Diagnosis of latent tuberculosis infection



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McGill

Importance of LTBI

- It is estimated that nearly one-third of the world's population is infected with *M. tuberculosis*
- In most individuals, *M. tuberculosis* infection is contained initially by host defences, and infection remains latent.
- However, latent TB infection (LTBI) has the potential to develop into active disease at any time.
- Identification and treatment of latent tuberculosis infection can reduce the risk of development of disease by as much as 60 - 90 percent, and so has potential to protect the health of the individuals as well as the public by reducing the number of potential sources of infection

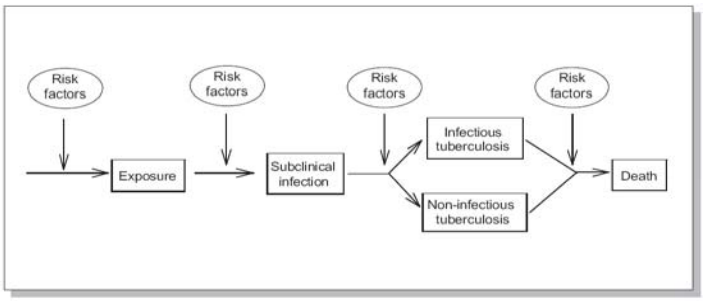
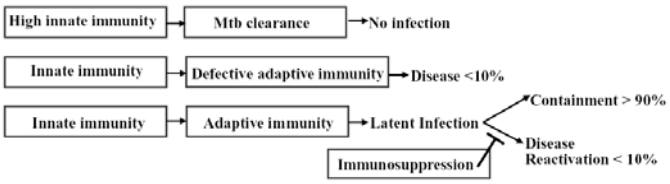


Figure 2. A model for tuberculosis epidemiology, following the pathogenesis of tuberculosis. Figure reproduced with the permission of Urban & Vogel from [2].

Hans L. Rieder, 1999



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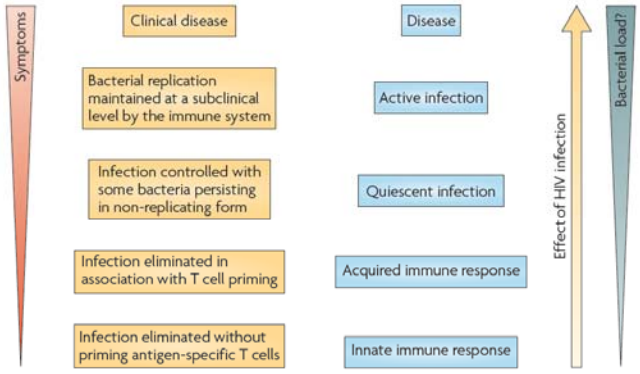
Bhatt, J Clin Immunol 2007

The spectrum of latent tuberculosis: rethinking the biology and intervention strategies

Clifton E. Barry 3rd[*], Helena I. Boshoff[*], Véronique Dartois[‡], Thomas Dick[‡], Sabine Ehrt[§], JoAnne Flynn[||], Dirk Schnappinger[§], Robert J. Wilkinson[¶#**] and Douglas Young[#**]*



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Nat Rev Micro 2009

LTBI vs. TB Disease

Latent TB Infection	Pulmonary TB Disease
• TST* or IGRA† positive	• TST or IGRA usually positive
• Negative chest radiograph	• Chest radiograph may be abnormal
• No symptoms or physical findings suggestive of TB disease	• Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
• Respiratory specimens are not smear or culture positive	• Respiratory specimens *may* be smear or culture positive
• Not infectious to others	• Potentially infectious

*tuberculin skin test

†IGRA = IFN-gamma release assay

Source: US CDC

Indications for LTBI testing

- The goal of testing for LTBI is to identify individuals who are at increased risk for the development of tuberculosis and therefore would benefit from treatment of latent TB infection.
- Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive.
- In general, testing for LTBI is warranted to identify individuals who are at risk of new infection, and to identify individuals at increased risk of reactivation due to associated conditions
- However, LTBI testing is a challenge
  - There is no definite method to confirm or rule out LTBI

LTBI: a diagnostic challenge [case #1]

My 19 year old son is being worked up for his 2nd kidney transplant and is currently on hemodialysis. He has been through numerous drug reactions (some of them extremely rare) and he is not too keen on the skin test. The TB skin test is a part of the protocol of the Ottawa Hospital as there were two people last year who died of TB post renal transplant.

From the studies I have found on the internet it appears that the TB skin test is not a very accurate method of detection of LTBI in hemodialysis patients.

Is there anyone in Canada who is using this test and would it be possible to bring it to Ottawa? We are told that the Ottawa hospitals have a great concern about TB as they service the Inuit population. That said, I would assume that employing a TB blood test would be of great benefit to our renal patient population.

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LTBI: a diagnostic challenge [case #2]

I am a healthcare worker, and have just had a positive TB skin test.

It's only been one year since my last skin test which was negative.

My primary care doctor read my chest x-ray as negative and did not recommend INH, but the Health Dept. here recommends taking INH for 6-9 months.

Doctors and nurses whom I work with say that false positives happen all the time and to not worry about it. I have read about the side effects of this drug, and want to be sure that I actually am a carrier before taking it.

I have been reading about the QFT-G and am wondering if it will help resolve my dilemma about taking INH?

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LTBI: a diagnostic challenge [case #3]

We are parents in distress looking for help. Our 18 month old daughter has been diagnosed with TB in virtue of a lung infiltration that appeared in her x-ray taken some 3 months ago. The infiltration is still there according to a new x-ray taken 10 days ago.

We tested her with the "skin test tuberculina" but got a negative result, even though she was vaccinated with the BCG. Our doctor said that was because she was in a state of "anergia" and insists it is TB that she has. Nevertheless, other two specialists –though not our doctor- have manifested contrary opinions to our paediatrician.

The issue here is that our doctor wants to commence treatment against active TB and my wife and I are not convinced our paediatrician's opinion is correct. We learned treatment is long and has secondary effects.

Worst of all, there seems to be no test available in Mexico that can assert if what our paediatrician says is correct.

Through the internet we learned about the new T-Spot.TB but we can't find it here in Mexico. We are willing to travel to Canada and beyond in order to make sure if our daughter is ill with TB but are not about ready to begin a lengthy and weighty treatment that may not be needed.

We are appalled to find there is such a state of lack of definition regarding TB diagnosis.

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Who should be tested?

