



TB Screening Tests and Their Use in TB Nurse Case Management

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Has the following disclosures to make:

- Consultant for Oak Therapeutics SBIR



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TB Infection Diagnosis Recommendations

Available Tools



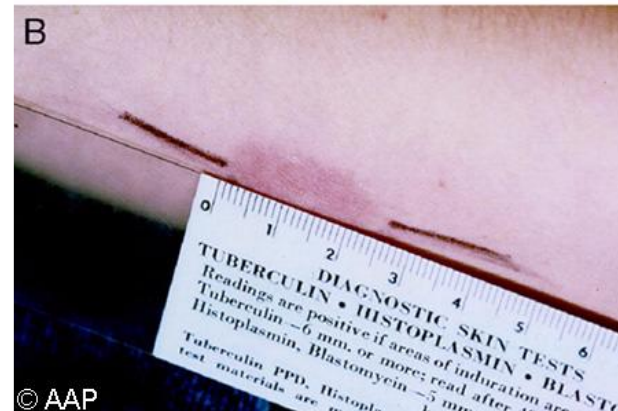
The Tuberculin Skin Test (TST)

- 0.1 ml of 5 TU PPD tuberculin injected intradermally
- Induration in millimeters read 48-72 hours after injection



Reading the TB Skin Test

Measure induration,
not erythema!!!



TB Skin Test (TST)

- Pros:

- Inexpensive
- Simple to perform
(if you know what you are doing)

- Cons:

- Must return in 48-72 hrs
- Interpretation is somewhat subjective
- False Negatives:
 - Elderly
 - Immunosuppressed
- False Positives:
 - Low risk populations
 - Non-tuberculous mycobacteria
 - BCG vaccination
- Boosting



Classifying the Tuberculin Reaction

- Requires that you know something about the patient
- 5 mm is classified as positive in High-Risk Individuals
 - HIV/Immune suppressed
 - Recent contact with a person with infectious TB
 - Persons with evidence of old disease
- 10 mm is positive in Persons in High-Risk Settings
 - Immigrants from countries with high rates of TB ($> 20/100K$) (Mexico 28/100K)
 - Residents/Employees of congregate settings
- 15 mm is positive.....period



Quick Detour.....

BCG

What does it do? Who does it protect?



Figure 2 BCG vaccination at birth and the risk of all tuberculosis, stratified by infection status and age

