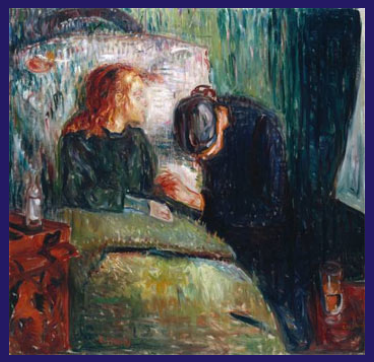
Beth Israel Deaconess Medical Center

A teaching hospital of Harvard Medical School



Munch
Sick child

IGRA guidelines: concordance, discordance or confusion?

Claudia Denkinger, MD PhD
Beth Israel Deaconess Medical Center, Boston, MA

No conflict of interest

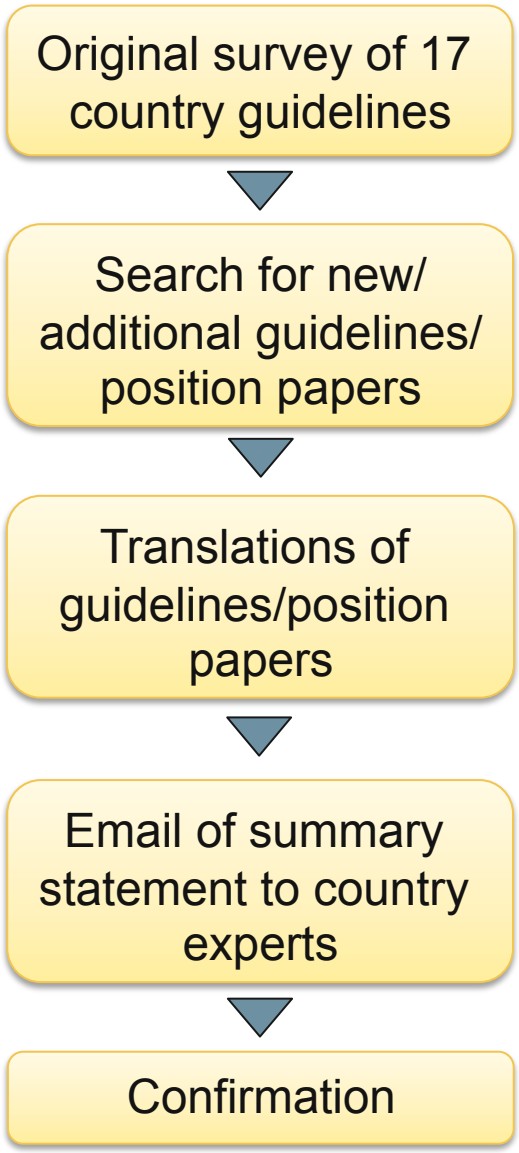
Background

- Latent TB diagnosis relies on immunodiagnostic methods with the tuberculin skin test (TST) and more recently the interferon-gamma release assays (IGRAs).
- Two commercial IGRAs are available
  - QuantiFERON-TB© Gold In-Tube (QFT-GIT, Cellestis Limited, Chadstone, Victoria, Australia)
  - TB-SPOT.TB© assay (Oxford Immunotec, Abingdon, UK)
- The use of IGRAs has increased substantially over the last five years, mostly in low-incidence countries.
- Many studies, meta-analyses and reviews have been performed to assess the role IGRAs in the diagnosis of latent and active TB.
- More and more guidelines and position papers have been published to direct clinical practice.

How to test? - TST versus IGRA

	TST	IGRA
+	• Simple, low-tech test • Can be done by trained HCW in remote locations • Effect of BCG on TST results is minimal if vaccination is given at birth and not repeated • Longitudinal studies have demonstrated its predictive value	• IGRA requires only one visit • Boosting effect eliminated by ex-vivo testing • IGRA interpretation is objective • IGRA results can be available within 24-48 hours • No cross-reactivity with BCG and less with NTM

Methods



- Literature search
- Contacting >50 experts
- Most updated guidelines included
- Guidelines from MOH vs professional organizations

- By authors
- By experts in countries

RICHTLIJN

Interferon Gamma Release Assays bij de diagnostiek van tuberculose

Updated Guidelines
Interferon Gamma Release Assays
to Detect *Mycobacterium tuberculosis*
Infection — United States, 2010

Retningslinjer for undersøgelse for latent og aktiv tuberkulose forud for behandling med TNF-س og andre biologiske lægemidler hos natologiske, reumatologiske, nterologiske og lungemedicinske patienter.

