

IGRAs in Children for the Detection of LTBI and Tuberculosis?

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Disclosure

- No shares of or fees from PPD or IGRA manufacturers
- No invitation to any of the three global symposia on IGRA by the sponsoring companies:
 - 21.02.-22.02.2007 Vancouver
 - 30.05.-01.06.2009 Dubrovnik
 - 12.01.-15.01.2012 Waikaloa, Hawaii
- Personalized attack from IGRA manufacturer subsequent to Nadal D. *CID* 2002 editorial

Evidence for IGRAs in Children?

- Children with microbiologically-confirmed TB disease – very few studies and low numbers of patients
- Children with clinically suspected TB disease
- Children identified as close contacts of TB cases
- Graduated risk in a contact investigation – e.g. schools

Use of TST or IGRA in children?

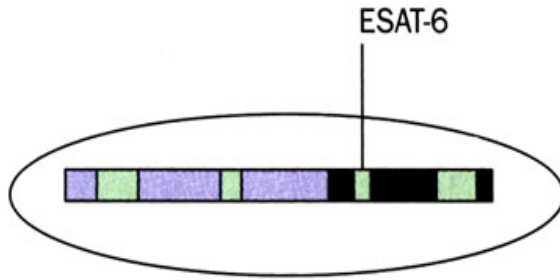
- Both tests have advantages and limitations, and they do not allow distinction active vs. latent TB
- IGRA may be more specific, but does cross-react in infections with non-tuberculous mycobacteria (NTM):
 - *Mycobacterium kansasii*
 - *Mycobacterium marinum*
 - *Mycobacterium szulgae*
 - *Mycobacterium flavescens*

Recommendation:

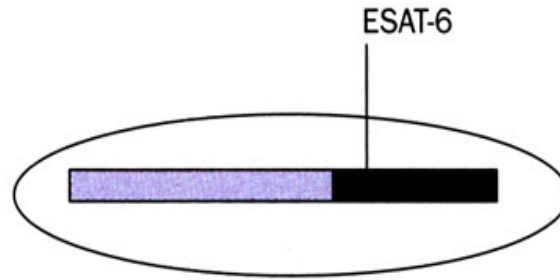
Diligent use of the tests, taking into consideration child's age, immune status, epidemiologic situation, and vaccination status

Vaccine (BCG) or NTM

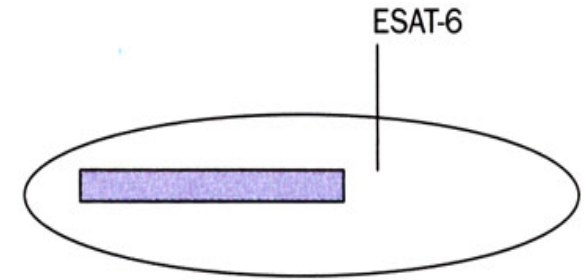
- Common mycobacterial genes
- Tuberculosis complex-specific genes
- Deleted region