UpToDate ONLINE 17.2

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Who should be tested for latent TB infection?*

Those with increased risk of new TB infection (all patients should be tested regardless of age)
Close contacts of patients with active pulmonary/respiratory TB•
Casual contacts of patients with highly contagious active TB•
Health care workers and other occupations in which there is risk of exposure to patients with untreated contagious active TB (prison facilities, homeless shelters)Δ
Those with increased risk of reactivation◊
High risk (all patients should be tested regardless of age)
HIV infection (any stage of illness)
Transplant, chemotherapy, or other major immunocompromising condition
Lymphoma, leukemia, head & neck cancer
Abnormal chest x-ray with apical fibronodular changes typical of healed TB (not including granuloma)
Silicosis
Renal failure (requiring dialysis)
Treatment with TNF-alpha inhibitors
Moderate risk (patients under age 65 should be tested)
Diabetes mellitus
Systemic glucocorticoids (≥15 mg/day for ≥1 month)§
Slightly increased risk (patients under age 50 should be tested)
Underweight (<85 percent of ideal body weight); for most individuals this is equivalent to body mass index (BMI) ≤20.
Cigarette smoker (1 pack/day)
Chest x-ray with solitary granuloma

* Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive.
• A second test is warranted if the first test is negative (see text).
Δ Baseline two-step testing should be performed, followed by annual testing.
◊ Generally need a single test.
§ The US Centers for Disease Control (CDC) recommends skin testing for all patients in this category. However, population based studies demonstrate that the relative risk for development of active tuberculosis in this category is moderate (2-4x that of healthy individuals). Therefore, an age cutoff of ≤65 is indicated, so that potential risks of INH toxicity in older patients do not outweigh potential benefit. (See separate table summarizing relative risk for development of active tuberculosis).

Pai & Menzies. UpToDate 2009

UpToDate. ONLINE 17.2

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Risk factors for the development of active tuberculosis among persons infected with *Mycobacterium tuberculosis*

Risk factor	Estimated risk for TB relative to persons with no known risk factor	References
High risk		
Acquired immunodeficiency syndrome (AIDS)	110-170	1,2
Human immunodeficiency virus infection (HIV)	50-110	3,4
Transplantation (related to immune-suppressant therapy)	20-74	5-8
Silicosis	30	9,10
Chronic renal failure requiring hemodialysis	10-25	11-14
Carcinoma of head and neck	16.0	15
Recent TB infection (≤2 years)	15.0	16,17
Abnormal chest x-ray with apical fibronodular changes typical of healed TB (not granuloma)	6-19	18-20
Tumor necrosis factor (TNF)-alpha inhibitors	1.7-9	21,22,35,36
Moderate risk		
Treatment with glucocorticoids	4.9	23
Diabetes mellitus (all types)	2-3.6	24-27
Young age when infected (≤4 years)	2.2-5	28
Slightly increased risk		
Underweight (<85 percent of ideal body weight); for most individuals this is equivalent to body mass index (BMI) ≤20.	2-3	29
Cigarette smoker (1 pack/day)	2-3	30,31
Chest x-ray with solitary granuloma	2	20,32
Low risk		
Infected person, no known risk factor, normal chest x-ray ("low risk reactor")	1	33
Very low risk		
Positive booster (two step test) with no other known risk factor and normal chest x-ray)	0.5	Extrapolated from 33 and 34

Pai & Menzies. UpToDate 2009

How do we test for LTBI?

- Tuberculin skin test
  - Mantoux method, using purified protein derivative (PPD) at the recommend dose of 5 tuberculin units (0.1 mL); in other regions, PPD RT-23 is used at the standard dose of 2 TU
- Interferon-gamma release assays (IGRAs)
  - QuantiFERON-TB Gold In Tube
  - T-SPOT.TB
- Both tests are imperfect!

Tuberculin skin test

- TST
  - Measures cell-mediated immune response (CMI)
    - Uses PPD: a crude antigenic mixture
- Limitations of TST:
  - false positives and false negatives are possible
  - technical issues in administration and interpretation
  - difficulty in separating true infection from the effects of BCG and non-tuberculous mycobacteria (NTM)
  - repeated TST boosts the immune response
  - requires a 3-dimensional interpretation

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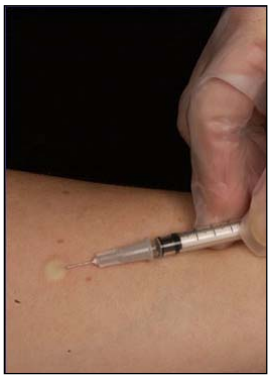
Administering the TST

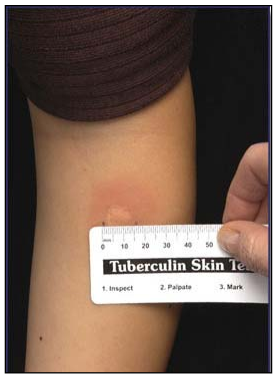
- Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-gauge needle
- Produce a wheal 6 to 10 mm in diameter



Source: US CDC

Reading the TST (1)

- Measure reaction in 48 to 72 hours
- Measure induration, not erythema
- Record reaction in millimeters, not “negative” or “positive”
- Ensure trained health care professional measures and interprets the TST



Source: US CDC

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Reading the TST (2)

- Educate patient and family regarding significance of a positive TST result
- Positive TST reactions can be measured accurately for up to 7 days
- Negative reactions can be read accurately for only 72 hours
- A period of up to 8 weeks after primary TB infection may be required for TST conversion to occur. Individuals with recent close contact to a known infectious case of TB, whose initial TST is negative, should have repeat TST 8 weeks after the end of exposure

Source: US CDC

TST Interpretation

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Interpretation of tuberculin skin test

Tuberculin skin test reaction size (mm)	Situation in which reaction is considered positive*
≥5	HIV infection
	Close contact of active contagious case
	Abnormal chest x-ray with fibrotic changes consistent with old TB
	Immunosuppressed patients: TNF-alpha inhibitors, chemotherapy, organ transplantation, glucocorticoid treatment (equivalent of ≥15 mg/d prednisone for ≥1 month)
≥10	Persons with clinical conditions that increase the risk of reactivation, including silicosis•, chronic renal failure requiring dialysis•, diabetes mellitus, some malignancies (leukemias, lymphomas, carcinoma of the head, neck, or lung), underweight (≥10 percent ideal body weight), jejunoileal bypass, injection drug users
	Children less than 4 years of age
	Foreign born from countries with incidence >25/100,000 Δ
	Residents and employees in high risk settings, such as prisons, jails, healthcare facilities, mycobacteriology labs, and homeless shelters
≥15	Healthy persons with low likelihood of true TB infection ◊

* The goal of testing for latent tuberculosis infection is to identify individuals who are at increased risk for the development of tuberculosis and therefore would benefit from treatment of latent TB infection. Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive (see text).
• The US Centers for Disease Control and Prevention (CDC) recommends a 10 mm induration definition for patients with silicosis or chronic renal failure. However, population based studies demonstrate that the relative risk for development of active tuberculosis in this category is high (≥10x that of healthy individuals). For this reason, many favor a lower threshold for a positive test (≥5 mm).
Δ The US Centers for Disease Control and Prevention (CDC) indicates that only those foreign born individuals who immigrated within the past 5 years should be tested (regardless of age), although others do not favor this practice since most recently arrived foreign born with positive TST have old (not recent) infection.
◊ Persons with a low likelihood of true TB infection should not be tested routinely unless they are entering a high risk setting such as starting employment at a healthcare facility. A threshold of 15 mm is used in the US, and is appropriate for healthy individuals with low likelihood of true TB infection and high likelihood of exposure to non-tuberculous mycobacteria (eg, Southern US). However, Canadian guidelines use a threshold of 10 mm for healthy individuals given the lower likelihood of exposure to nontuberculous mycobacteria. (See "Epidemiology of nontuberculous mycobacterial infections").