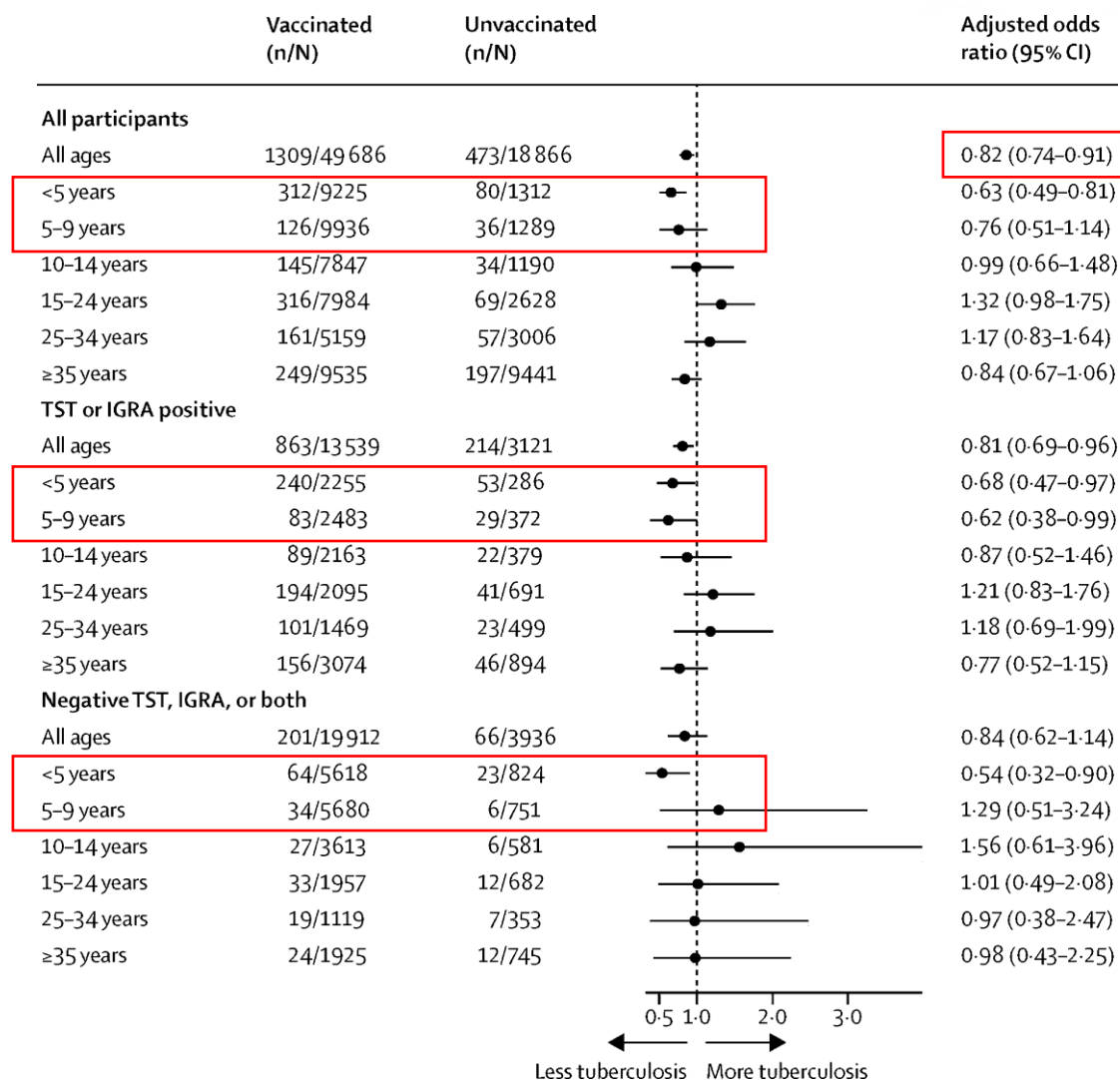
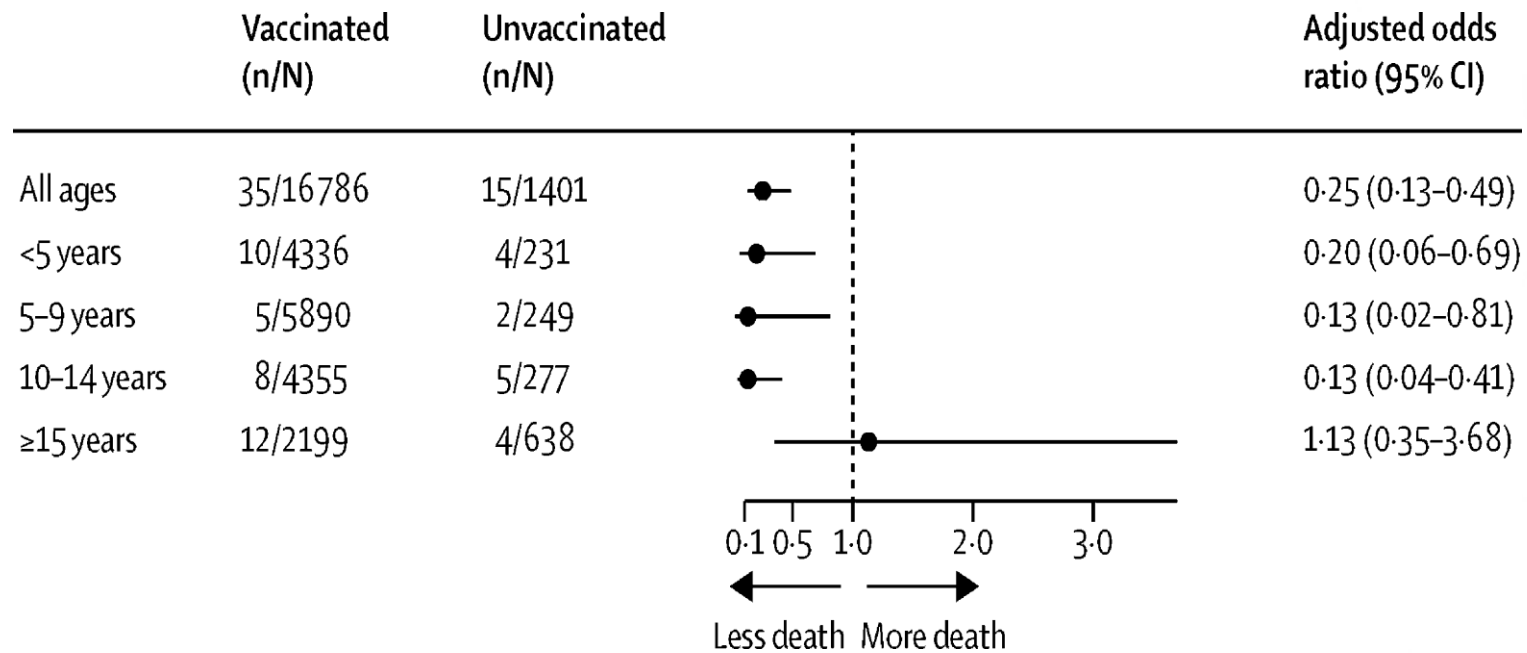