M bovis BCG



M tuberculosis



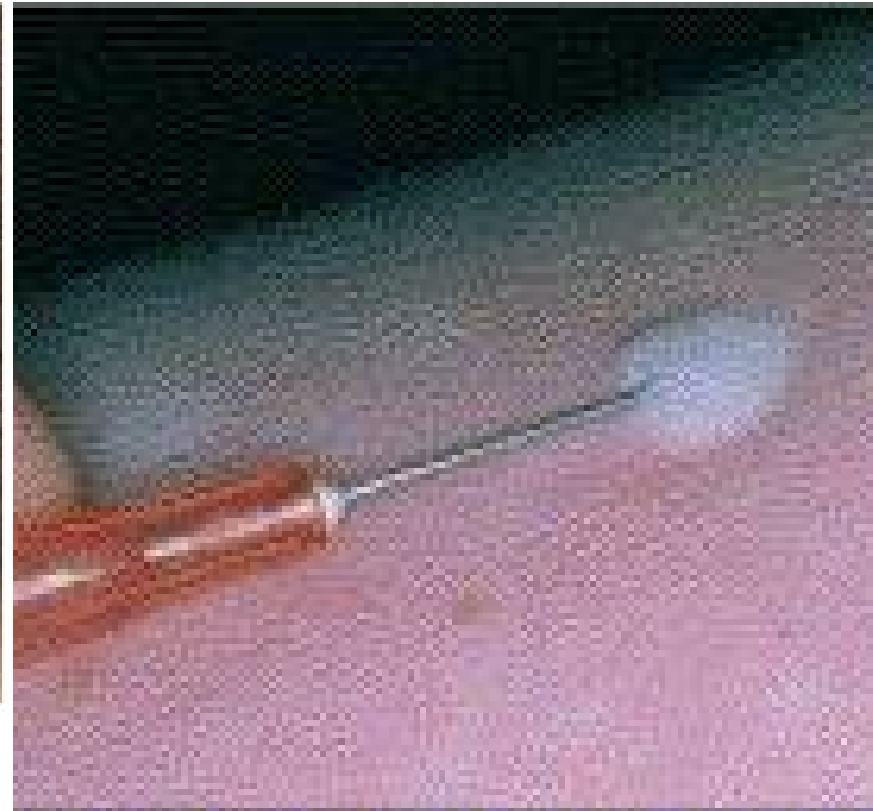
M avium



Albert Calmette
1863-1933



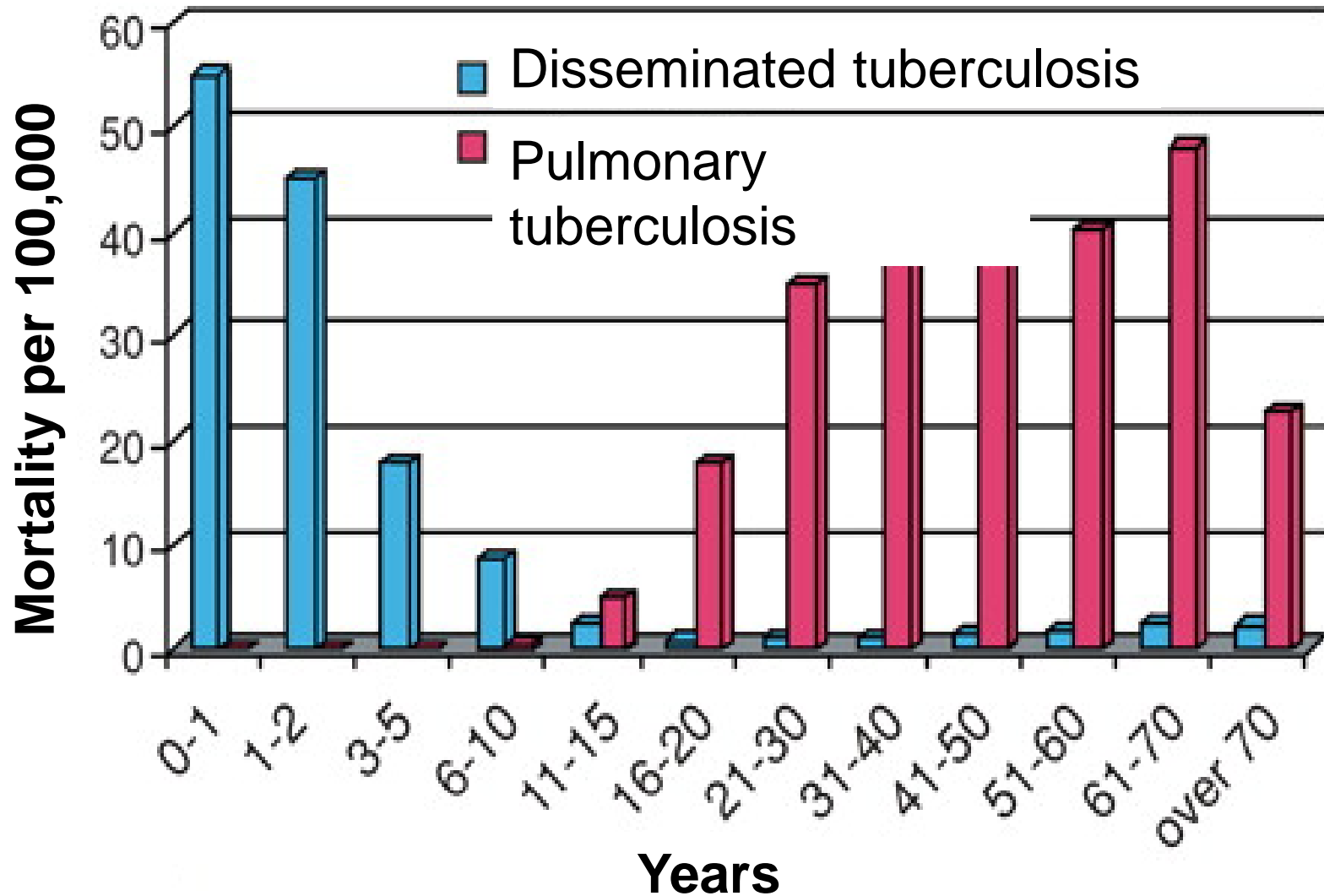
Camille Guérin
1872-1961



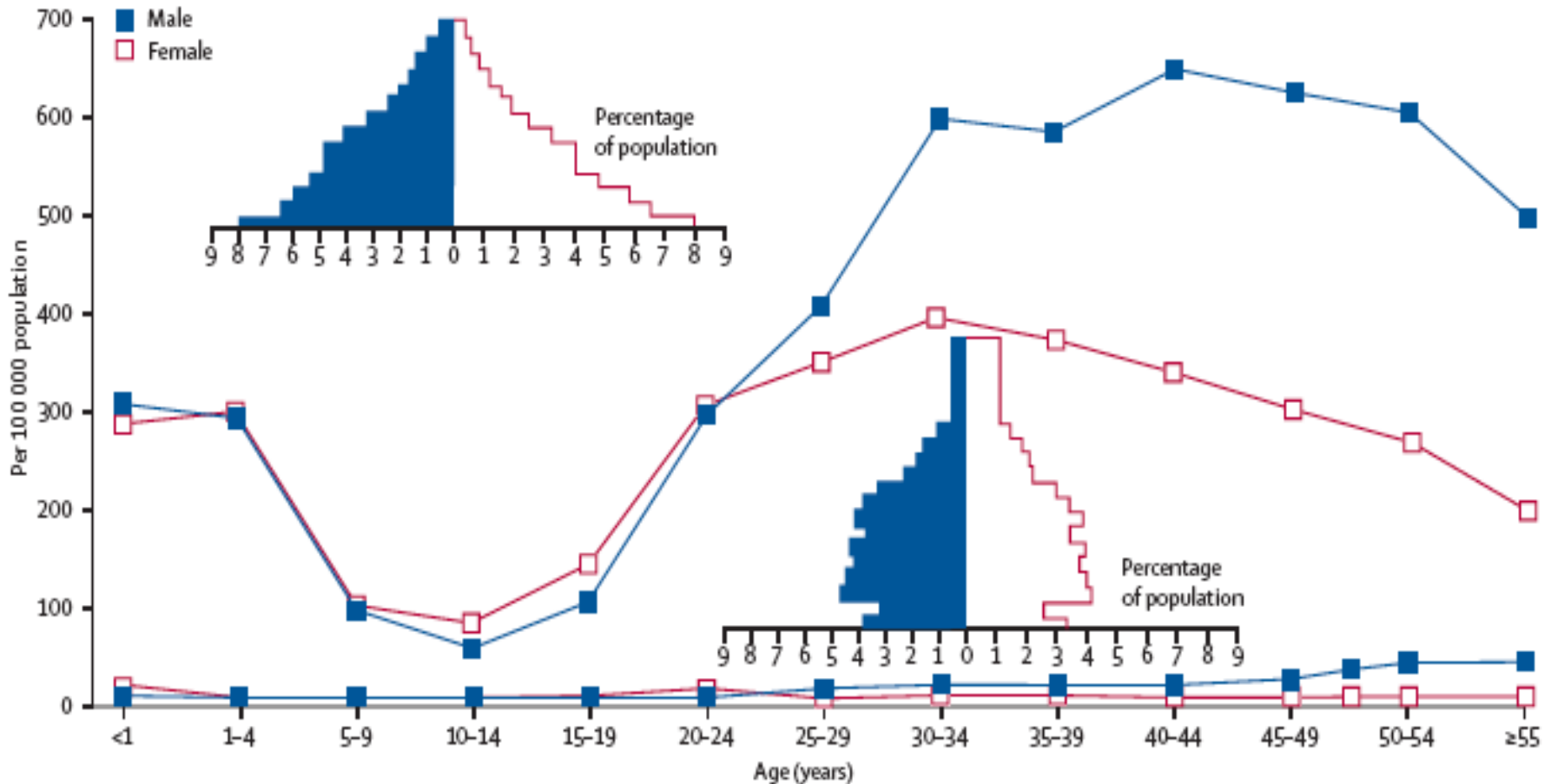
IGRAs: Advantages for Children

- Enhanced specificity: optimal for BCG-immunized persons and exposure to environmental non-tuberculous mycobacteria (NTM)