Pai & Menzies. UpToDate 2009

Factors That May Cause False-Positive TST Reactions

- Nontuberculous mycobacteria
  - Reactions caused by nontuberculous mycobacteria are usually ≤ 10 mm of induration
- BCG vaccination
  - Reactivity in BCG vaccine recipients generally wanes over time; positive TST result is likely due to TB infection if risk factors are present

Source: US CDC

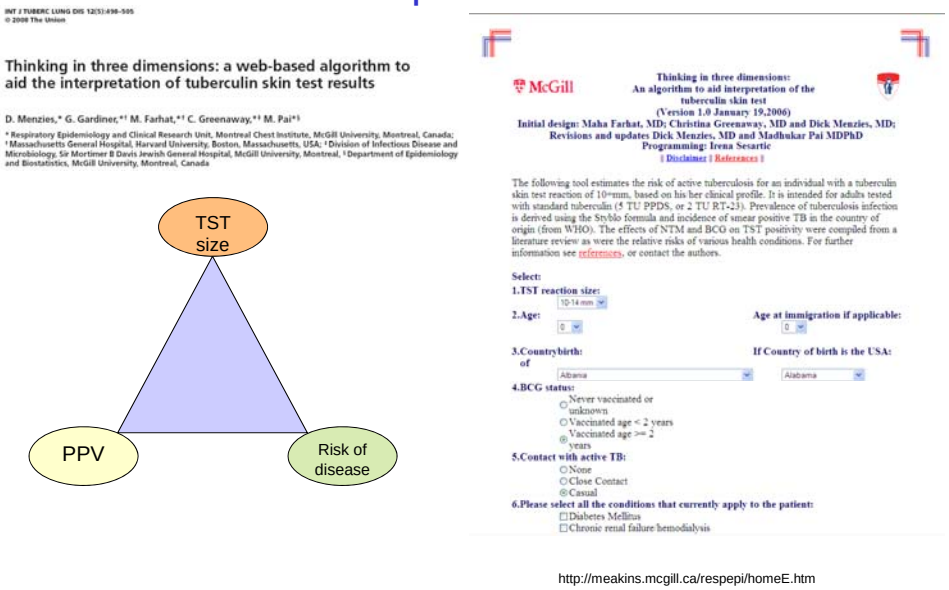
Factors That May Cause False-Negative TST Reactions

Potential causes of false negative tuberculin tests

Technical (potentially correctable)
Tuberculin material:
Improper storage (exposure to light or heat)
Contamination, improper dilution, or chemical denaturation
Administration:
Injection of too little tuberculin, or too deeply (should be subcutaneous)
Administration more than 20 minutes after drawing up into the syringe
Reading:
Inexperienced or biased reader
Error in recording
Biologic (not correctable)
Infections:
Active TB (especially if advanced)
Other bacterial infection (typhoid fever, brucellosis, typhus, leprosy, pertussis)
HIV infection (especially if CD4 count <200)
Other viral infection (measles, mumps, varicella)
Fungal infection (South American blastomycosis)
Live virus vaccination: (measles, mumps, polio)
Immunosuppressive drugs: (corticosteroids, TNF inhibitors, and others)
Metabolic disease: chronic renal failure, severe malnutrition, stress (surgery, burns)
Diseases of lymphoid organs: (lymphoma, chronic lymphocytic leukemia, sarcoidosis)
Age: infants <6 months, elderly

Pai & Menzies. UpToDate 2009

TST requires a 3-dimensional interpretation



http://meakins.mcgill.ca/respepi/homeE.htm

When BCG is given after infancy or repeated many times, it can affect TST results

INT J TUBERC LUNG DIS 10(11):1192–1204

REVIEW ARTICLE

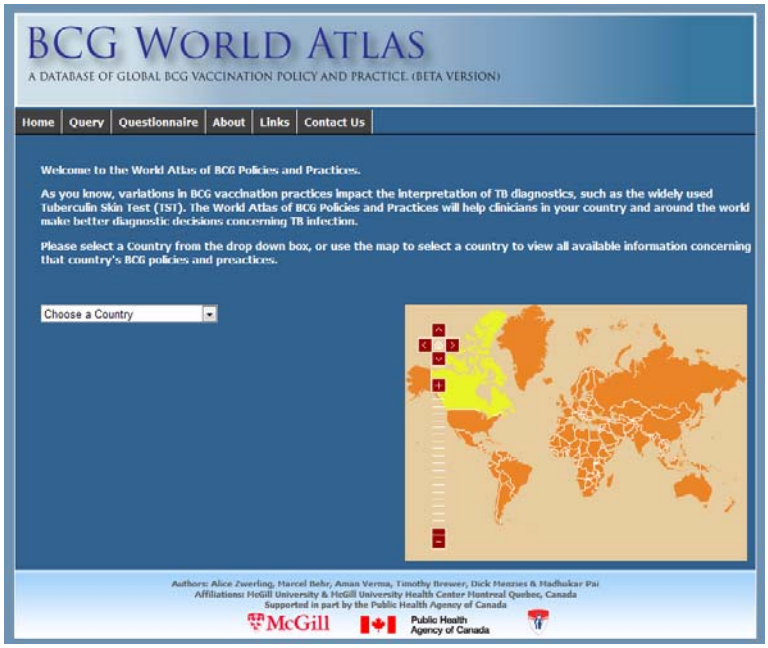
False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria?

M. Farhat,*† C. Greenaway,*‡ M. Pai,*§ D. Menzies*

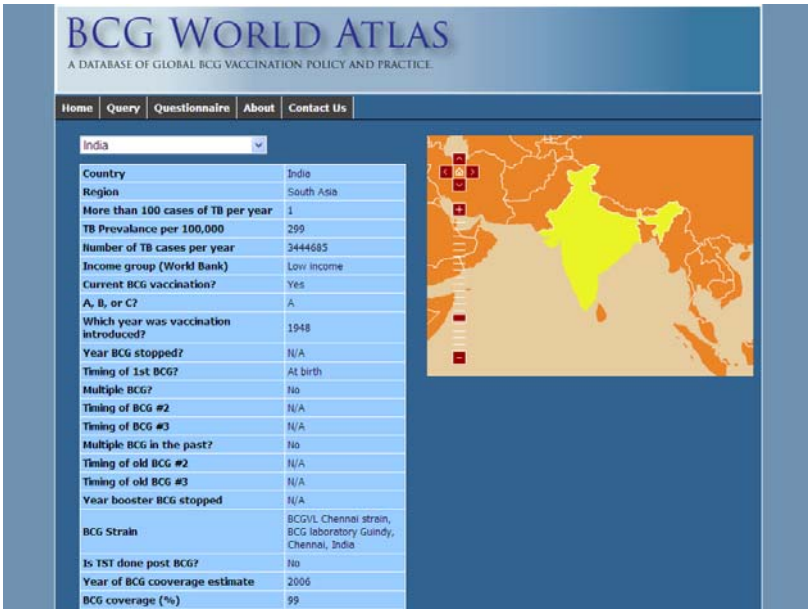
* Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, Quebec, Canada; † Massachusetts General Hospital, Harvard University, Boston, Massachusetts, USA; ‡ Division of Infectious Disease and Microbiology, SMBD-Jewish General Hospital, McGill University, Montreal, § Joint Departments of Epidemiology & Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

