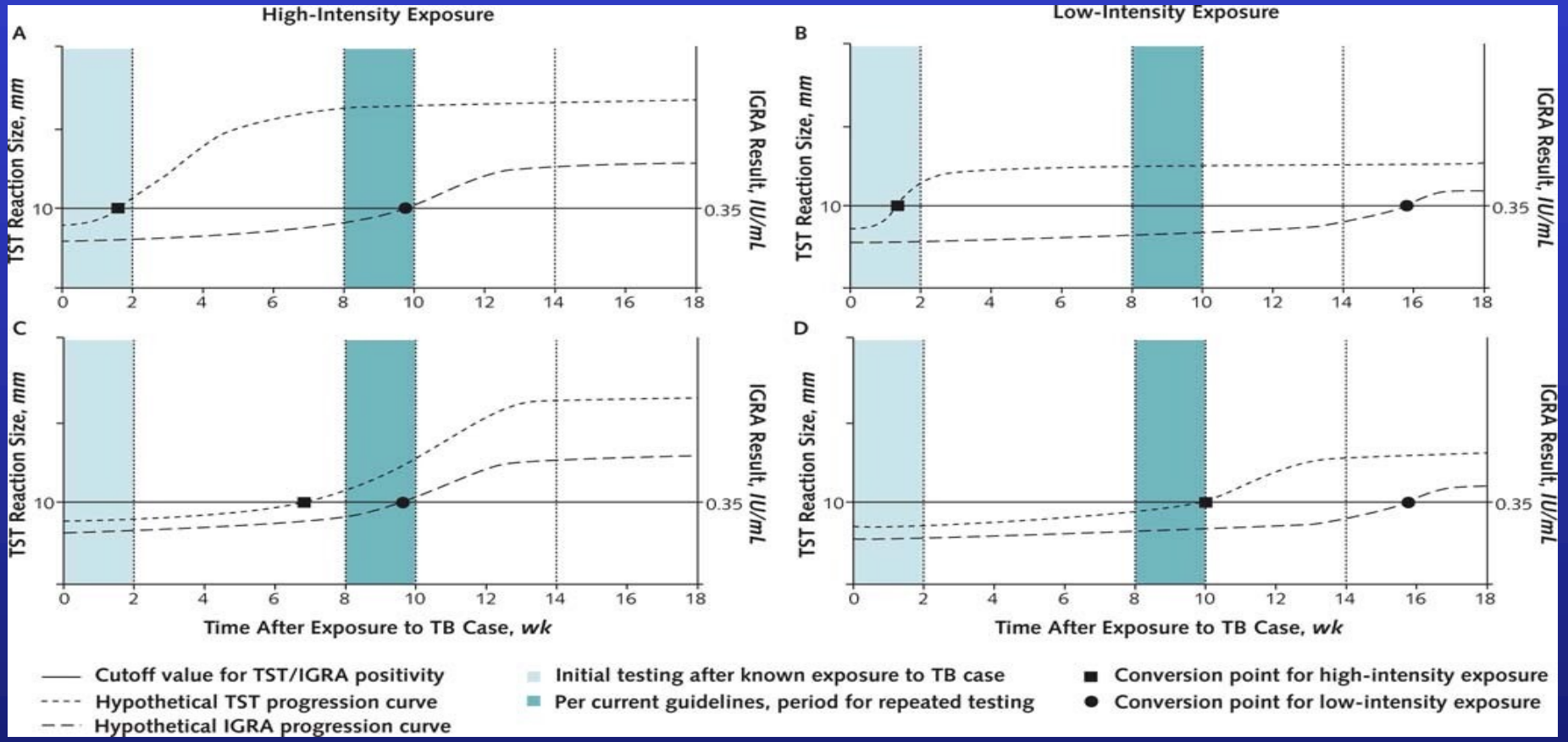
- Close contacts in Brazil
- TST/IGRA 8 weeks after exposure
- TST/IGRA concordance increased with more intense exposures
- TST diameters/IGRA readouts also increased