- Help differentiating TB vs. NTM disease
- Decreased confusion about interpretation: one cut-off irrespective of age, immune status, and tuberculosis risk factors
- One visit: optimal if adherence issues

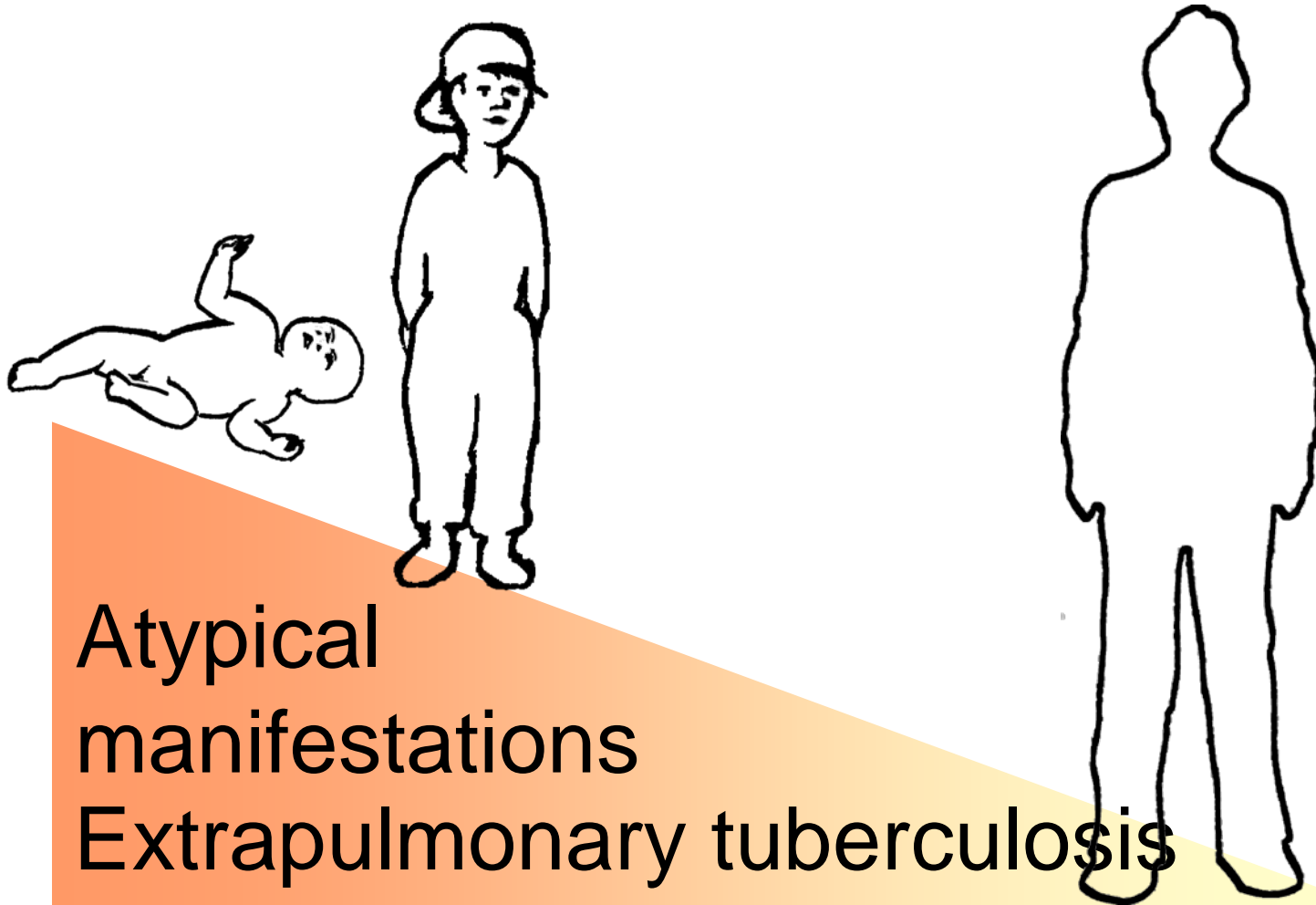
Mortality of Tuberculosis Disease in Relation to Age