TEST DE DÉTECTION DE LA PRODUCTION D'INTERFÉRON γ POUR LE DIAGNOSTIC DES INFECTIONS TUBERCULEUSES

Saudi guidelines for testing and treatment of latent tuberculosis infection

Joint Statement of the Saudi Thoracic Society, the Saudi Society of Medical Microbiology and Infectious Diseases, the Saudi Association of Public Health, and the Society of Family and Community Medicine

culosis

Empfehlungen für die Umgebungsuntersuc
bei Tuberkulose
Deutsches Zentralkomitee zur Bekämpfung der Tuberkulose

医療施設内結核感染対策について

日本結核病学会予防委員会

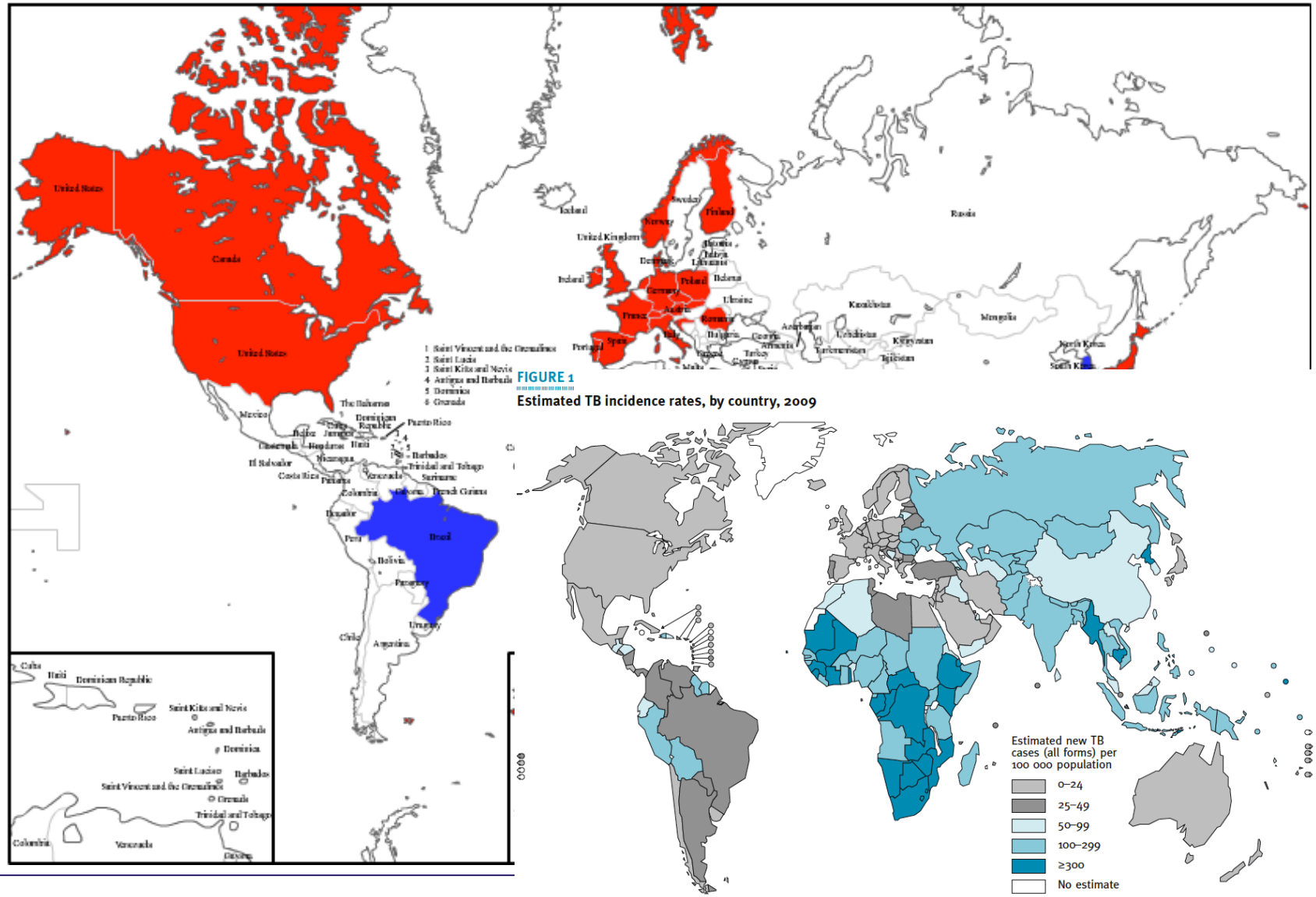
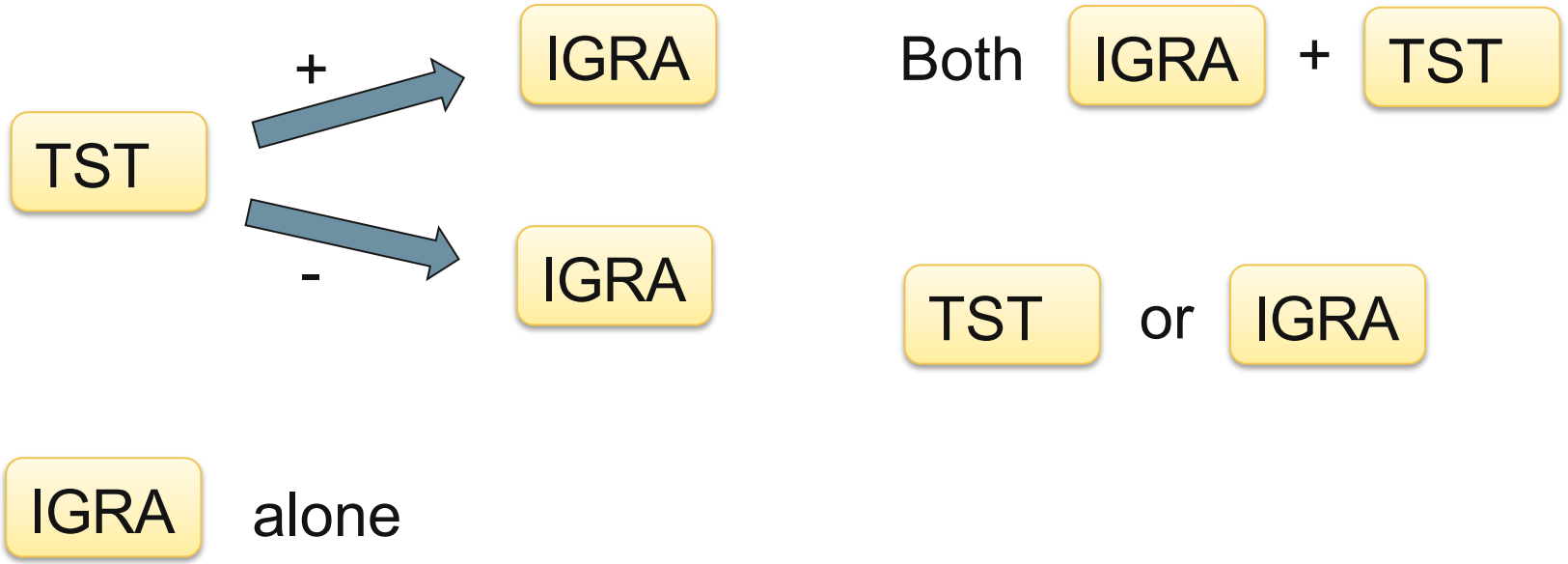