Figure 3 BCG vaccination at birth and the risk of death, stratified by age



RESEARCH ARTICLE

Tuberculosis Infection in the United States: Prevalence Estimates from the National Health and Nutrition Examination Survey, 2011-2012

Roque Miramontes*, Andrew N. Hill, Rachel S. Yelk Woodruff, Lauren A. Lambert, Thomas R. Navin, Kenneth G. Castro, Philip A. LoBue

Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America

- 9756 total participants
- 7821 age 6+
- 5421 foreign born
- 6064 with both TST and IGRA results

Table 6. Agreement between the Tuberculin Skin Test and Interferon Gamma Release Assay Test Results for Tuberculosis Infection in the Civilian, Noninstitutionalized U.S. Population, Ages 6+, 2011–2012.

	Overall Prevalence,%	U.S.-born Prevalence,%	Foreign-born Prevalence,%
TST Positive/IGRA Positive	2.1	0.6	9.3
TST Positive/IGRA Negative	2.6	0.9	11.2
TST Negative/IGRA Positive	2.9	2.2	6.6
TST Negative/IGRA Negative	92.4	96.3	72.9

} ~20%

doi:10.1371/journal.pone.0140881.t006

Miramontes R, Hill AN, Yelk Woodruff RS, Lambert LA, Navin TR, et al. (2015) Tuberculosis Infection in the United States: Prevalence Estimates from the National Health and Nutrition Examination Survey, 2011-2012. PLOS ONE 10(11): e0140881.

<https://doi.org/10.1371/journal.pone.0140881>

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0140881>

Antigens for Newer Generation IGRAs

- Negative control or nil (e.g., saline, heparin)
- Positive control or mitogen:
 - non-specific immune response stimulator (e.g., phytohemagglutinin)
- *M. tuberculosis*-specific antigens
 - Unlike PPD used in TST, do not cross-react with BCG or NTM (some exceptions)
 - ESAT-6, CFP-10 (actually simulated using overlapping peptides)



QuantiFERON[®]-TB Gold Plus



	Mitogen – Positive Control Low response may indicate inability to generate IFN- γ
	Nil – Negative Control Adjusts for background IFN- γ
	TB1 – Primarily detects CD4 T cell response
	TB2 – Optimized for detection of CD4 and CD8 T cell responses