Acuna-Villaorduna et al, Eur Resp Journal, January 2018

EFFECT OF EXPOSURE ON TST IGRA DISCORDANCE

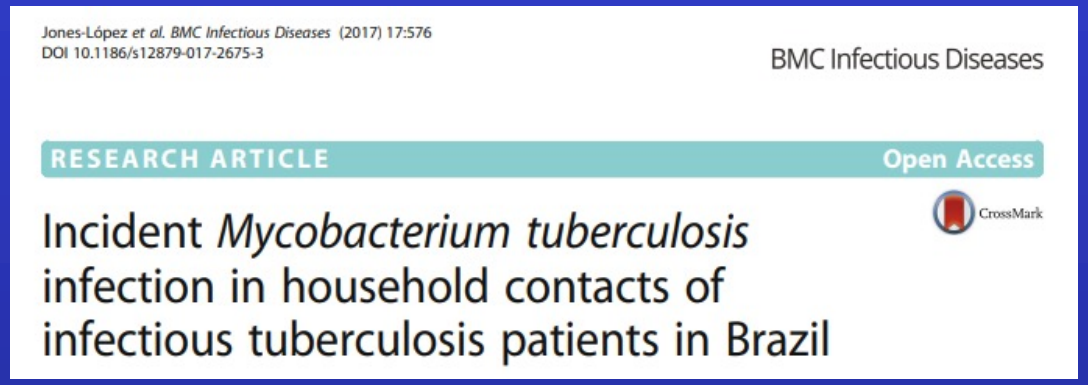
- Clear negative relationship between exposure and discordance
- Mainly driven by TST+/IGRA- in lower-level exposures
- TST more sensitive OR IGRA better marker of bacterial replication
- Higher risk of TB disease with more intense exposures

EFFECT OF INTENSITY OF EXPOSURE



Collins et al, Annals of Int Med, January 2016

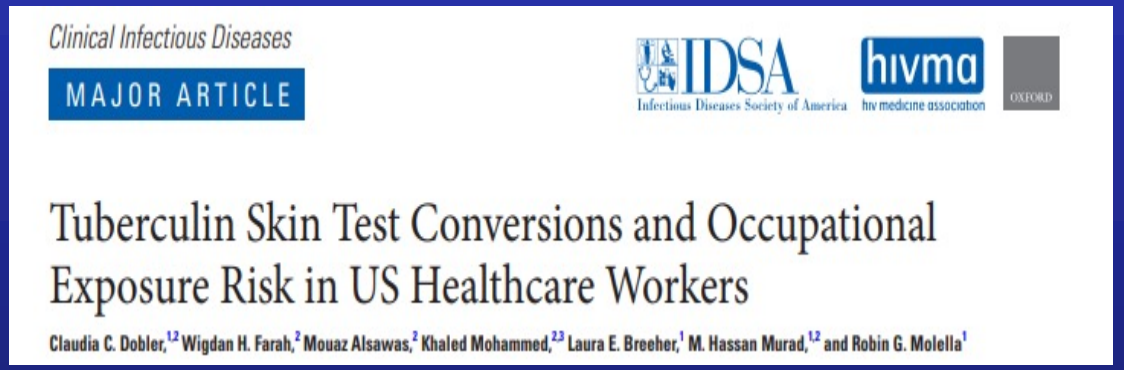
IGRA DISCORDANCE IN TST CONVERTERS


Jones-López *et al. BMC Infectious Diseases* (2017) 17:576
DOI 10.1186/s12879-017-2675-3

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Incident *Mycobacterium tuberculosis* infection in household contacts of infectious tuberculosis patients in Brazil


Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association

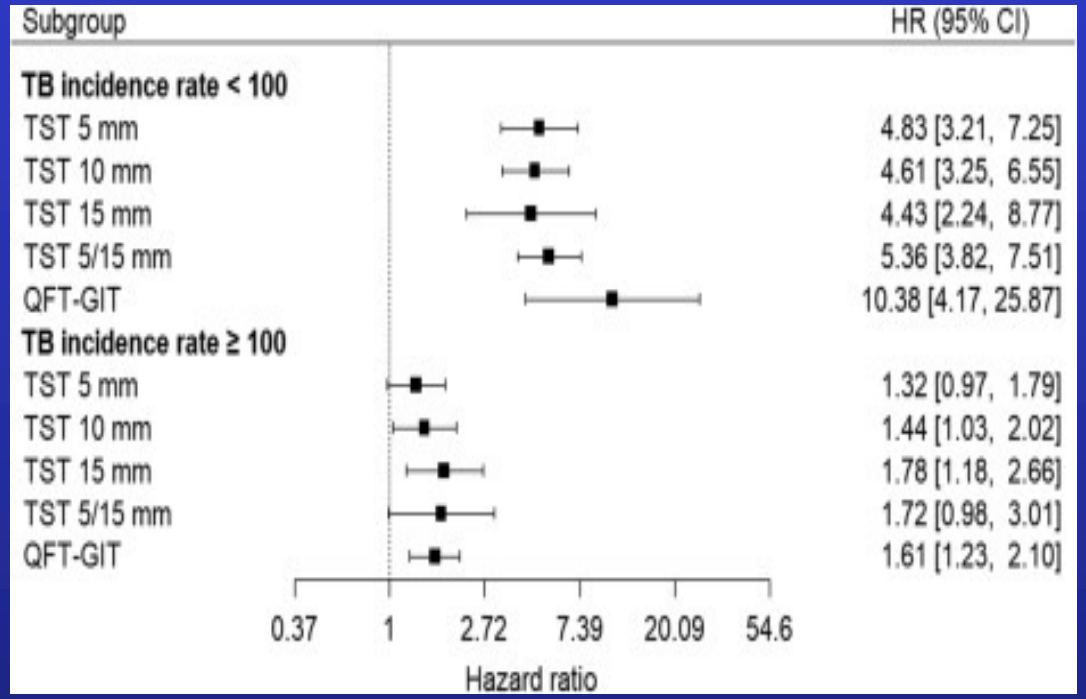
Tuberculin Skin Test Conversions and Occupational Exposure Risk in US Healthcare Workers

Claudia C. Dobler,[1,2] Wigdan H. Farah,[2] Mouaz Alsawas,[2] Khaled Mohammed,[2,3] Laura E. Breeher,[1] M. Hassan Murad,[1,2] and Robin G. Molella[1]

- **Brazil: Close contacts N = 838**
  TST converters N = 62 (7%)
  IGRA negative N = 18 (31%)

- **USA: HCW Mayo Clinic N = 40142**
  TST converters N = 123 (0.3%)
  IGRA negative N = 60/91 (66%)

Is IGRA better than TST to predict progression?



- IGRA slightly better than TST in low incidence settings
- IGRA equal to TST in high incidence settings.

Hamada et al; EClinical Medicine, January 2023

Case 1

- 45 yo M with HIV with CD4 250, VL <20 (on Biktarvy) and history of IVDU and numerous incarcerations. Numerous previous TSTs and T-spots have been negative.
- After his most recent incarceration, his T-spot was found to be positive. Unconvinced about the T-spot, he requested a TST which was negative (4mm).

What would you do?

a. Offer treatment for LTBI based on positive T-spot
b. Repeat T-spot assay in 12 months
c. Repeat TST in 12 months
d. No further testing needed

Case 2

- A US born nurse presents with a positive TST (10mm) on annual screening.
- Previous TSTs have been negative.
- She requested an IGRA for confirmation which was negative (TB1-Nil: 0.32; TB2-Nil: 0.26)

What would you do?

a. Offer treatment for LTBI based on positive TST
b. Obtain a T-spot assay as a tie breaker and treat for LTBI if positive
c. Repeat TST in 12 months and treat for LTBI if positive
d. Repeat IGRA in 3-6 months and treat for LTBI if positive

Case 3

- 78 years-old gentleman who immigrated to Boston from Haiti 35 years ago and has not left Massachusetts since then.
- As part of the screening process, an Quantiferon gold plus was done which was positive (TB1Ag-Nil 0.56; TB2Ag-Nil: 0.68) whereas a TST done 3 months previously was negative (4mm). No travel, hospitalization, or exposures since then.

What would you do?

a. Offer treatment for LTBI based on positive IGRA
b. Repeat TST and treat for LTBI if positive
c. Repeat IGRA in 3-6 months to see if still positive
d. No further testing or treatment necessary