A 100 year update on diagnosis of latent tuberculosis infection – From TST to IGRA

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Rambam Health Care Campus
Tuberculosis – WHO Global Emergency

• Third of the world population (~2 billion people) is infected with latent TB
• 9 million cases of active TB in 2011
• 1.4 million deaths in 2011
• TB death rate has fallen by 41% between 1990 and 2011
מקורי שדافت לפס מואזא ישראל 1999-2011

% מוניות אחות
מגניצים לנשים
נשים מביאות לשלבי
נשים מתאימים
ילידי ישראל
ילדי מבוגרים

_department of TB & AIDS, MOH, Jerusalem
Active and latent tuberculosis

TB patient → Exposed contact (65%)

Exposed contact → TST- (35%)

TST- → TST+ (10%)

TB patient → TB (10%)
Active and latent tuberculosis

Exposure to a person with active TB

Insufficient exposure for MTB to become established. All MTB then cleared.

Person becomes infected

- No symptoms, but MTB still present but cannot be detected
- Chest X-ray/CT scan can be normal
- No antibody response
- Diagnosis difficult
- Historically the only detection method has been the TST

Sub-clinical infection controlled by T cells

5%

Symptomatic disease. Subjects are infectious.

- Pathogen may be detected using smear, culture or PCR
- Chest X-ray or CT may be abnormal
- Complicated in non-pulmonary TB (especially children)

Infection present until death

LATENT TB

Reactivation

5%

ACTIVE TB
WHO recommendations in low incidence countries

The most important additional elements of a more aggressive approach are:

1. Ensuring early detection of tuberculosis disease and treating until cured to prevent avoidable death and onward transmission.

2. Reducing the incidence of Latent TB infection by testing and treating:
   1. Groups with high risk of converting to active disease
   2. In institutional settings to prevent TB outbreaks
   3. Friends and family of index cases (contact tracing)
TB or not TB –
Current diagnostic test for latent TB

Tuberculin Skin Test (TST)
aka PPD or Mantoux

The skin test enters its 6th decade of use. (Canada 1957)
1890 - Robert Koch (isolated *M. tuberculosis* in 1882) announced at a medical congress in Berlin that he had developed a substance capable of preventing the growth of the bacterium. He called this substance *Tuberculin*, while keeping its formulary secret.

January 1891 - Rudolf Virchow published negative findings about tuberculin.

At the same time, 50 years old Koch divorcing to marry his teenaged mistress, an actress named Hedwig Freiberg.
Tuberculin Skin Test History

• Koch noticed that tuberculin injected into the skin produced a reaction spot within 48 hours in subjects who previously had tuberculosis.

• 1906 - Clemens von Pirquet, (a Viennese pediatrician and a former assistant of Theodor Escherich) noticed that patients who had received injections of horse serum usually had quicker, more severe reactions to second injections (and coined the term “Allergy”).

• 1907 – Von Pirquet report that a drop of tuberculin applied subcutaneously can serve as a test for tuberculosis.
Tuberculin Skin Test History

• 1908 - Felix Mendel in Germany and Charles Mantoux in France began inoculating tuberculin intradermal, which produced a more reliable reaction and became the preferred method.

• 1910 - Robert Koch passed away

• 1929 - Von Pirquet (though nominated five times for the tuberculin test, never won the Nobel) and his wife committed suicide using cyanide.

• 1932 - American biochemistry Florence Seibert purified tuberculin by ammonium sulfate precipitation obtaining a purified protein derivative - PPD.
Tuberculin skin test limitations

- Low sensitivity, especially in immunosuppressed, young and elderly
- Poor specificity due to:
  - Prior BCG vaccination
  - Environmental mycobacteria
- Requires a return visit for reading
- Inoculation and reading are technique-dependent
- Can cause painful inflammation & scarring

- On the other hand: Very cheap and no Lab is needed
Interferon-γ release assays

PPD
ESAT-6/CFP-10/TB7.7

antigens/peptides

APC

T cell

cytokine induction

Skin test

ELISA

QuantiFERON TB gold

ELISPOT assay

T.SPOT.TB
In-Vitro Interferon Gamma Release Assays (IGRAs) for TB

- QuantiFERON® TB Gold (QFT-G), Cellestis 2005
- QuantiFERON® In-Tube (QFT-IT), Cellestis 2007
- T-Spot TB™, Oxford Immunotec, 2008
**M. tuberculosis** specific antigens

- ESAT-6: 6 kDa early secretory antigenic target
- CFP-10: 10 kDa culture filtrate protein

RD-1 encodes
ESAT-6 and CFP-10

RD-1 present in
- *M. tuberculosis*
- *M. bovis*
- *M. kansasii*
- *M. marinum*
- *M. szulgai*
- *M. riyadhense*

RD-1 deletion in
- *M. bovis BCG*
- atypical mycobacteria
  (e.g. *M. avium*)