- Analysis of 24 studies with N = 240,243 subjects
- When BCG is given in infancy, false-positive TST results due to BCG occur in 6% of vaccinated subjects
- When BCG is given after infancy, false-positive TST results due to BCG occur in 40% of vaccinated subjects

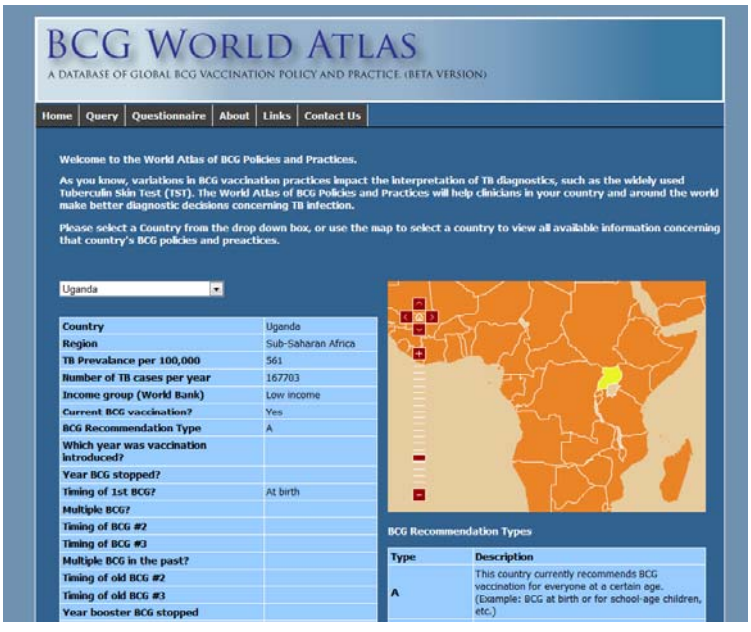
WWW.BCGATLAS.ORG



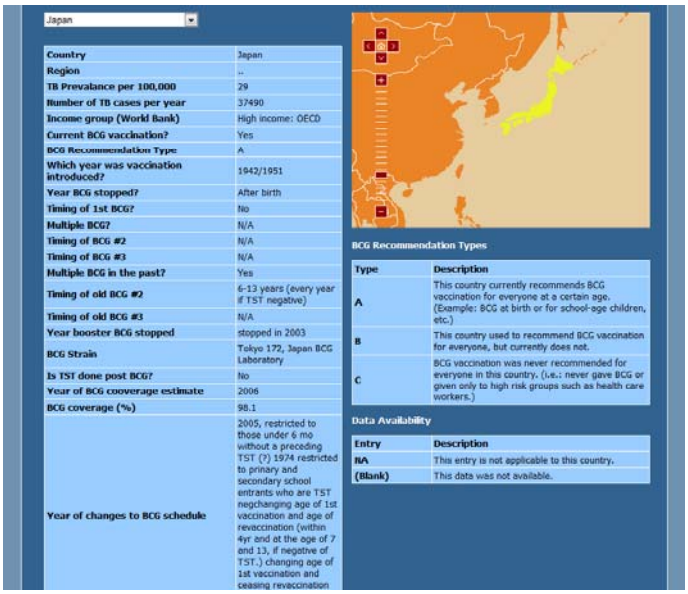
In India, BCG has limited effect on TST



In Uganda, BCG has limited effect on TST



In Japan, BCG has a major effect on TST



Japan

Country	Japan
Region	..
TB Prevalance per 100,000	29
Number of TB cases per year	37490
Income group (World Bank)	High income: OECD
Current BCG vaccination?	Yes
BCG Recommendation Type	A
Which year was vaccination introduced?	1942/1951
Year BCG stopped?	After birth
Timing of 1st BCG?	No
Multiple BCG?	N/A
Timing of BCG #2	N/A
Timing of BCG #3	N/A
Multiple BCG in the past?	Yes
Timing of old BCG #2	6-13 years (every year if TST negative)
Timing of old BCG #3	N/A
Year booster BCG stopped	stopped in 2003
BCG Strain	Tokyo 172, Japan BCG Laboratory
Is TST done post BCG?	No
Year of BCG coverage estimate	2006
BCG coverage (%)	98.1
Year of changes to BCG schedule	2005, restricted to those under 6 mo without a preceding TST (?) 1974 restricted to primary and secondary school entrants who are TST negchanging age of 1st vaccination and age of revaccination (within 4yr and at the age of 7 and 13, if negative of TST.) changing age of 1st vaccination and ceasing revaccination

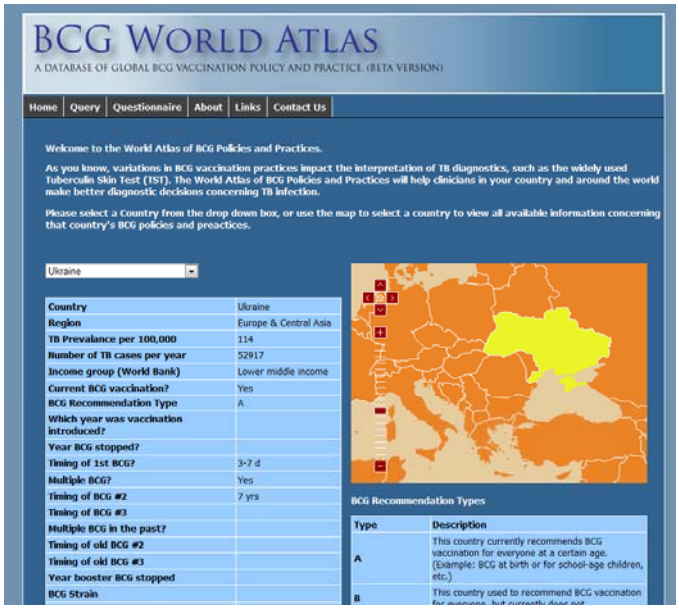
BCG Recommendation Types

Type	Description
A	This country currently recommends BCG vaccination for everyone at a certain age. (Example: BCG at birth or for school-age children, etc.)
B	This country used to recommend BCG vaccination for everyone, but currently does not.
C	BCG vaccination was never recommended for everyone in this country. (i.e.: never gave BCG or given only to high risk groups such as health care workers.)

Data Availability

Entry	Description
NA	This entry is not applicable to this country.
(Blank)	This data was not available.

In Ukraine, BCG has a major effect on TST



BCG WORLD ATLAS

A DATABASE OF GLOBAL BCG VACCINATION POLICY AND PRACTICE (BETA VERSION)

Home | Query | Questionnaire | About | Links | Contact Us

Welcome to the World Atlas of BCG Policies and Practices.