Age-related and Sex-related Incidence of Tuberculosis

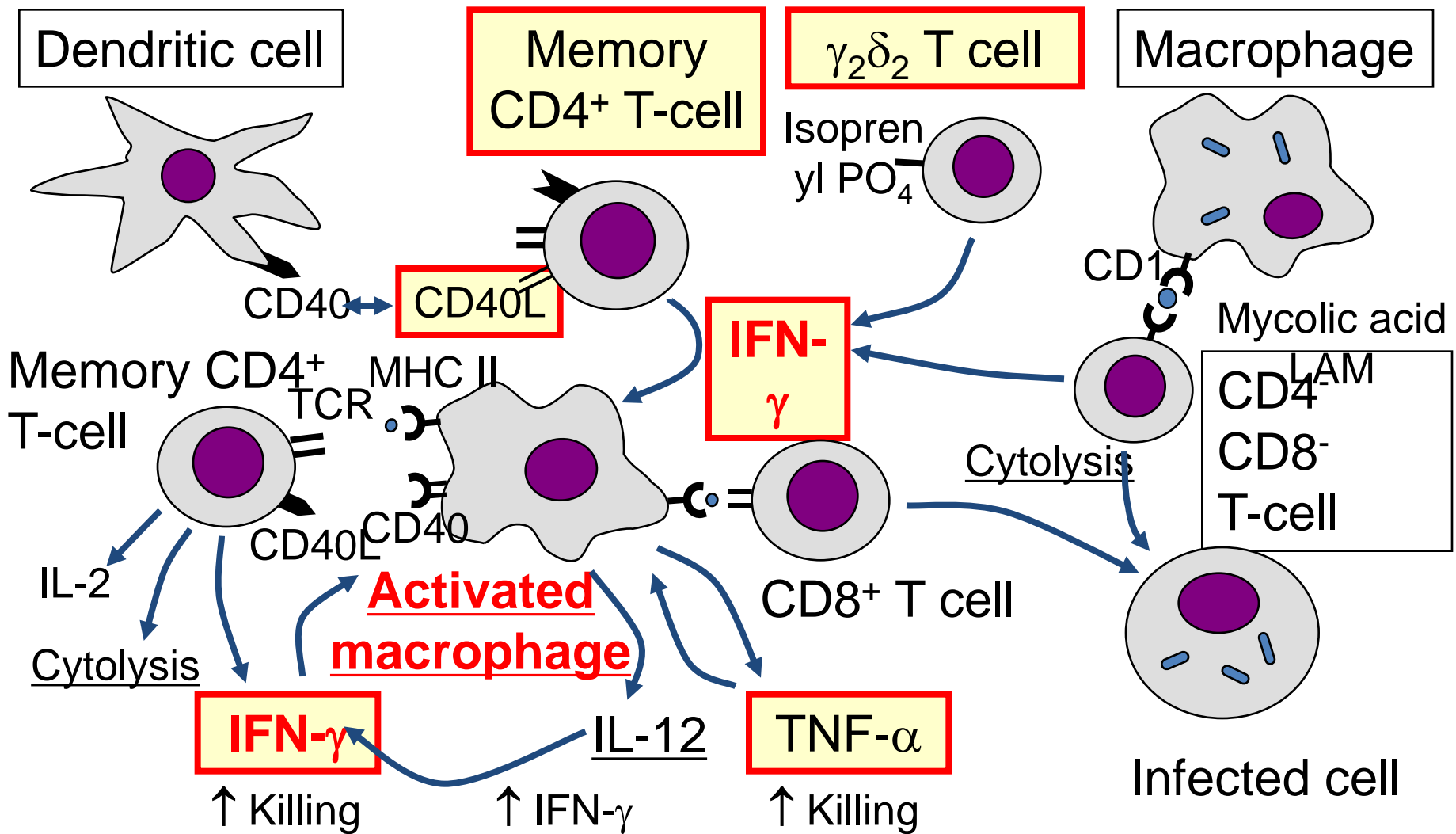


Tuberculosis Disease: Child versus Adult

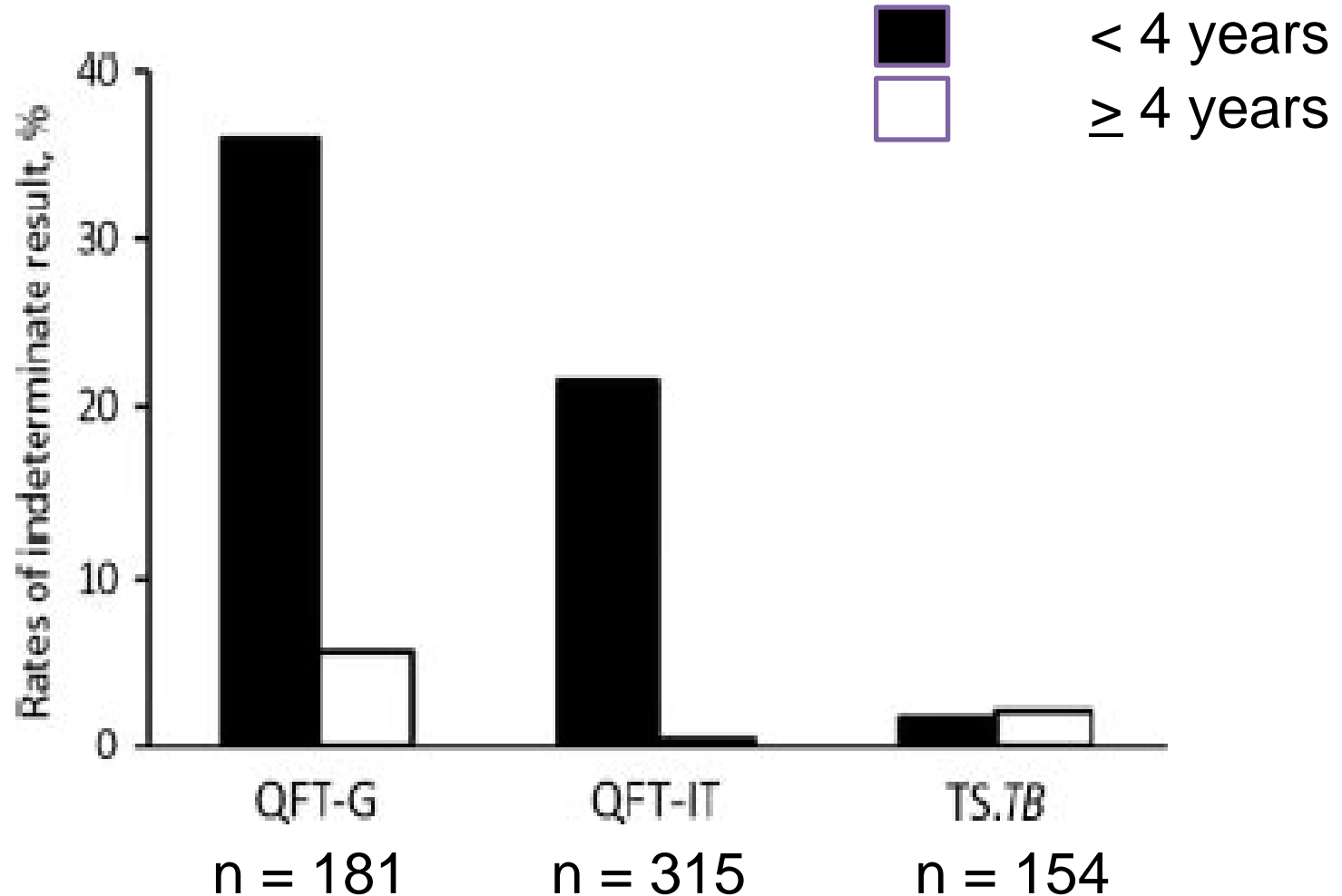


Atypical
manifestations
Extrapulmonary tuberculosis

Secondary Immune Responses: Lymphatic Tissue and Metastatic Foci



High Rate of Indeterminate Results of IGRA in Children < 4 Years of Age



Eur Respir J 2009; 33: 1374–1382
DOI: 10.1183/09031936.00153408
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Interferon- γ release assays do not identify more children with active tuberculosis than the tuberculin skin test

B. Kampmann, E. Whittaker, A. Williams, S. Walters, A. Gordon, N. Martinez-Alier, B. Williams, A.M. Crook, A-M. Hutton and S.T. Anderson

The Utility of an Interferon Gamma Release Assay for Diagnosis of Latent Tuberculosis Infection and Disease in Children

A Systematic Review and Meta-analysis

Shingai Machingaidze, BSc,† Charles Shey Wiysonge, MD,*† Yulieth Gonzalez-Angulo, BSc,*†
Mark Hatherill, MD,*† Sizulu Moyo, MB ChB, Willem Hanekom, FCP (Paed),*†
and Hassan Mahomed, MMed*†*

Pediatric Infectious Diseases Journal 2011;30:694-700

Conclusions: There was no clear evidence that IGRAs should replace TST for detecting LTBI in children. Sensitivity of the IGRA for TB disease was no different from TST, and a significantly reduced IGRA sensitivity was found in high-burden TB settings compared with low-burden TB settings. Further studies are needed to determine the value of IGRAs in LTBI and TB disease diagnosis in children.