QFT and T-SPOT procedure

QFT

Incubate 16-24h

cut-off:
0.35 IU IFN-γ/ml
QFT and T-SPOT procedure

- Plasma
- PBMCs
- Red cells

T-SPOT

Incubate 16-24h

Person A

Person B

Cut-off:
>5 SFC/250,000 PBMC

Negative Result

Positive Result

Nil Control

ESAT-6 Panel A

CFP 10 Panel B

Positive Control
Some Data...
מדדי תוקף: بدיקות לشفфт הביניית

Gold standard אינן כל הבדיקות לشففت הבינוית בודיקים נוספים
AIMs קיווים לחקור גם נוכחות החידק
ריגשון בדיקת על חולי שפחת ריאודת עליה
סגוליות בדיקת על בדיקים שכרוב לא
נחשפו לشفף

מדדי התוקף נגזרים ממרומש סף שנועת
Interferon-γ release assays for the diagnosis of latent *Mycobacterium tuberculosis* infection: a systematic review and meta-analysis


Included 60 studies out of 432 potentially relevant citations
Specificity in low risk patients

<table>
<thead>
<tr>
<th>First author [ref.]</th>
<th>Country (burden)</th>
<th>Participants</th>
<th>IGRA(s) used</th>
<th>Age mean±sd* yrs</th>
<th>Subjects assigned as low risk for M. tuberculosis infection n</th>
<th>Subjects with negative tests/all tested subjects n/N</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Detjen [26]</td>
<td>Germany (low)</td>
<td>Children with confirmed non-TB lymphadenitis (median 44) or respiratory infections</td>
<td>T-SPOT®.TB/QFT-G-IT</td>
<td>NTM infection: median 44 months; others: 52.5 months</td>
<td>45</td>
<td>T-SPOT®.TB: 31/40; QFT-G-IT: 39/40; T-SPOT®.TB: 40/40; TST: 22/40</td>
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</tr>
<tr>
<td>Franken [27]</td>
<td>The Netherlands (low)</td>
<td>Dutch Armed Forces personnel</td>
<td>QFT-G-IT</td>
<td>19.6 ± 2.8</td>
<td>171</td>
<td>QFT-G-IT: 166/168; TST: 136/145</td>
<td></td>
</tr>
<tr>
<td>Palladino [28]</td>
<td>Italy (low)</td>
<td>Healthy blood donors as controls for TB suspects</td>
<td>QFT-G-IT</td>
<td>RBC-unwasc.: 37.2 ± 2; DCG-unwasc.: 35.2 ± 2</td>
<td>24</td>
<td>QFT-G-IT: 14/14; TST: NA</td>
<td></td>
</tr>
<tr>
<td>Ruewald [29]</td>
<td>Denmark (low)</td>
<td>86 high school students and 38 high school staff</td>
<td>QFT-G-IT</td>
<td>Students: 17.6 ± 1.3; staff: 64.5 ± 6.5</td>
<td>124</td>
<td>QFT-G-IT: 124/124; TST: 118/124</td>
<td></td>
</tr>
</tbody>
</table>

Rounded specificity of IGRA(s)/TST % (95% CI)

- T-SPOT®.TB: 98 (86.8–99.9); QFT-G-IT: 100 (92.8–100); TST: 55 (38.5–70.7)
- QFT-G-IT: 99 (95.8–99.9); TST: 94 (88.6–97.1)
- QFT-G-IT: 100 (80.7–100); TST: NA
- QFT-G-IT: 100 (97.6–100); TST: 95 (87.7–97.2)
NPV in TB suspects

QFT

Pooled NPV: 0.88 (0.85–0.92)
Chi squared = 40.88, df 5, p < 0.0001
Inconsistency I² = 85.1%

T-SPOT

Pooled NPV: 0.94 (0.92–0.96)
Chi squared = 41.14, df 11 (p < 0.0001)
Inconsistency I² = 73.3%
NPV in negative patients

**QFT**

- **Aichburg [19]**
  - NPV: 1.00
  - 95% CI: 1.00–1.00
  - Patients n/N: 738/738
- **Diel [20]**
  - NPV: 1.00
  - 95% CI: 0.99–1.00
  - Patients n/N: 535/535
- **Kik [21]**
  - NPV: 0.98
  - 95% CI: 0.94–1.00
  - Patients n/N: 146/149
- **Silverman [45]**
  - NPV: 1.00
  - 95% CI: 0.83–1.00
  - Patients n/N: 20/20

Pooled NPV: 0.996 (0.994–1.00)
Chi-squared = 13.67; df = 3 (p = 0.003)
Inconsistency I² = 78.1%

**T-SPOT**

- **Clark [22]**
  - NPV: 1.00
  - 95% CI: 0.92–1.00
  - Patients n/N: 47/47
- **Kik [21]**
  - NPV: 0.98
  - 95% CI: 0.94–1.00
  - Patients n/N: 116/118
- **Lee [41]**
  - NPV: 0.88
  - 95% CI: 0.64–0.99
  - Patients n/N: 15/17

Pooled NPV: 0.98 (0.94–0.99)
Chi-squared = 5.88; df = 2 (p = 0.053)
Inconsistency I² = 65.9%
## Pooled Meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>TST</th>
<th>QFT</th>
<th>T-SPOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Sensitivity</td>
<td>70-77</td>
<td>75-85</td>
<td>89-90</td>
</tr>
<tr>
<td>% Specificity</td>
<td>60-90</td>
<td>96-99</td>
<td>86-95</td>
</tr>
<tr>
<td>% Indeterminate</td>
<td>2-4</td>
<td>3-6</td>
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</table>