As you know, variations in BCG vaccination practices impact the interpretation of TB diagnostics, such as the widely used Tuberculin Skin Test (TST). The World Atlas of BCG Policies and Practices will help clinicians in your country and around the world make better diagnostic decisions concerning TB infection.

Please select a Country from the drop down box, or use the map to select a country to view all available information concerning that country's BCG policies and preactices.

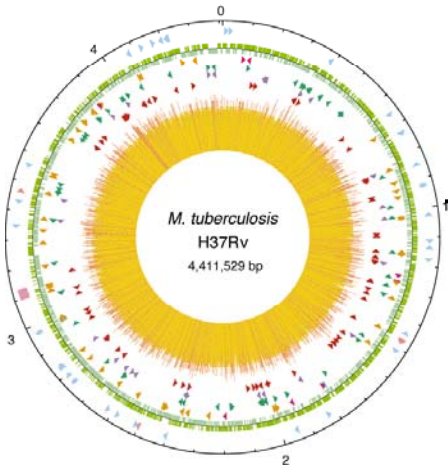
Ukraine

Country	Ukraine
Region	Europe & Central Asia
TB Prevalance per 100,000	114
Number of TB cases per year	52917
Income group (World Bank)	Lower middle income
Current BCG vaccination?	Yes
BCG Recommendation Type	A
Which year was vaccination introduced?	
Year BCG stopped?	
Timing of 1st BCG?	3-7 d
Multiple BCG?	Yes
Timing of BCG #2	7 yrs
Timing of BCG #3	
Multiple BCG in the past?	
Timing of old BCG #2	
Timing of old BCG #3	
Year booster BCG stopped	
BCG Strain	

BCG Recommendation Types

Type	Description
A	This country currently recommends BCG vaccination for everyone at a certain age. (Example: BCG at birth or for school-age children, etc.)
B	This country used to recommend BCG vaccination

Advances in the development of antigens specific to *M. tuberculosis*



Genomics
Proteomics

ESAT-6

CFP-10

Cole et al, Nature 1998

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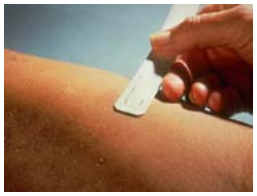
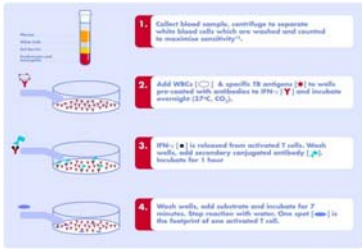
IGRAs





T-SPOT.*TB*® [Oxford Immunotec, UK]

QuantiFERON-TB Gold® In Tube [Cellestis Ltd, Australia]

Quick Summary of Evidence

- TST specificity is high in BCG non-vaccinated; but low and variable in BCG vaccinated
- IGRAs (especially QFT) have very high specificity (>95%)
  - IGRA specificity is higher than TST
  - IGRAs are not affected by BCG vaccination
    - Maybe very helpful in settings that give BCG after infancy or give multiple vaccinations
- Sensitivity of IGRAs and TST is not consistent across tests and populations
  - Overall, IGRAs are ~80% sensitive in culture+ TB patients
    - Sensitivity is lower in high incidence countries
  - QFT is as sensitive as TST (~80%)
    - QFT sensitivity is higher in low incidence than high incidence countries
  - T-SPOT.TB appears to be more sensitive (~90%) than both QuantiFERON tests and TST
    - But this may partly be because of cut-offs used for T-SPOT vs QFT
- In low-incidence settings, IGRAs correlate well with markers of exposure

Pai et al. Annals Int Med 2008

IGRAs in immunocompromised

- Immunocompromised groups are highly variable, and most studies are small:
  - All tests underperform in severely immunocompromised patients
    - Using both TST and IGRA might help increase sensitivity
  - IGRA sens in HIV+ is lower (~60 – 65%) than HIV- (~80 – 90%)
  - About 15% of HIV+ TB patients have indeterminate IGRA results
  - Indeterminate IGRA results increase with level of immunosuppression (i.e. low CD4 counts)
  - Very limited data on predictive value
  - Utility as rule out test for active TB is not well established
    - Unlikely to have a rule out value, given the modest sensitivity

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IGRAs for active TB diagnosis

- No role in adults
  - Cannot distinguish between latent and active TB
  - Sensitivity is not high
    - Cannot rule out
  - Specificity will always be low in high TB incidence settings
    - Cannot rule in
  - No evidence that IGRAs offer any added value over conventional microbiological tests
- In children
  - Cannot be used in isolation
  - Cannot replace microbiological investigations
  - Useful as “evidence of infection” which should be interpreted with other information (e.g. contact, symptoms, radiological findings)

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Predictive value of IGRAs

High Incidence

Immune Responses to the *Mycobacterium tuberculosis*-Specific Antigen ESAT-6 Signal Subclinical Infection among Contacts of Tuberculosis Patients

T. Mark Doherty, Abebech Demissie, Joseph Olobo, Dawit Wolday, Sven Britton, Tewodros Eguale, Pernille Ravn, and Peter Andersen

OPEN ACCESS Freely available online PLoS one

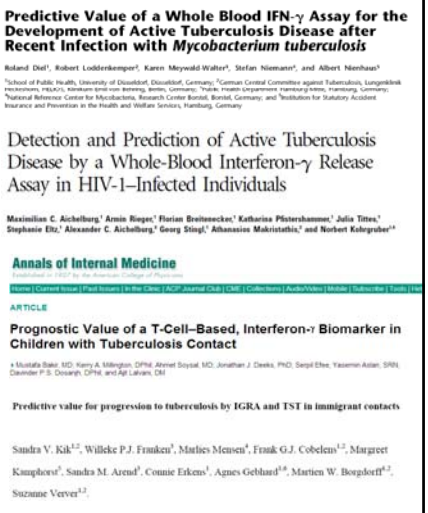
Incidence of Tuberculosis and the Predictive Value of ELISPOT and Mantoux Tests in Gambian Case Contacts

Philip C. Hill, Dolly J. Jackson-Sillah, Annette Fox, Roger H. Brookes, Bouke C. de Jong, Moses D. Lugos, Ifedayo M. Adetifa, Simon A. Donkor, Alex M. Aiken, Stephen R. Howie, Tumani Corrah, Keith P. McAdam, Richard A. Adegbola

Bacterial Diseases Programme, Medical Research Council (MRC) Laboratories, Banjul, The Gambia

Unpublished: S Africa, Senegal, Colombia

Low Incidence



Predictive Value of a Whole Blood IFN-γ Assay for the Development of Active Tuberculosis Disease after Recent Infection with *Mycobacterium tuberculosis*

Roland Diel, Robert Loddenkemper, Karen Meywald-Walter, Stefan Niemann, and Albert Nienhaus

Detection and Prediction of Active Tuberculosis Disease by a Whole-Blood Interferon-γ Release Assay in HIV-1–Infected Individuals