FIGURE 1

Estimated TB incidence rates, by country, 2009

Results Summary

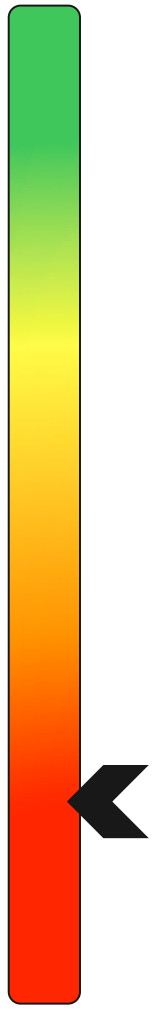


Outline

- Active TB
- Contact tracing in adults
- Contact tracing in children
- LTBI screening in HIV
- LTBI screening in patients with IMIDs starting on TNF-α inhibitors
- LTBI screening in immigrants
- Serial screening for LTBI in healthcare workers

Diagnosis of active tuberculosis - Background

- Recent meta-analysis of studies in low- and middle-income countries
  - In HIV-infected patients pooled sensitivity was 76% for the T-SPOT.TB assay and 60% for the QFT-GIT.
  - In non-HIV-infected patients pooled sensitivity was 83% for T-SPOT.TB and 69% for QFT-GIT.
  - The specificity estimates of IGRAs were low for both non-HIV-infected (T-SPOT.TB 61%, QFT-GIT 52%) and HIV-infected individuals (T-SPOT.TB 52%, QFT-GIT 50%).
- Another recent meta-analysis from both high and low-incidence countries confirmed these findings.
- In summary, both reviews/meta-analyses concluded that IGRAs should not be used in the diagnostic workup of active TB in adults.