IGRA: Limitations for Children

- Important pre-analytic obstacles (sampling, etc.)
- One cut-off irrespective of age, immune status, and TB risk factors
 - Is this appropriate across ages?
- Indeterminate results: decrease the utility of a screening tool
- Unknown dynamics of when assays become positive – “window” prophylaxis
- Discordance: interpretation if TST and IGRA provide different results
- Limited pediatric data: especially for the most vulnerable risk groups

TST preferred, IGRA acceptable

- Children < 5 years of age

IGRA preferred, TST acceptable:

- Children who have had BCG vaccine
- Children in a group with historically low rates of return for TST reading

Note: In Switzerland, routine BCG vaccination has been abandoned, and the vast majority of patients return for TST reading

Either TST or IGRA can be used

- Children identified in contact investigations

Nevertheless, in Switzerland a two-step approach using TST first is justified.

Both TST and IGRA should be considered for children when:

- The TST is positive and NTM disease is suspected
- The initial IGRA is indeterminate or borderline
- The initial test (TST or IGRA) is *negative* and:
 - Clinical suspicion for TB disease exists
 - Risk of infection, progression, and poor outcome are higher
- The initial test (TST or IGRA) is *positive* and:
 - Need additional evidence to increase compliance
 - Healthy with low risk for both infection and disease progression

What to do with discordant results between a TST and an IGRA?

- In patients in whom disease is suspected or at high risk for progression from infection, treat if any test positive
- For immunocompetent patients with low risk, treat if the more specific test is positive
- A positive TST and negative IGRA in a child with chronic lymphadenitis suggests NTM disease

Latent Tuberculosis Infection in the United States

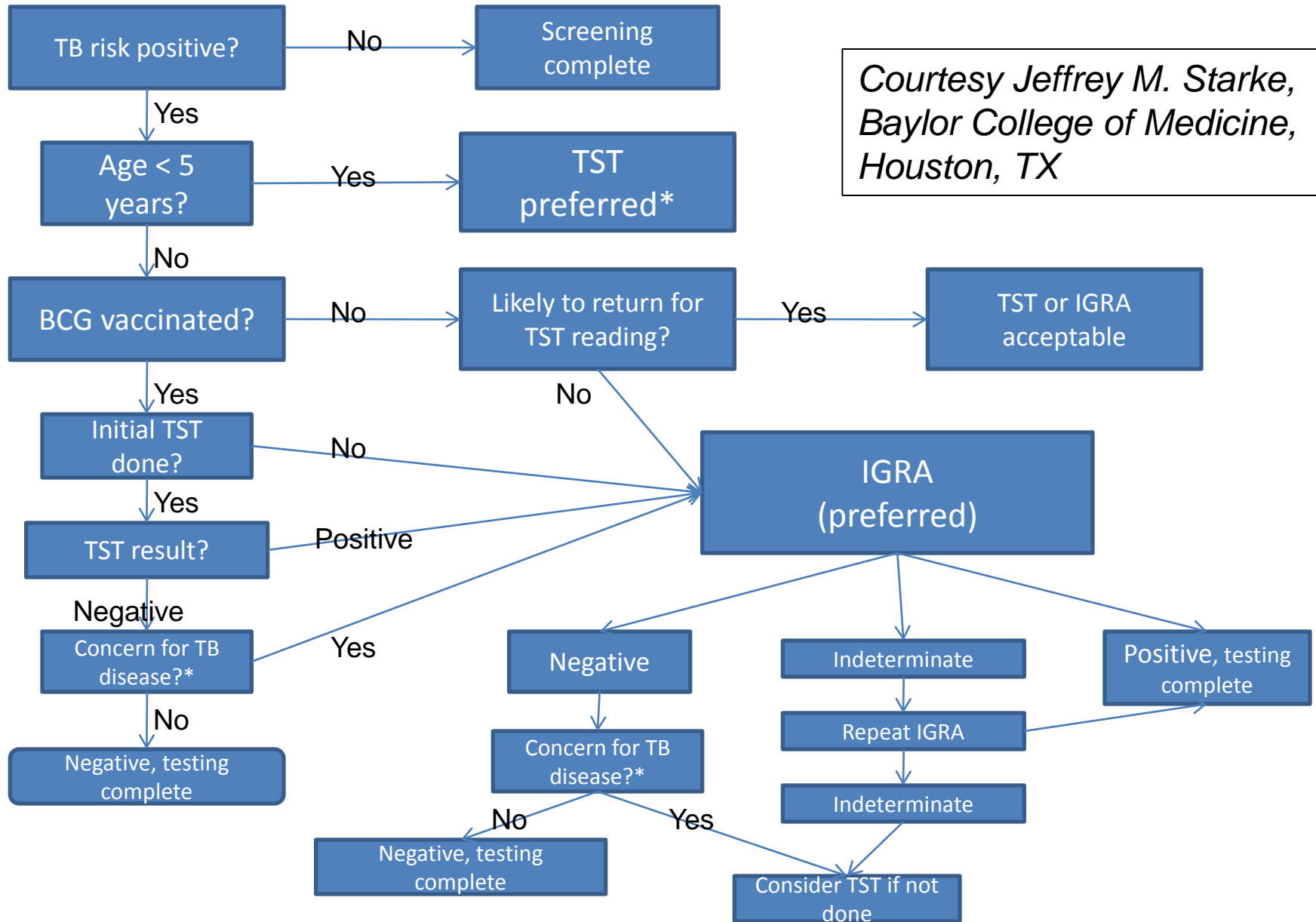
C. Robert Horsburgh, Jr., M.D., and Eric J. Rubin, M.D., Ph.D.