Maximilian C. Aichelburg, Armin Rieger, Florian Breitenecker, Katharina Pfistershammer, Julia Tittes, Stephanie Eltz, Alexander C. Aichelburg, Georg Stingl, Athanasios Makristathis, and Norbert Kohrgruber

Annals of Internal Medicine

ARTICLE

Prognostic Value of a T-Cell–Based, Interferon-γ Biomarker in Children with Tuberculosis Contact

Predictive value for progression to tuberculosis by IGRA and TST in immigrant contacts

Sandra V. Kik, Willeke P.J. Franken, Marlies Mensen, Frank G.J. Cobelens, Margreet Kamphorst, Sandra M. Arend, Connie Erkens, Agnes Geblard, Marlien W. Borgdorff, Suzanne Verver

Unpublished: Japan

Rates of disease progression by test

IGRA = TST	IGRA > TST	IGRA+ > IGRA-
Gambia (26 cases)	Germany (6 cases)	Ethiopia (7 cases)
Netherlands (9 cases)		Austria (3 cases)
South Africa (50 cases)		
Turkey (15 cases)		

Most TST or IGRA positive individuals will not progress to active TB

Promising but both tests may have only modest predictive abilities

- A substantial % of TST or IGRA+ persons will not progress to TB disease
- Why is predictive value likely to be only modest?
  - IFN-gamma alone might not be sufficiently predictive of progression (or correlate of protection)
  - A single (cross-sectional) TST or IGRA result cannot tell us about the underlying phenotype of when infection occurred and how the host immune system responded

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What are the key unresolved issues?

- What is the predictive value of IGRAs for the development of active TB? Will this vary by high vs. low incidence setting?
- Will treatment of IGRA positive subjects reduce the future probability of active TB?
- What is the interpretation of IGRA conversions and reversions?
- What is the exact role of IGRAs in high incidence countries?
- Can IGRAs be used to rule out active TB diagnosis?
- What is the exact role of IGRAs in children and HIV+?

T-cell assays for the diagnosis of latent tuberculosis infection: moving the research agenda forward

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Guidelines on IGRAs: A global survey

May 30 – June 1, 2009
Dubrovnik, Croatia

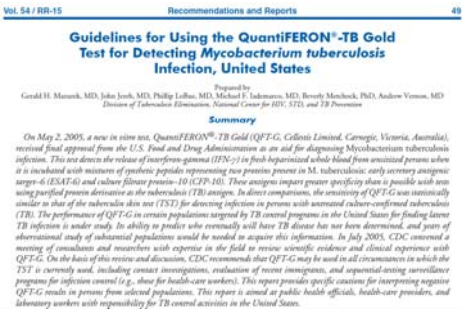
Results*

General testing approach	Countries
TST may be replaced by IGRA (i.e. only IGRA is used)	Germany (anti-TNF-a), Swiss (anti-TNF-a), Poland (anti-TNF-a), Denmark (anti-TNF-a, BCG-vaccinated contacts/adults)
Either TST or IGRA may be used	USA (QFT preferred in BCG+), France, Australia(refugees), Japan (QFT preferred in all groups except in children <5 y), Denmark(child contacts)
Two-step approach: TST first, followed by IGRA (either to improve specificity or sensitivity)	Canada, UK, Italy, Spain, Australia, Slovakia Germany (contacts), Swiss (contacts), Netherlands (contacts, immigrants), Norway, Korea(contacts)

* some guidelines recommend more than one approach, depending on the risk group tested (e.g. contacts, immunocompromised, children, etc)

North American Guidelines

USA: CDC Guidelines 2005: QFT-G [2G]



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Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting *Mycobacterium tuberculosis* Infection, United States

Prepared by
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Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention

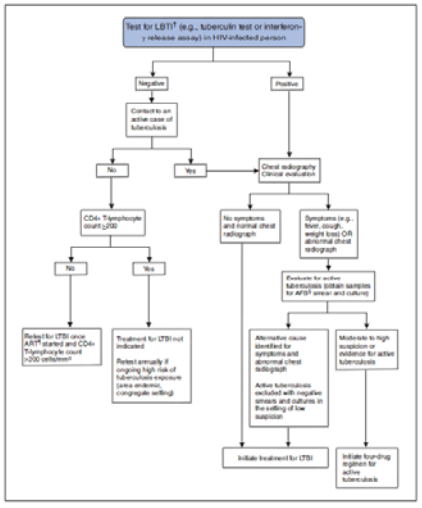
Summary

On May 2, 2005, a new in vitro test, QuantiFERON®-TB Gold (QFT-G, Cellestis Limited, Carnegie, Victoria, Australia), received final approval from the U.S. Food and Drug Administration as an aid for diagnosing Mycobacterium tuberculosis infection. This test detects the release of interferon-gamma (IFN-γ) in fresh heparinized whole blood from unsensitized persons when it is incubated with mixtures of synthetic peptides representing two proteins present in M. tuberculosis: early secretory antigenic target-6 (ESAT-6) and culture filtrate protein–10 (CFP-10). These antigens impart greater specificity than is possible with tests using purified protein derivative as the tuberculosis (TB) antigen. In direct comparisons, the sensitivity of QFT-G was statistically similar to that of the tuberculin skin test (TST) for detecting infection in persons with untreated culture-confirmed tuberculosis (TB). The performance of QFT-G in certain populations targeted by TB control programs in the United States for finding latent TB infection is under study. Its ability to predict who eventually will have TB disease has not been determined, and years of observational study of substantial populations would be needed to acquire this information. In July 2005, CDC convened a meeting of consultants and researchers with expertise in the field to review scientific evidence and clinical experience with QFT-G. On the basis of this review and discussion, CDC recommends that QFT-G may be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants, and sequential-testing surveillance programs for infection control (e.g., those for health-care workers). This report provides specific cautions for interpreting negative QFT-G results in persons from selected populations. This report is aimed at public health officials, health-care providers, and laboratory workers with responsibility for TB control activities in the United States.

CDC recommends that QFT-G may be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants, and sequential-testing surveillance programs for infection control (e.g., those for health-care workers).

USA: CDC/NIH/IDSA Guidelines 2009

FIGURE 1. Schema for the diagnosis of latent tuberculosis infection*



MMWR
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

Recommendations and Reports April 10, 2009 / Vol. 58 / No. RR-4

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

Given the high risk for progression to active disease in HIV-infected persons, any HIV-infected person with reactivity on any of the current LTBI diagnostic tests should be considered infected with *M. tuberculosis*

USA: AAP Red Book 2009

At this time, neither an IGRA nor the TST can be considered a "gold standard" for diagnosis of LTBI. Current recommendations for use of IGRAs in children are as follows:

- For immune-competent children 5 years of age and older, IGRAs can be used in place of a TST to confirm cases of **tuberculosis** or cases of LTBI and likely will yield fewer false-positive test results.
- Children with a positive result from an IGRA should be considered infected with *M **tuberculosis*** complex. A negative IGRA result cannot universally be interpreted as absence of infection.
- Because of their higher specificity and lack of cross-reaction with BCG, IGRAs may be useful in children who have received BCG vaccine. IGRAs may be useful to determine whether a BCG-immunized child with a reactive TST more likely has LTBI or has a false-positive TST reaction caused by the BCG.
- IGRAs cannot be recommended routinely for use in children younger than 5 years of age or for immune-compromised children of any age because of a lack of published data about their utility with these groups.
- Indeterminate IGRA results do not exclude **tuberculosis** infection and should not be used to make clinical decisions.