Metcalfe J Infec Dis 2011
Sester Eur Resp J 2011

Diagnosis of active TB - Guidelines

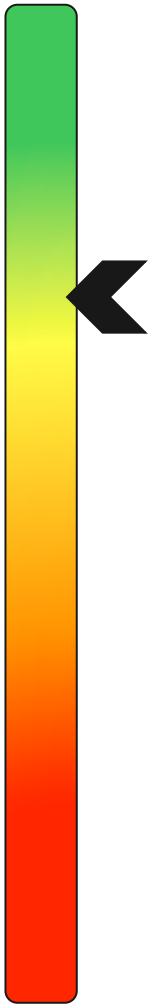
- ECDC: "IGRAs should not replace the standard diagnostic methods […] for diagnosing active TB. […] However, based on limited evidence, in certain clinical situations (e.g. patients with extrapulmonary TB, patients who test negative for acid-fast bacilli in sputum and/or negative for MTB on culture, TB diagnosis in children, or in the differential diagnosis of infection with NTM) IGRAs could contribute supplementary information as part of the diagnostic work-up."
- Some guidelines (i.e. Canada) explicitly recommend against the use of IGRAs in the diagnosis of active TB in adults but include them as part of the diagnostic algorithm in children as tests which provide evidence of TB infection.
- The WHO recommends against the use of IGRAs for active TB in low and middle income countries due to the poor specificity on account of a high background prevalence of LTBI.

Diagnosis of active TB - Guidelines

Recommendation	Subgroup	Guideline or position statement*
For the use of IGRAs but only as an adjunct (some guidelines specify the use only when other diagnostic tests have been unrevealing)	In adults	ECDC, USA-CDC, UK, France (only for extrapulmonary TB), Australia, Slovakia, Japan, Netherlands, Norway, Bulgaria, Portugal, Denmark, Austria
	In children	ECDC, Canada, USA (CDC and AAP), UK, Switzerland, Australia, Slovakia, Japan (children >12 years of age), Saudi Arabia, Netherlands, Norway, Bulgaria, Portugal, Croatia, Denmark, Austria
Against the use of IGRAs	In adults	WHO, Canada, Switzerland, Saudi Arabia, Croatia, Ireland, South Korea, Brazil
	In children	WHO, France, Ireland, South Korea, Brazil
No recommendations		Germany, Italy, Spain, Finland, Poland, Czech Republic

Contact Investigation in Adults - Background

- The most obvious strength of IGRAs is their high specificity, as they allow the clinician to differentiate between a sensitization due to BCG vaccination or non-tuberculous mycobacteria (NTM) exposure and contact with an active TB case.
- However, recent cohort studies suggested that IGRAs, similar to the TST, have only modest predictive ability. Similar to the TST, only 1 to 3% of IGRA-positive contacts develop active TB over 2 years of follow-up.
- A combination of TST/IGRA and risk factor information may be more helpful. Web-based algorithms and information of country – specific policies are available
  - http://www.bcgatlas.org
  - http://www.tstin3d.com



Menzies Ann Int Med 2007
Mori J Infec Chemo 2009
Pai Lancet ID 2004
Del Corral PLoS One 2009
Hill PLoS One 2008
Pao Nat Rev Microbiol 2010

THE BC

A DATABASE OF GLOBAL BC

Home | Questionnaire | A

Welcome to the World A

This interactive website policies and practices fo resource for clinicians, that may be helpful for new TB vaccines.