N Engl J Med 2011;364:1441-8

Table 4. Screening Guidelines from the United States, Canada, and the United Kingdom for Selected Groups at Risk for Latent Tuberculosis (TB) Infection.*

Risk Group	U.S. Guideline	Canadian Guideline	U.K. Guideline
Close contacts of persons with infectious TB	TST or IGRA, but not both	TST, with IGRA to confirm positive TST	TST, with IGRA to confirm positive TST
Persons who may not return for TST reading because of circumstances (e.g., homelessness or injection-drug use) or logistic difficulties	IGRA preferred	No specific recommendation	IGRA preferred
Immunosuppressed persons (e.g., those infected with HIV or receiving treatment with prednisone or TNF- α inhibitor)	TST or IGRA; use both if first is negative and suspicion is high	TST, followed by IGRA if TST is negative	TST or IGRA
Foreign-born persons	Screening only for those who have immigrated in past 5 yr; use TST or IGRA, but not both	Screening only for those <15 yr old who have immigrated in past 2 yr; use TST, with IGRA to confirm positive TST	Screening for new immigrants only; use TST with IGRA to confirm positive TST for those 5-15 yr of age and IGRA for those 16-35 yr of age
BCG vaccine recipients (if they belong to another risk group)	IGRA preferred	No specific recommendation	TST or IGRA
Health care workers (screening program)	TST or IGRA, but not both	TST preferred	TST or IGRA, depending on specific circumstances
Children <5 yr old	TST preferred	No specific recommendation	TST preferred
Other risk groups	TST or IGRA, but not both	TST, with IGRA to confirm positive TST	TST, with IGRA to confirm positive TST

Algorithm for TB Testing in Children



*Courtesy Jeffrey M. Starke,
Baylor College of Medicine,
Houston, TX*

*Either positive TST or IGRA considered significant if clinical suspicion of TB disease

Studies Comparing the Performance of IGRA vs. TST in Children

Author	Year*	Country	Sample Size	Age (yr)	Test Type	TB Burden	TST Cutoff (mm)	Overall Agreement Between TST and QFT (κ^{\dagger})
Okada et al ¹⁰	2008	Cambodia	195	<5	QFT-G	High	10	0.63
Hesseling et al ¹⁵	2007	South Africa	29	<5	QFT-G	High	10	0.78
Nakaoka et al ¹²	2006	Nigeria	207	<5	QFT-G IT	High	10	0.50
Dogra et al ¹¹	2006	India	105	1–12	QFT-G IT	High	10	0.73
Tsiouris et al ¹³	2006	South Africa	184	5–15	QFT-G IT	High	10	0.56
Lighter et al ⁶	2009	United States	207	<18	QFT-G	Low	10	0.17
Connell et al ¹⁸	2006	Australia	106	<18	QFT-G	Low	10	0.3
Dominguez et al ²⁵	2007	Spain	134	<18	QFT-G IT	Low	5	0.71
Bianchi et al ²⁰	2009	Italy	336	<16	QFT-G IT	Low	10	0.53
Haustein et al ²²	2009	United Kingdom	237	<16	QFT-G IT	Low	6	0.71
Bergamini et al ¹⁹	2009	Italy	496	<19	QFT-G	Low	10	0.35
Connell et al ¹⁶	2008	Australia	96	<19	QFT-G IT	Low	10	0.75
Nsutebu et al ²⁶	2008	United Kingdom	190	13–14	QFT-G	Low	—	—
Tavast et al ¹⁷	2009	Finland	99	<18	QFT-G IT	Low	10	0.86
Higuchi et al ²⁷	2009	Japan	61	8–12	QFT-2G	Low	10	—
Chun et al ²¹	2008	South Korea	227	<15	QFT-G IT	Low	5	0.53
Higuchi et al ²⁹	2009	Japan	313	<16	QFT-G	Low	—	—
Bramford et al ²⁴	2009	United Kingdom	333	<16	QFT-G IT	Low	15	0.54
Kampmann et al ²³	2009	United Kingdom	209	<16	QFT-G IT	Low	15	0.57
Hermann et al ²⁸	2009	France	131	<16	QFT-G IT	Low	10	—

*Year of publication.

[†] κ values between 0.61 and 0.80 imply good agreement (adapted from Landis and Kock, 1977¹⁴).