USA: CDC Guidelines 2009: QFT-GIT/TSPOT.TB

To be released later this year

At the 2nd Global IGRA Symposium, it was announced that the new guideline will allow for the use of either TST or IGRA

IGRA will be preferred over TST for BCG vaccinated

TST will be preferred over IGRA in young children <5 years of age

USA: ATS/CDC/IDSA
Revised Diagnostic Standards for TB
2009: QFT-GIT/TSPOT.TB

American Thoracic Society

Diagnostic Standards and Classification of Tuberculosis in Adults and Children

This Official Statement of the American Thoracic Society and the Centers for Disease Control and Prevention was Adopted by the ATS Board of Directors, July 1999. This Statement was endorsed by the Council of the Infectious Disease Society of America, September 1999

Am J Respir Crit Care Med Vol 161. pp 1376–1395, 2000

To be released

Will be broadly consistent with the new CDC 2009 recommendations

Will cover all TB diagnostics, not just LTBI

Canadian IGRA guidelines


Canada Communicable Disease Report ◆ Relevé des maladies transmissibles au Canada

CCDR•RMTC

1 NOVEMBER 2007 • VOLUME 33 • ACS-10 — LE 1ER NOVEMBRE 2007 • VOLUME 33 • DCC-10

Contained in this issue:
INTERFERON GAMMA RELEASE ASSAYS FOR LATENT TUBERCULOSIS INFECTION 1

Contenu du présent numéro :
TESTS DE LIBÉRATION D'INTERFÉRON-GAMMA POUR LA DÉTECTION DE L'INFECTION TUBERCULEUSE LATENTE 1

AN ADVISORY COMMITTEE STATEMENT (ACS)

Canadian Tuberculosis Committee[1,11]

INTERFERON GAMMA RELEASE ASSAYS FOR LATENT TUBERCULOSIS INFECTION

Preamble

UNE DÉCLARATION D'UN COMITÉ CONSULTATIF (DCC)

Le comité canadien de lutte antituberculeuse[1,11]

TESTS DE LIBÉRATION D'INTERFÉRON-GAMMA POUR LA DÉTECTION DE L'INFECTION TUBERCULEUSE LATENTE

Préambule

2007


Canada Communicable Disease Report ◆ Relevé des maladies transmissibles au Canada

CCDR•RMTC

OCTOBER 2008 • VOLUME 34 • ACS-6 — OCTOBRE 2008 • VOLUME 34 • DCC-6

Contained in this issue:

An Advisory Committee Statement (ACS)

Canadian Tuberculosis Committee (CTC)[11]

UPDATED RECOMMENDATIONS ON INTERFERON GAMMA RELEASE ASSAYS FOR LATENT TUBERCULOSIS INFECTION

Preamble

Contenu du présent numéro :

Une déclaration d'un comité consultatif (DCC)

Le comité canadien de lutte anti-tuberculeuse (CCLA)[11]

RECOMMANDATIONS MISES À JOUR SUR LES TESTS DE LIBÉRATION D'INTERFÉRON-GAMMA POUR LA DÉTECTION DE L'INFECTION TUBERCULEUSE LATENTE

Préambule

2008

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IGRAs for active TB diagnosis

Table 1. Recommendations on Interferon Gamma Release Assays (IGRAs) for specific indications or subgroups

No	Specific subgroup or clinical indication	Previous ACS recommendation [CCDR 2007]	Updated recommendation	What has changed and why?
1	Diagnosis of active TB in adults with suspected TB disease	IGRAs are not recommended for the diagnosis of active TB. Clinicians who manage patients with suspected TB disease should align their practice with the *Canadian Tuberculosis Standards* and the *International Standards for Tuberculosis Care*, and use sputum smear microscopy and culture to investigate patients with suspected active TB.	IGRAs are not recommended for the diagnosis of active TB in adults. Clinicians who manage patients with suspected TB disease should align their practice with the *Canadian Tuberculosis Standards* and the *International Standards for Tuberculosis Care*, and use sputum smear microscopy and culture to investigate adult patients with suspected active TB.	The previous recommendation is now sub-divided into separate adult and children (< 18 years of age) sections. The recommendation for adults remains unchanged. For children, please see below, #2.
2	Diagnosis of active TB in children (< 18 years of age) with suspected TB disease	–	Evidence of TB infection in children is often used in making a diagnosis of active TB, in addition to symptoms, radiological abnormalities, history of exposure, and microbiological investigations such as microscopy and culture. While collection of clinical specimens for definitive microbiologic diagnosis remains paramount, IGRAs may be used as a supplementary diagnostic aid in combination with the TST and other investigations to help support a diagnosis of TB. However, IGRA should not be a substitute for, or obviate the need for, appropriate specimen collection.	This new recommendation allows the use of IGRAs as a supplementary diagnostic aid in children with suspected TB disease.

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CCDR 2008

IGRAs for contact investigation

Table 1. Recommendations on Interferon Gamma Release Assays (IGRAs) for specific indications or subgroups

No	Specific subgroup or clinical indication	Previous ACS recommendation [CCDR 2007]	Updated recommendation	What has changed and why?
3	Adult and childhood contacts of a case of active infectious tuberculosis	1. IGRAs may be used as a confirmatory test for a positive TST in contacts who, on the basis of an assessment of the duration and degree of contact with an active infectious case, are felt to have a low pretest probability of recently acquired LTBI and who have no other high or increased risk factors for progression to active disease if infected. 2. For close contacts or those contacts who have high or increased risk of progression to active disease if infected, a TST (or both TST and IGRA) should be used, and if either is positive the contact should be considered to have LTBI. 3. If both TST and IGRA testing will be used, it is recommended that blood be drawn for IGRA before or on the same day as placing the TST.	1. IGRAs may be used as a confirmatory test for a positive TST in contacts (adult or child) who, on the basis of an assessment of the duration and degree of contact with an active infectious case, are felt to have a low pretest probability of recently acquired LTBI and who have no other high or increased risk factors for progression to active disease if infected. 2. For close contacts or those contacts who have high or increased risk of progression to active disease if infected, a TST (or both TST and IGRA) should be used, and if either is positive the contact should be considered to have LTBI. 3. If both TST and IGRA testing will be used, it is recommended that blood be drawn for IGRA on or before the day when the TST is read.	This recommendation is largely unchanged, but the scope has been expanded to cover adults as well as children. Because of the practical difficulties in drawing blood for IGRAs before or on the same day as placing the TST, the third point has been changed to allow for more time. This is based on the fact that there is no strong evidence that tuberculin skin testing will impact the results of IGRAs within a short period.
4	'Low risk' adults and children (< 18 years of age) with a positive TST result	IGRA may be performed in TST-positive, immunocompetent adults who are at relatively low risk of being infected with TB and of progressing to active disease if infected. Persons with a positive IGRA result may be considered for treatment of LTBI.	IGRA may be performed in TST-positive, immunocompetent adults and children who are at relatively low risk of being infected with TB and of progressing to active disease if infected. Persons with a positive IGRA result may be considered for treatment of LTBI.	This recommendation is largely unchanged, but the scope has been expanded to cover children as well as adults.