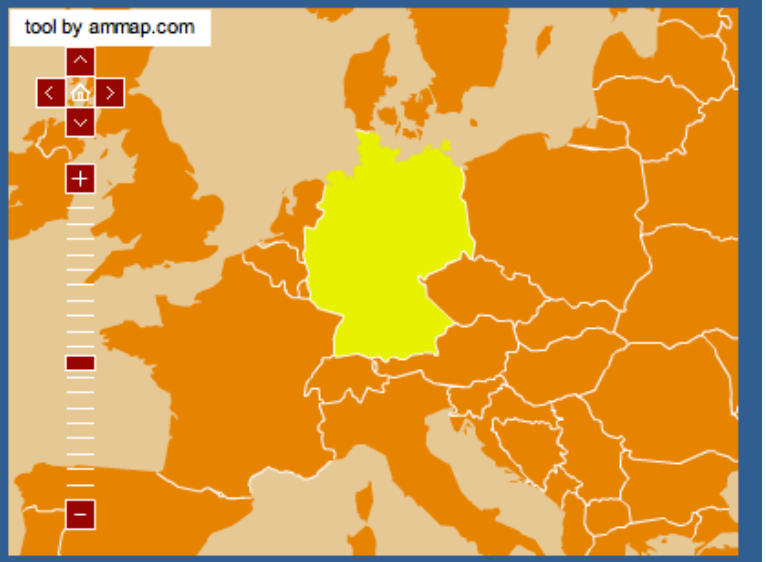
The rationa PLoS Medi

Please sel select a co country's E

Choose a Country

Germany

Country	Germany
Region	..
TB Incidence (per 100 000 per year) * †	5
TB Incidence (Count) * †	4000
TB Prevalence (per 100 000 per year) * ‡	6
TB Prevalence (Count) * ‡	4900
Income group (World Bank)	High income: OECD
Current BCG vaccination?	No
BCG Recommendation Type	B
Which year was vaccination introduced?	1961
Year BCG stopped?	1998
Timing of 1st BCG?	At birth
Multiple BCG?	No
Timing of BCG #2	N/A
Timing of BCG #3	N/A
Multiple BCG in the past?	No
Timing of old BCG #2	N/A
Timing of old BCG #3	N/A
Year booster BCG stopped	N/A
BCG Strain	Kopenhagen 1331, Chiron-Behring, Germany
Is TST done post BCG?	Yes
Year of BCG cooverage estimate	DK
BCG coverage (%)	DK
Year of changes to BCG schedule	1951 & 1975
Details of changes	Histories different for West and East Germany (East: 1951, revacc of TST neg at age 15years, also used different strains, more info in questionnaire...1975-move to vaccinate high risk kids only



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.

The Online TST/IGRA Interpreter

Version 3.0

English

The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of ≥5mm, based on his/her clinical profile. It is intended for adults tested with standard tuberculin (5 TU PPDS, or 2 TU RT-23) and/or a commercial Interferon Gamma release assay (IGRA).

Enter

Review & Analysis:
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Dick Menzies, MD, MSc
Madhukar Pai, MD, PhD
Andrea Benedetti, PhD

V2.0
V3.0

Design & Programming:
Stephanie Law, MSc

Trans
Chantal

Affili
McGill University & McGill University H

McGill

Suppo

Public Health Agency of Canada | Agence de publique du

Calculator | About | Disclaimer | References | Links

The Online TST/IGRA Interpreter

Version 3.0

The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of ≥5mm, based on his/her clinical profile. It is intended for adults tested with standard tuberculin (5 TU PPDS, or 2 TU RT-23) and/or a commercial Interferon Gamma release assay (IGRA). For more details about the algorithm used, go to the About page. The current version of the algorithm contains modifications of the original version, which was detailed in a paper by Menzies, et al. (2008). For further information see references, or contact dick.menzies@mcgill.ca

Results

Once you have completed the form, click on "Submit" and your results will show up in this space.

For inquiries, and suggestions please contact dick.menzies@mcgill.ca.

Please select the best response for each field:

TST Size: Select...

IGRA Result: IGRA Not Done

Age: Select...

Age at immigration (if person immigrated to a low TB incidence country): N/A

Country of birth: Select...

BCG status: Select...

For more info, visit: BCG World Atlas.

Recent contact with active TB: No Contact

Please select all the conditions that currently apply to the patient:
(If none of these conditions apply, please leave boxes unchecked)

- ☐ AIDS
- ☐ Abnormal chest x-ray: fibronodular disease
- ☐ Chronic renal failure requiring hemodialysis
- ☐ Diabetes Mellitus (all types)
- ☐ Recent TB infection (TST conversion ≤ 2 years ago)
- ☐ Abnormal chest x-ray: granuloma
- ☐ Carcinoma of head and neck
- ☐ Cigarette smoker(>1 pack/day)
- ☐ HIV infection
- ☐ Transplantation (requiring immune-suppressant therapy)

Contact Investigation in Adults - Guidelines

- Most guidelines favor a two-step testing approach. A TST is done in the first step and if positive, it is followed-up with an IGRA.
- The two-step approach is primarily intended to increase specificity in individuals with prior BCG-vaccination.
- Some guidelines, i.e. Canada, use a differentiated approach based on the risk of the patient.
- Some guidelines suggest that either an IGRA or a TST should be used for contact investigation (i.e. USA) and specify certain subgroups in which the IGRA should be used preferentially.
- The WHO issued a recommendation against the use of IGRAs and for the use of TST in low and middle income settings.