- Essentially 2 tests in one blood draw
- TB1 and TB2 should be close in value

Antigens for Gamma-Release Assays

Tuberculosis complex	Antigens		Environmental strains	Antigens	
	ESAT	CFP		ESAT	CFP
M tuberculosis	+	+	M abcessus	-	-
M africanum	+	+	M avium	-	-
M bovis	+	+	M branderi	-	-
BCG substrain			M celatum	-	-
gothenburg	-	-	M chelonae	-	-
moreau	-	-	M fortuitum	-	-
tice	-	-	M gordonii	-	-
tokyo	-	-	M intracellulare	-	-
danish	-	-	M kansasii	+	+
glaxo	-	-	M malmoense	-	-
montreal	-	-	M marinum	+	+
pasteur	-	-	M oenavense	-	-
			M scrofulaceum	-	-
			M smegmatis	-	-
			M szulgai	+	+
			M terrae	-	-
			M xenopi	-	-



Interpretation Criteria for the QFT-GIT Test

Nil (IU/mL)	TB Antigen minus Nil (IU/mL)	QFT-GIT (IU/mL)	Mitogen	Interpretation
≤ 8.0	≤ 0.35 or $< 25\%$ of Nil value	Negative	≥ 5.0	<i>M. tuberculosis</i> infection unlikely
≤ 8.0	≥ 0.35 and $\geq 25\%$ of Nil value	Positive	ANY	<i>M. tuberculosis</i> infection likely
≥ 8.0	ANY	Indeterminate	ANY	Indeterminate
≤ 8.0	≤ 0.35 and or $< 25\%$ of Nil value	Indeterminate	< 5.0	Indeterminate