Madhukar Pai, MD, PhD, Alice Zwerling, MSc, and Dick Menzies, MD, MSc
McGill University and Montreal Chest Institute, Montreal, Quebec, Canada

Conclusion—The IGRAs, especially QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube, have excellent specificity that is unaffected by BCG vaccination. Tuberculin skin test specificity is high in non-BCG-vaccinated populations but low and variable in BCG-vaccinated populations. Sensitivity of IGRAs and TST is not consistent across tests and populations, but T-SPOT.TB appears to be more sensitive than both QuantiFERON tests and TST.
Interferon-Gamma Release Assay for the Diagnosis of Latent TB Infection – Analysis of Discordant Results, when Compared to the Tuberculin Skin Test

Albert Nienhaus¹*, Anja Schablon¹, Roland Diel²

Conclusions: After adjustment for potential risk factors for positive or negative TST results, agreement of QFT and TST is excellent with little potential that the TST is more likely to detect old infections than the QFT. In surveillance programs for LTBI in high-income, low TB incidence countries like Germany the QFT is especially suited for persons with BCG vaccination or migrants due to better specificity and in older persons due to its superior sensitivity.
The Utility of an Interferon Gamma Release Assay for Diagnosis of Latent Tuberculosis Infection and Disease in Children: A Systematic Review and Meta-analysis

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

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.
Interferon-gamma release assays and childhood tuberculosis: systematic review and meta-analysis

A. M. Mandalakas,*† A. K. Detjen,‡‡ A. C. Hesseling,† A. Benedetti,§¶ D. Menzies§

CONCLUSIONS: Available data suggest that TST and IGRAs have similar accuracy for the detection of TB infection or the diagnosis of disease in children. Heterogeneous methodology limited the comparability of studies and the interpretation of results. A rigorous, standardized approach to evaluate TB diagnostic tests in children is needed.
CONCLUSIONS—Current evidence suggests that IGRAs perform similarly to the TST at identifying HIV-infected individuals with LTBI. Given that both tests have modest predictive value and sub-optimal sensitivity, the decision to use either test should be based on country guidelines and resource and logistical considerations.
Many Head-to-Head single studies support the superiority of IGRA on TST in Immunosuppressed and Pediatric patients.
IGRA vs. TST

Pros:
- High specificity and sensitivity
- High reproducibility
- Not affected by BCG vaccination
- Does not cross-react with most environmental mycobacteria
- Immunosuppression has little effect
- Simple blood sample, results available next day
- No return visit required

Cons:
- Limited time to deliver blood to the Lab
- Requires a trained Lab
- High cost
דוגמאות להנחיות מארצות
مفتوחות אזורות
הנחיות להנחיות מארצות
דוגמאות לחנויות מארצות מתחלחות克拉ט

CDC (2010): ב- איר"ב

- TST מקירם בדם מומלח ו- IGRA מקירם בדם
- נבדקים שיקים סטטיים של איר"ב, לחדר בידור
- נבדקים שיקומי ב-BCG

- TST מקירם בדם מומלח ו- IGRA מקירם בדם
- ילד ממתה ליגי 5

- מיצבים בדם אפשר ולא ליגי lub 할בד
- מרגיע של חוול השפה פטעלו
- סקורות וודא, בריאות

- IGRA מקירם בדם מומלח לשת狺ב ב- TSTวง ב- IGRA מקירם בדם
- מבצע ראשו שליל, על אח שיקום חשד קלין/אפידמיולוגיה על הדבקה
- מבצע ראשו חיוב, בן שיקום עם סיכוך נגוע, ההששים לבריאות
- intermediate הוא IGRA מקירם כשיר מבצע
Tuberculosis

Clinical diagnosis and management of tuberculosis, and measures for its prevention and control

This is the full version of NICE clinical guideline 117. It contains details of the methods and evidence used to develop the guideline. It updates and replaces the full version of 'Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control' that was developed by the National Collaborating Centre for Chronic Conditions and published by the Royal College of Physicians in March 2005. The updated recommendations have been developed by the Centre for Clinical Practice at NICE following the NICE short clinical guideline process.
ענquiries להנחות מארצות מפותחות אתורט

בריטניה (NICE 2011):* 

* מגע עם חולה – TST

* המג рагים ממדיניות שחורות בוהה ואו IGRA+TST או IGRA ידם ≥2

* ילדים <2 – TST

*インターフェ日讯 – IGRA

* מודיכי חיסון – IGRA או IGRA+TST

* עובדי בריאות – TST. במידה וחוייבי או载 בולו BCG ואם עלו ממידה

* ב_charset utf-8; IGRA

* חסרי בית, מגרים לא חוקיים – IGRA
доброхотство заинтересовало "мфоххот" рате

ישראל:

העודו המיסענת לעמ"ל משל"ב בחתומ השקת...
תודה רבה

Virginia Health Bulletin - October 1908