Contact Investigation in Adults - Guidelines

Recommendation	Guideline or position statement*
TST alone	WHO, Brazil, ECDC (high-incidence countries)
TST followed by IGRA, if TST positive (either IGRA only in BCG vaccinated persons or independent of BCG vaccine)	Canada (low-risk contacts), Germany, Italy, Switzerland, Spain, Saudi Arabia, Netherlands, Norway, Bulgaria, Portugal, Ireland, ECDC (low-incidence countries), and for UK and South Korea only in adults <35 of age
Both TST and IGRA	Canada (high-risk contacts), Czech Republic, Croatia, Austria, Australia (IGRA may be considered in addition)
Either TST or IGRA	USA, Denmark, Finland (IGRA preferred if BCG vaccinated in all three countries), South Korea (only in adults <35 of age), Austria
IGRA alone	Slovakia, Japan, France

Contact Tracing in Children - Background

- There are limited data on the use of IGRAs for the diagnosis of LTBI in children.
- The data are especially sparse in the very young children, and very few studies have assessed the predictive value of IGRAs in children.
- Two recent meta-analyses concluded that TST and IGRAs have similar accuracy for the detection of TB infection or the diagnosis of disease in children.
- Treatment for LTBI based on a positive TST result only, regardless of BCG vaccination or even if a TST is negative but a high clinical suspicion persists, is justified by the fact that young children are at high risk for progression to active TB.

Mandalakas IJTLD 2011
Machingaidze Ped J ID 2011

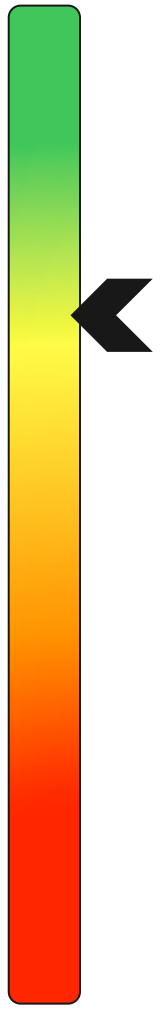
Contact Tracing in Children - Guidelines

- Guidelines regarding children are very heterogeneous and reflect the uncertainties in the evidence base.
- Many continue to prefer a TST alone, either for all children or only for children under five years of age.
- Most other guidelines recommend a TST in combination with an IGRA if the TST is positive, especially for BCG vaccinated children.
- A few countries recommend both tests together (e.g. Canada- for high-risk contacts) or suggest that an IGRA may be used if initial TST is negative in certain age-groups to increase sensitivity.

Recommendation	Guideline or position statement*
TST alone	WHO, ECDC, France, Brazil, Switzerland (IGRA in addition only in case of doubt), Slovakia (in BCG non-vaccinated children), South Korea (for children <5)
TST alone (in children 0-4 years old); TST followed by IGRA, if TST positive (for children 5-17 years old)	Canada (low-risk contacts), Japan, Ireland, USA-AAP (for children >5, IGRA may also replace TST)
TST followed by IGRA, if TST positive	Germany, Italy, Spain, Saudi Arabia, Netherlands (dependent on BCG-vaccination status and result of TST, only TST might be sufficient), Bulgaria, and for children >5 years of age only in Portugal and UK
TST followed by IGRA, if TST negative	Portugal (for children <5), UK (for children 2-5)
Either TST or IGRA	Denmark, USA-CDC (but TST is preferred in children <5), South Korea (for children >5, but TST preferred), Finland
Both TST and IGRA	Canada (high-risk contacts), Czech Republic, Croatia, Australia (IGRA may be considered in addition for children >2)
IGRA alone	Norway

LTBI in Individuals with HIV Infection - Background

- Data on the use of IGRAs in people living with HIV were summarized in a recent systematic review.
- The sensitivity estimate in HIV-infected patients with culture-confirmed TB was higher for T-SPOT.TB (72%) than for QFT-GIT (61%), but not consistently more sensitive than the TST in head-to-head comparisons.
- The agreement between the two IGRA and TST was higher in the high-income countries were BCG-vaccination was used less frequently.
- Some evidence suggests that IGRAs, and especially the T-SPOT. TB assay, are less affected by HIV-related immunosuppression than the TST, but the differences between the tests were small.
- Overall, the data thus far indicates that IGRAs perform similarly to the TST in identifying HIV-infected individuals with LTBI.



LTBI in Individuals with HIV Infection - Guidelines

- This equivocal data is also reflected in the wide array of different country recommendations.
- The guidelines for low-resource and high-TB-incidence settings, the Brazilian and the WHO guidelines, recommend the TST.
- The other guidelines and position papers clearly show a trend towards greater use of IGRAs.
- While some countries recommend the use of IGRA alone, other countries/organizations (e.g. ECDC, USA, and UK for CD4 count <200) suggest the use of both tests together (upfront or if the chosen initial test is negative) in order to increase the sensitivity.
- Yet others suggest a two-step approach with a negative TST followed by an IGRA to increase sensitivity.