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IGRAs for immunocompromised

5	Immunocompromised adults and children (< 18 years of age)	1. In an immunocompromised person, the TST should be the initial test used to detect LTBI. If the TST is positive, the person should be considered to have LTBI. 2. However, in light of the known problem with false-negative TST results in immunocompromised populations, a clinician still concerned about the possibility of LTBI in an immunocompromised person with a negative initial TST result may perform an IGRA test. If the IGRA result is positive, the person might be considered to have LTBI. If the IGRA result is indeterminate, the test should be repeated to rule out laboratory error. If the repeat test is also indeterminate, the clinician should suspect anergy and rely on the person's history, clinical features, and any other laboratory results to make a decision as to the likelihood of LTBI. The approach of accepting either test result (TST or IGRA) as positive will improve the sensitivity of detecting LTBI in immunocompromised populations, which would appear a desirable goal. However, in a meta-analysis of five randomized trials, all conducted in countries with a high TB incidence, isoniazid was of no benefit in TST-negative HIV-infected adults. Thus the clinician must weigh the potential benefit of detecting more persons with positive test results against the lack of evidence for the benefit of isoniazid treatment in such persons.	1. In an immunocompromised person (adult or child), the TST should be the initial test used to detect LTBI. If the TST is positive, the person should be considered to have LTBI. 2. However, in light of the known problem with false-negative TST results in immunocompromised populations, a clinician still concerned about the possibility of LTBI in an immunocompromised person with a negative initial TST result may perform an IGRA test. If the IGRA result is positive, the person might be considered to have LTBI. If the IGRA result is indeterminate, the test should be repeated to rule out laboratory error. If the repeat test is also indeterminate, the clinician should suspect anergy and rely on the person's history, clinical features, and any other laboratory results to make a decision as to the likelihood of LTBI. Although both IGRAs may be used as described above, there is evidence that the T-SPOT.TB assay may be more sensitive than the QFT-GIT assay in active TB, and this characteristic might be especially relevant in immunocompromised populations. While the approach of accepting either test result (TST or IGRA) as positive will improve the sensitivity of detecting LTBI in immunocompromised populations, there are no data supporting the efficacy of preventive therapy in TST-negative but IGRA-positive individuals. Thus the clinician must weigh the potential benefit of detecting more persons with positive test results against the lack of evidence for the benefit of preventive therapy in such persons.	This recommendation is largely unchanged, but the scope has been expanded to cover adults as well as children. Also, a note has been added that the T-SPOT.TB test may be more sensitive and therefore helpful in immunocompromised populations.

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IGRAs for immigrant screening, HCWs, prevalence surveys

7	Routine immigrant screening	Routine or mass screening for LTBI of all immigrants, with either TST or IGRA, is not recommended. However, targeted screening for LTBI after arrival in Canada is recommended among foreign-born individuals with clinical conditions that increase their risk of reactivation of LTBI. For these persons, the TST should be used.	Routine or mass screening for LTBI of all immigrants (adults and children), with either TST or IGRA, is not recommended. However, targeted screening for LTBI after arrival in Canada is recommended among foreign-born individuals and travelers (adults and children) with risk factors for reactivation of LTBI (these risk groups are listed below). For these persons, recommendations 1, 2, 3 and 5 apply. Immigrants who should receive targeted screening: 1. HIV infection 2. transplantation (related to immunosuppressant therapy) 3. silicosis 4. chronic renal failure requiring hemodialysis 5. carcinoma of head and neck 6. recent TB infection (≤ 2 years) 7. abnormal chest radiographic result – fibronodular disease or granuloma 8. treatment with glucocorticoids 9. treatment with tumor necrosis factor (TNF)-alpha inhibitors 10. diabetes mellitus (all types) 11. underweight (for TB purposes, this is a body mass index < 20 for most persons) 12. cigarette smoker 13. children < 15 years of age who have lived in a country with high TB incidence and have immigrated within the past 2 years 14. persons ≥ 15 years of age who have lived in a country with high TB incidence, have immigrated within the past 2 years and have either been living with or in known contact with a TB case in the past or are at high risk of development of active TB	This recommendation is largely unchanged, but the scope has been expanded to cover adults as well as children (< 18 years of age). Also, for targeted screening, recommendations 1, 2, 3 and 5 apply. High TB incidence countries have a rate of sputum smear positive pulmonary TB (3 years average), as estimated by the World Health Organization, of 15 per 100,000 or greater. See www.publichealth.gc.ca/tuberculosis for international tuberculosis incidence rates.
8	Serial testing of healthcare workers, prison inmates and staff, and in-employee screening programs	There is insufficient published evidence to recommend serial IGRA testing in populations exposed to TB, such as health care workers or prison staff and inmates. Serial screening for LTBI should continue to be done using the TST, as recommended by the *Canadian Tuberculosis Standards*.	There is insufficient published evidence to recommend serial IGRA testing in populations exposed to TB, such as health care workers or prison staff and inmates. Serial screening for LTBI should continue to be done using the TST, as recommended by the *Canadian Tuberculosis Standards*. IGRAs may be used as a confirmatory test for a positive baseline TST in an immunocompetent health care worker or prison staff/inmate who is felt to have a low pretest probability of LTBI and who has no other high or increased risk factors for progression to active disease if infected. Persons with a positive IGRA result may be considered for treatment of LTBI. If an IGRA is negative, this person could be tested again with IGRA, if an exposure occurs (i.e. post-exposure testing). In the absence of data on optimum timing for post-exposure IGRA testing, the time-window recommended by the *Canadian Tuberculosis Standards* for repeating TST after exposure (i.e. at least 8 weeks after the last exposure) may be used for IGRA as well.	No change, but it has been clarified that IGRAs may be used as a confirmatory test if a false-positive TST is suspected in a low-risk healthcare worker or prison staff/employee or inmate. In such persons, IGRAs may be used for post-exposure screening. See *Canadian Tuberculosis Standards*, Chapter 4, Table 2, for a list of high and increased risk factors for progression of LTBI to active disease.
9	Population (or community-based) surveys for prevalence of LTBI	-	While IGRAs may be useful research tools for prevalence estimation, there is insufficient published evidence to recommend the routine use of IGRAs in population or community-based surveys for estimating the prevalence of LTBI. Prevalence surveys should continue to be done using the TST.	This new recommendation addresses the use of IGRAs in prevalence surveys.

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Ongoing research in Montreal

- CIHR funded studies on:
  - Cost-effectiveness of IGRAs
  - IGRAs in serial testing of healthcare workers
  - IGRAs in household contacts
  - IGRAs in diagnosis and management of TB infection in children
  - IGRAs and other biomarkers for LTBI treatment monitoring