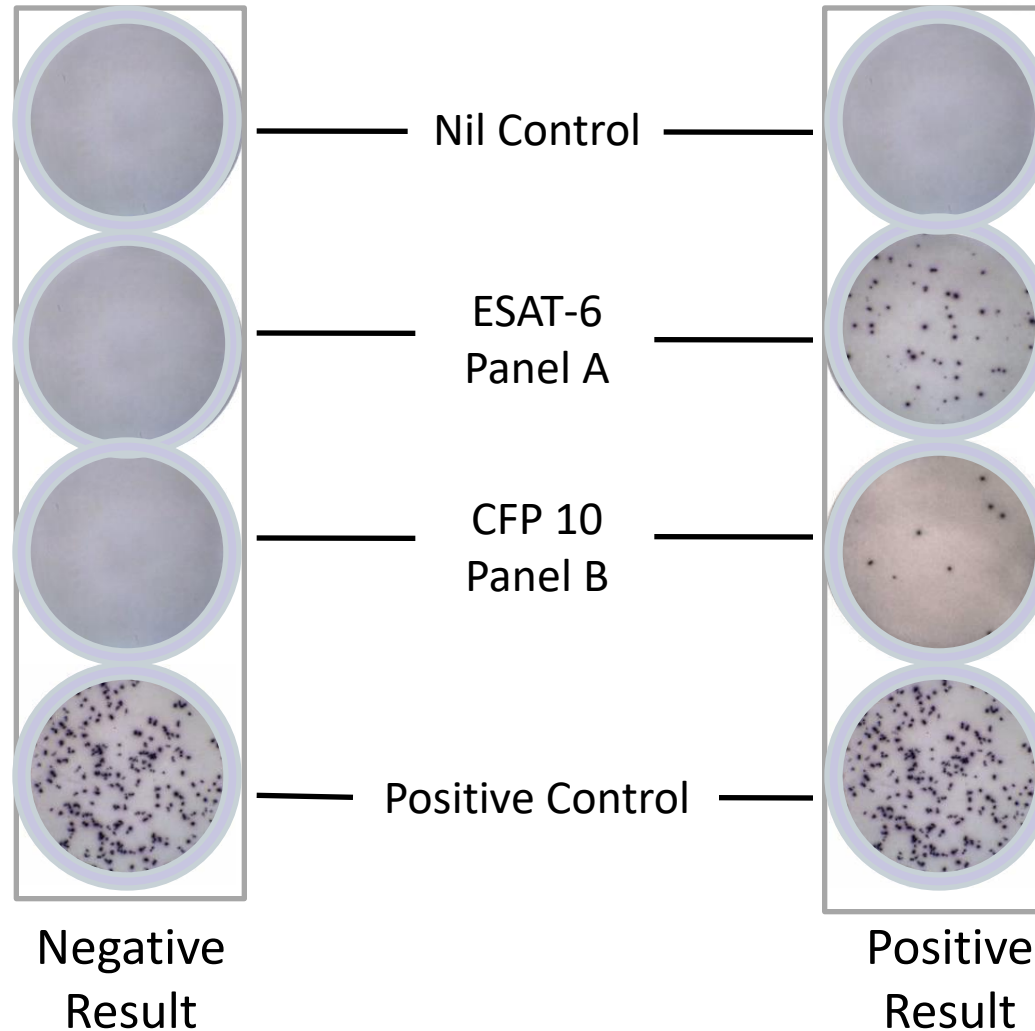
QuantiFERON-TB Gold

TABLE 2. TEST SENSITIVITY AND SPECIFICITY FOR CFP-10 AND ESAT-6 AT VARIOUS CUTOFFS IN WHOLE-BLOOD IFN- γ ASSAY

Cutoff, IFN- γ (IU/ml)	CFP-10		ESAT-6		CFP-10 and/or ESAT-6	
	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)
0.05	92.5	81.4	94.8	94.9	89.4	97.5
0.10	94.4	77.1	96.2	90.7	92.0	95.8
0.15	95.8	72.9	97.6	88.1	93.9	93.2
0.20	96.7	71.2	99.1	86.4	96.2	91.5
0.25	97.2	67.8	99.1	84.7	96.7	91.5
0.30	97.7	66.9	99.1	83.1	97.2	89.8
0.35	98.6	65.3	99.5	81.4	98.1	89.0
0.40	98.6	61.9	99.5	79.7	98.1	88.1
0.45	98.6	60.2	100.0	78.8	98.6	86.4
0.50	99.1	60.2	100.0	75.4	99.1	83.9

Sensitivity was determined on the basis of data from 118 patients with culture-positive tuberculosis, and specificity was determined on the basis of data from 213 low-risk subjects. The chosen cutoff (0.35) is in boldface.

Interpretation of Results



Interpretation Criteria for the T-Spot.TB

Result	Nil*	TB Response# #	Mitogen++	Interpretation+
Positive	≤ 10 spots	≥ 8 spots	Any	<i>M.tuberculosis</i> infection likely
Borderline	≤ 10 spots	5, 6, or 7 spots	Any	Uncertain likelihood of <i>M. tuberculosis</i> infection
Negative	≤ 10 spots	≤ 4 spots		M Tb infection unlikely
Indeterminate	> 10 ≤ 10	Any < 5 spots	Any < 20 spots	Uncertain likelihood of <i>M. tuberculosis</i> infection



Indeterminate and Borderline Results

- Indeterminate

- Negative control result is too high
 - High background production of IFN- γ
- Positive control result is too low
 - Immunocompromised patients may not respond to mitogen

- Borderline (T-Spot only)

- Falls within borderline zone close to negative/positive cut point



IGRA Boosting and Special Considerations

- IGRA boosting by prior TST has been observed in as little as 3 days post-TST and may wane over several months
- If both tests are to be used, do the IGRA first
- Because the IGRAs are a functional assessment of viable lymphocytes, special attention should be paid to technical aspects of the test (how blood is drawn/stored, etc.)



TB Testing Take Homes

- TST expertise is fading fast
 - When can I still use it?
 - If you trust the person placing/reading it knows what they are doing
 - US born
 - No history of BCG
 - To add sensitivity
 - Repeatedly indeterminate or borderline IGRAs
- IGRAs are becoming the preferred screening tests for TB
 - Single visit
 - Objective result (positive or negative.....ish)
- TB screening tests are tools that add to the answer
 - They are not the answer themselves
 - They do not distinguish between TB infection (LTBI) and TB disease