QFT indicates QuantiFERON; TST, tuberculin skin test; TB, tuberculosis; QFT-G, QuantiFERON Gold; QFT-G IT, QuantiFERON Gold In-Tube.

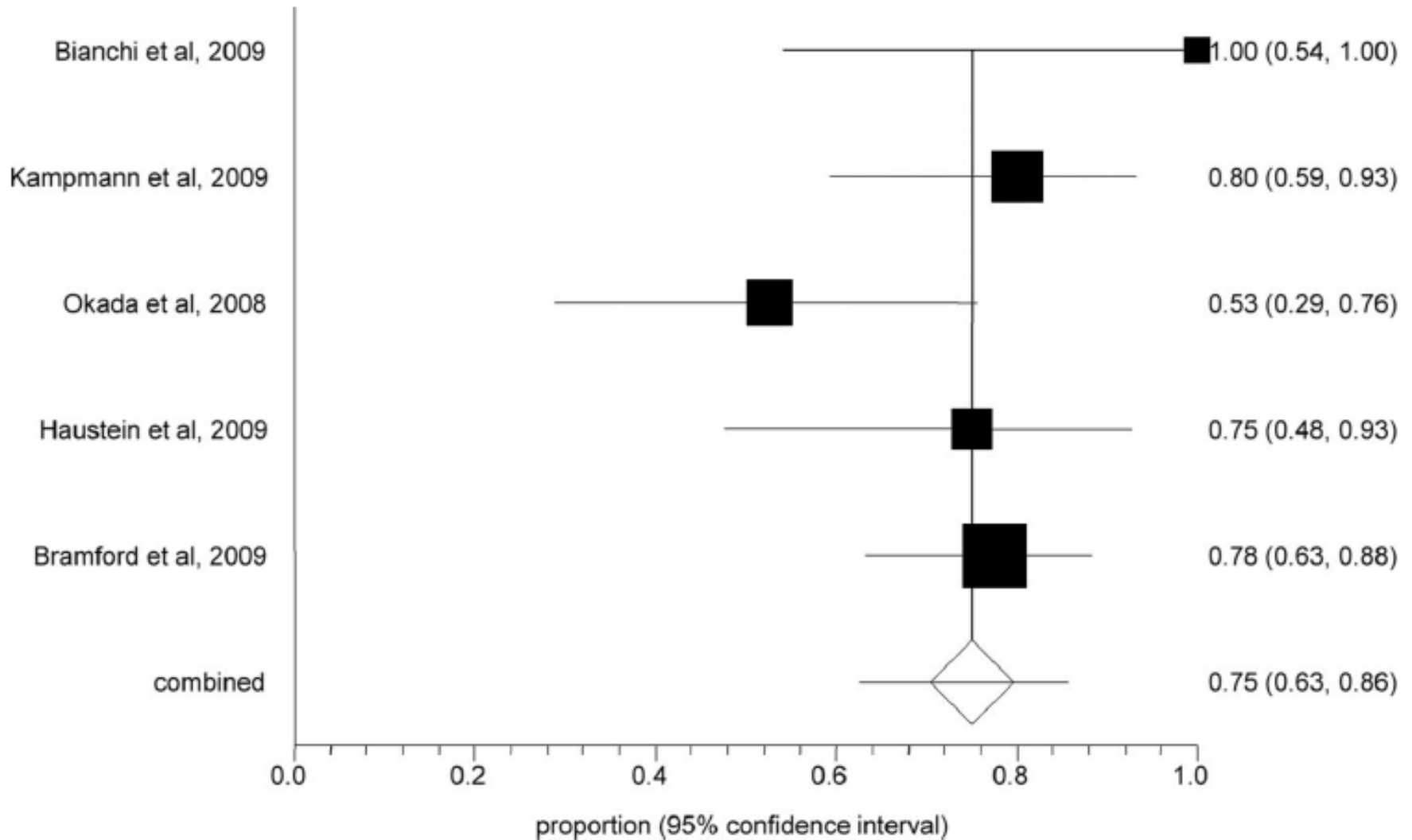
Studies Comparing Sensitivity of IGRAs vs. TST in Active TB in Children

Author, Year*	Test Type	TB Burden	Age (yr)	Sample Size	No. TB Cases	TST Cutoff (mm)	Sensitivity (%)	
							TST	QFT
Okada et al, ¹⁰ 2008	QFT-G	High	<5	195	19	10	79%	53%
Dogra et al, ¹¹ 2006	QFT-G IT	High	1–12	105	8	10	63%	63%
Bianchi et al, ²⁰ 2009	QFT-G IT	Low	<16	336	15	10	86%	94%
Haustein et al, ²² 2009	QFT-G IT	Low	<16	237	27	6	72%	78%
Bramford et al, ²⁴ 2009	QFT-G IT	Low	<16	333	195	15	55%	52%
Kampmann et al, ²³ 2009	QFT-G IT	Low	<16	209	63	15	60%	63%

*Year of publication.

QFT indicates QuantiFERON; TST, tuberculin skin test; TB, tuberculosis; QFT-G, QuantiFERON Gold; QFT-G IT, QuantiFERON Gold In-Tube.

Meta-analysis of IGRA Sensitivity for Dx of Active (Culture+) TB in Children



Meta-analysis of IGRA Sensitivity for Dx of Active (All Cases) TB in Children