LTBI in Individuals with HIV Infection - Guidelines

Recommendation	Guideline or position statement*
TST alone	WHO, Brazil
TST followed by IGRA, if TST positive (and BCG vaccinated)	Spain
TST followed by IGRA, if TST negative	Canada, Italy, Saudi Arabia, Spain, Ireland
Either TST or IGRA	Denmark, South Korea, Austria
Both TST and IGRA	ECDC, Portugal, Croatia, Slovakia, Netherlands, USA (if either initial test negative), South Korea, UK
IGRA alone	Switzerland, Bulgaria, France, UK (if CD4 200-500)
No specific recommendations	Germany, Czech Republic, Norway, Japan, Finland, Australia

LTBI in persons on TNF-α inhibitors - Background

- Only few and very heterogeneous studies have evaluated the performance of IGRAs in screening for LTBI in patients with IMIDs. Two recent reviews have synthesized the data.
- The differences in the studies relate to:
  - the level of immunosuppression
  - the types of TNFa-inhibitors used
  - the IMIDs treated
  - the tests that were evaluated
  - the rate of BCG-vaccination in the population.
- In addition, the lack of any data on predictive value of IGRA limited the studies.
- In summary, the authors concluded that the current evidence does not suggest superiority of IGRAs over the TST in identifying latent TB in individuals with IMIDs.

Smith Curr Opin Rheum 2011
Winthrop Int J Adv Rheum 2010

LTBI in persons on TNF-a inhibitors - Guidelines

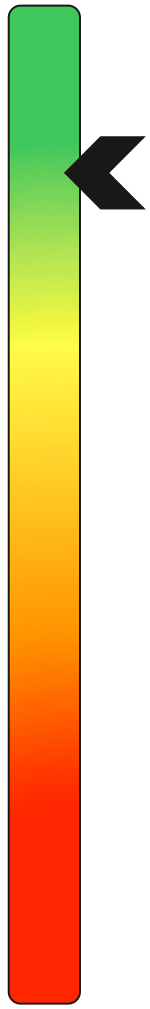
- Similar to HIV, the guidelines for LTBI screening for patients on TNFa-inhibitors reflect the lack of definitive data and a number of different strategies are recommended.
- Again a trend towards an increase use of IGRAs is seen.
- A few countries favour the IGRAs as the only test.
- Many guidelines combine both tests in order to increase sensitivity (e.g. ECDC, USA, UK) either upfront or if the initially chosen test is negative.
- Alternatively, a two-step approach with an IGRA following a TST, if the TST is negative, is recommended to increase sensitivity but limit cost (i.e. Canada).

LTBI in persons on TNF-a inhibitors - Guidelines

Recommendation	Guideline or position statement*
TST alone	Brazil
TST followed by IGRA, if TST positive	Spain, Norway
TST followed by IGRA, if TST negative	Canada, Italy, Spain, Saudi Arabia
Either TST or IGRA	Australia-ARA, Denmark (IGRA favored), South Korea
Both TST and IGRA	ECDC, UK (alternatively IGRA alone), USA (if either initial test negative), Portugal, Croatia, Czech Republic, Slovakia, Netherlands, South Korea, Ireland (TST preferred)
IGRA alone	Germany, Switzerland, Bulgaria, Japan, France, Poland, Austria
No recommendations	Finland, Australia-NTAC

LTBI Screening of Immigrants – Background/Guidelines

- In low-incidence countries, a majority of the TB cases occur among recent immigrants and foreign-born persons.
- Most guidelines that include recommendations on immigrant screening are from low-incidence countries and focus on immigrants from high-incidence settings.
- Others also include recommendations for immigrants who are likely to develop active disease (i.e. children or persons with underlying disease that predisposes them to a reactivation of a LTBI) independent of their country of origin.
- All guidelines that do make recommendations for immigrant screening incorporate IGRAs.
- The most common algorithm is a TST followed by an IGRA if positive. This algorithm is intended to increase specificity given the widespread use of BCG vaccination in TB endemic countries.