Clinical Infectious Diseases

IDSA GUIDELINE



Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children

David M. Lewinsohn,^{1,a} Michael K. Leonard,^{2,a} Philip A. LoBue,^{3,a} David L. Cohn,⁴ Charles L. Daley,⁵ Ed Desmond,⁶ Joseph Keane,⁷ Deborah A. Lewinsohn,¹ Ann M. Loeffler,⁸ Gerald H. Mazurek,³ Richard J. O'Brien,⁹ Madhukar Pai,¹⁰ Luca Richeldi,¹¹ Max Salfinger,¹² Thomas M. Shinnick,³ Timothy R. Sterling,¹³ David M. Warshauer,¹⁴ and Gail L. Woods¹⁵

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ATS/IDSA/CDC

Clinical Practice Guidelines: Diagnosis of TB in Adults and Children

- **Recommend** IGRA rather than TST for persons ≥ 5

- 1) **likely** to be infected with MTB
- 2) **low or intermediate risk** of progression to disease
- 3) decided testing is warranted and
- 4) *have either a history of BCG or are unlikely to return for reading*

(**Strong** recommendation, moderate quality evidence)

TST acceptable if IGRA not available, too costly, too burdensome.



ATS/IDSA/CDC

Clinical Practice Guidelines: Diagnosis of TB in Adults and Children

- **Suggest** IGRA rather than TST for all other persons ≥ 5 :

- 1) **likely** to be infected with MTB
- 2) **low or intermediate risk** of progression to disease
- 3) decided testing is warranted

(**Conditional recommendation, moderate quality evidence**)

TST acceptable if IGRA not available, too costly, too burdensome.



ATS/IDSA/CDC

Clinical Practice Guidelines: Diagnosis of TB in Adults and Children

Guidelines **recommend** persons at **low risk** for MTB infection and disease progression NOT be tested.

- If testing is performed in those unlikely to be infected despite guidelines to contrary:
 - We **suggest performing an IGRA instead of a TST.**
 - *(conditional recommendation, very low-quality evidence)*
 - We **suggest a 2nd diagnostic test if initial test positive**
 - Confirmatory test may be either IGRA or TST
 - Person **considered infected only if both tests positive.**
 - *(conditional recommendation, very low-quality evidence)*



ATS/IDSA/CDC

Clinical Practice Guidelines: Diagnosis of TB in Adults and Children

- 
- **Insufficient data to recommend a preference either a TST or IGRA** for all other persons ≥ 5 :
 - 1) **likely** to be infected with MTB
 - 2) have a **high risk** of progression to disease
 - 3) decided testing is warranted

**May want to consider both tests*

ATS/IDSA/CDC

Clinical Practice Guidelines: Diagnosis of TB in Adults and Children

- 
- **Suggest** performing a TST rather than an IGRA in healthy children under 5:
 - 1) for whom it has been decided testing is warranted
 - *(conditional recommendation, very low-quality evidence)*

New 2024 version of Pediatric Red Book
recommends IGRA at any age you use a TST

Pediatric Considerations for TB Screening

- Young immune systems, like young bodies, are growing
- By the time you have 5 candles on your birthday cake, your immune system behaves like an adult's
- There is grey area in children < 6 months of age (any test....every test), treat any positive and some negatives
- Drawing blood in a small child can present challenges
- We overtreat and we are not sorry



TB Testing in Pregnant Persons

- Test in every instance you would test if they were not pregnant
 - HIV
 - Contact to an active case
 - Immigrant from a high-risk country
- The immune system may not react as expected
- Yes, you can/should get a CXR



Immune Suppression

- Individuals with immune suppression who have significant contact with an infectious person should have
 - A CXR
 - A physical exam
 - A TST or IGRA
- IGRAs are dependent on T-cell function. This can be impaired by HIV or other biologics. The tests may not work!



IGRA/TST do not.....

- Do not always test positive if a patient is infected. These tests may not be accurate in patients with HIV, who are very young, who are on biologics or who are pregnant
- Do not necessarily revert to negative when patients are adequately treated. Patients may have a positive screening test for life.
- Do not change with treatment reliably enough to use it to follow treatment success



Conclusions

- IGRA and TST are a tool not an answer. There are gaps in current TB screening test coverage
- Knowledge about potential for exposure is important. Take a good history! If the test does not match the patient, repeat the test.
- Better tests are needed and are being investigated



Questions?

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