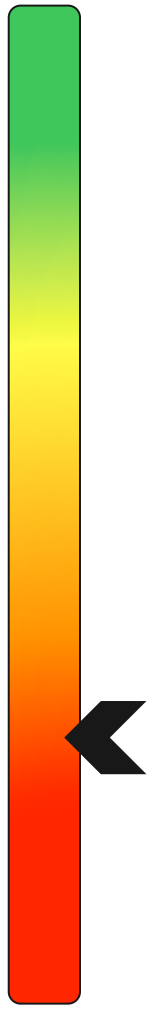
Geng NEJM 2002
Jasmer Ann Int Med 1999

LTBI Screening of Immigrants - Guidelines

Recommendation	Guideline or position statement*
TST followed by IGRA, if TST positive	UK (for children age 5-15), Italy, Switzerland, Spain, Norway, Ireland, Bulgaria, France (in children), Slovakia, Netherlands (for children only; dependent on BCG-vaccination status and result of TST, only TST might be sufficient)
Both TST and IGRA	Czech Republic, UK (for adults age 16-35; or IGRA alone alternatively)
Either TST or IGRA	USA (IGRA preferred in BCG-vaccinated persons), Canada, Australia
IGRA alone	France (in adults)
No recommendations/ not recommended	Germany, Japan, Saudi Arabia, Brazil, Portugal, Croatia, Denmark, South Korea, Finland, Poland, Austria

Serial Testing of Healthcare Workers - Background

- The value of IGRAs in the testing of healthcare workers has been investigated in over 50 studies, summarized in a recent systematic review.
- The review differentiates between initial testing (e.g. pre-employment) and serial (repeated) testing of healthcare workers.
- Overall, the review concluded that the use of IGRAs instead of TST for one-time screening may result in a lower prevalence of positive tests and fewer healthcare workers who require LTBI treatment, particularly in low TB incidence settings.
- However, the use of IGRAs for serial testing is complicated by
  - lack of data on optimal cut-offs for serial testing
  - unclear interpretation and prognosis of conversions and reversions.



Serial Testing of Healthcare Workers - Guidelines

- The uncertainty in the data is also reflected in the guidelines.
- Many guidelines and position papers do not make recommendations for the serial screening of healthcare workers.
- Some countries suggest the use of IGRAs alone or as an alternative to the TST for serial healthcare worker screening.
- Some of the guidelines specifically comment on the limitations of the IGRAs for serial testing:
  - The Canadian guideline states that "there is insufficient published evidence to recommend serial IGRA testing in populations exposed to TB, such as healthcare workers or prison staff and inmates".
  - The CDC guideline states that "the criteria for interpreting changes in an IGRA that identify new infections remain uncertain".
- Because of such concerns, many countries actually favor a TST only or a TST with a second-step IGRA if the TST is positive.

Serial Testing of Healthcare Workers - Guidelines

Recommendation	Guideline or position statement*
TST alone	Brazil, South Korea, Canada, Saudi Arabia, Ireland, Austria
TST followed by IGRA, if TST positive	Spain, Netherlands, Bulgaria
Either TST or IGRA	USA, Switzerland, Italy (in BCG-vaccinated IGRA preferred)
IGRA alone	Slovakia, Japan, Switzerland, Netherlands, Portugal, France
No recommendations/ Not recommended	Australia, Czech Republic, Norway, Croatia, Denmark, Germany, UK, Finland, ECDC

Conclusions

- A growing number of guidelines and position papers now address the use of IGRAs. Overall, the use of IGRAs is increasingly recommended, primarily in low-incidence settings.
- There is considerable heterogeneity in guidelines.
- In high-incidence and low-resource countries, the TST is still favored as there is no strong evidence that IGRAs are superior to the TST in such settings.
- In low-incidence and high-resource settings, the higher specificity of IGRAs and their logistical advantages seem to enhance their adoption and usage.
- An increased amount of data has recently become available especially with respect to the use of IGRAs in patients starting TNFα-inhibitors or in children younger than 5 years of age, rendering older guidelines outdated.

Limitations of guidelines

- While most guidelines (78%) cited systematic reviews of available data, most (70%) did not use objective and transparent grading systems (e.g. GRADE) for guideline development.
- The majority did not include statements on conflict of interest.
- These findings are consistent with published data on poor methodological quality of TB guidelines.
- On the positive side, several countries have attempted to update their guidelines, as the evidence base on IGRAs has steadily matured.
- Future IGRA guidelines should aim to be transparent, evidence-based, periodically updated, and free of financial conflicts and industry involvement.

Limitations of review

- Language:
  - Language barrier
  - Mistakes with translation
  - Difficulties with interpretation: “I am not sure if this is how I would interpret our guidelines.” (Quote from one national expert writing to the other)
- Unidentified guidelines
- Limited responses from national experts (although only happened on 2 occasions)
- Limited guidelines from high-incidence countries

Acknowledgement

- Dr. Madhukar Pai

- Over 50 colleagues from 28 countries who provided input and information.

Clin Microbiol Infect. 2011 Jun;17(6):806-14. doi: 10.1111/j.1469-0691.2011.03555.x.

Guidelines on interferon-γ release assays for tuberculosis infection: concordance, discordance or confusion?

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Thank you/ Danke!!!