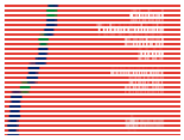
Diagnosis of tuberculosis

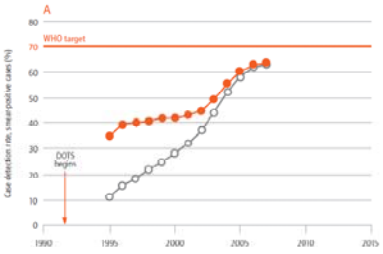
Madhukar Pai, MD, PhD
Assistant Professor, Epidemiology
McGill University, Montreal, Canada
madhukar.pai@mcgill.ca

McGill

Global TB Case Detection
A major concern



- 2.6 million new smear + cases notified in 2007
- 64% of the estimated 4.1 million cases



- 5.3 million new cases overall notified in 2007
- 57% of the estimated 9.3 million cases

WHO Report 2009 – Global Tuberculosis Control

Why is diagnosis the Achilles' heel of TB control?

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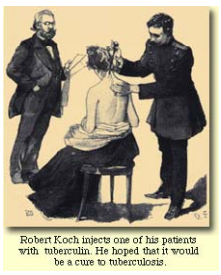
Diagnostic tools that Koch used…

Microscopy

Culture



Tuberculin test

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are still in use today!

- Active TB
  - Sputum microscopy [1882]
  - Mycobacterial culture [1882]
  - Chest X-rays [1896]
- Latent TB (LTBI)
  - Tuberculin skin test [1890]

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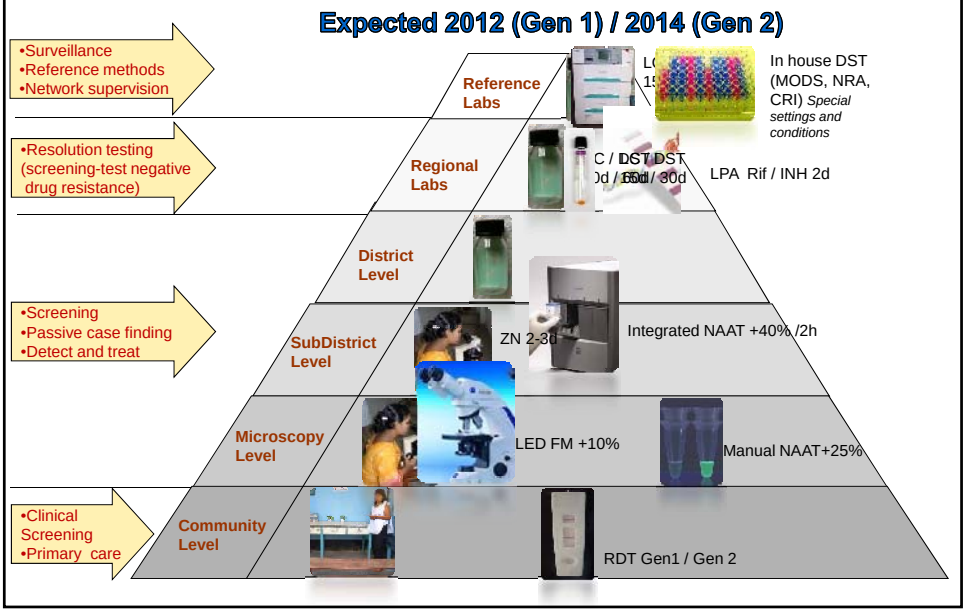
The landscape in 2010 is much improved



Diagnosis of latent tuberculosis infection (LTBI)



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

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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Who should be tested?

UpToDate ONLINE 17.2

Print Email

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

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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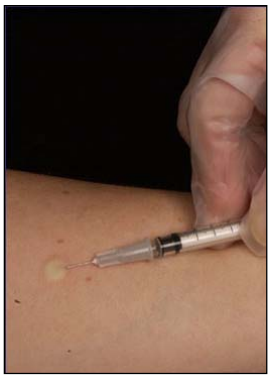
Administering the TST

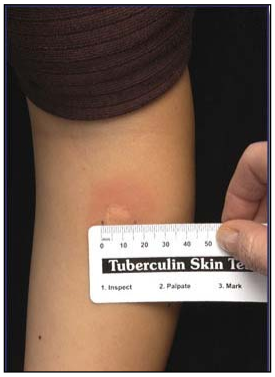
- Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-gauge needle
- Produce a wheal 6 to 10 mm in diameter



Source: US CDC

Reading the TST

- 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
- Self reading is not accurate



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

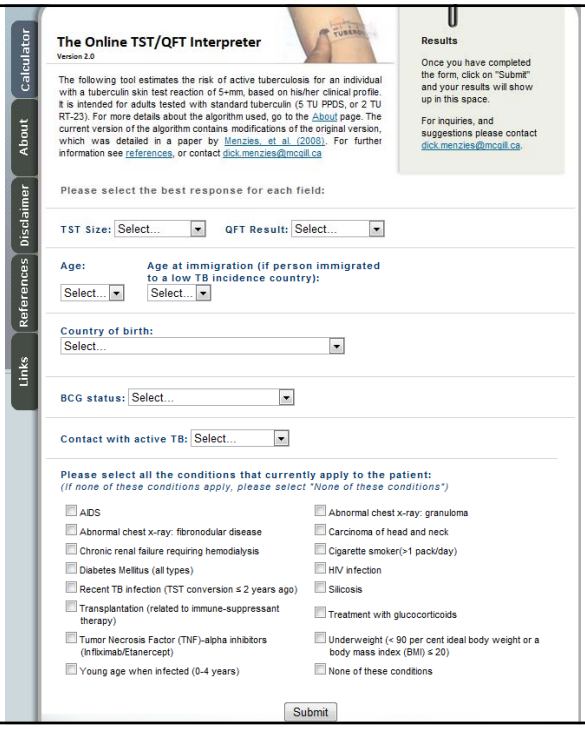
Potential causes of false negative tuberculin tests

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

www.tstin3d.com



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

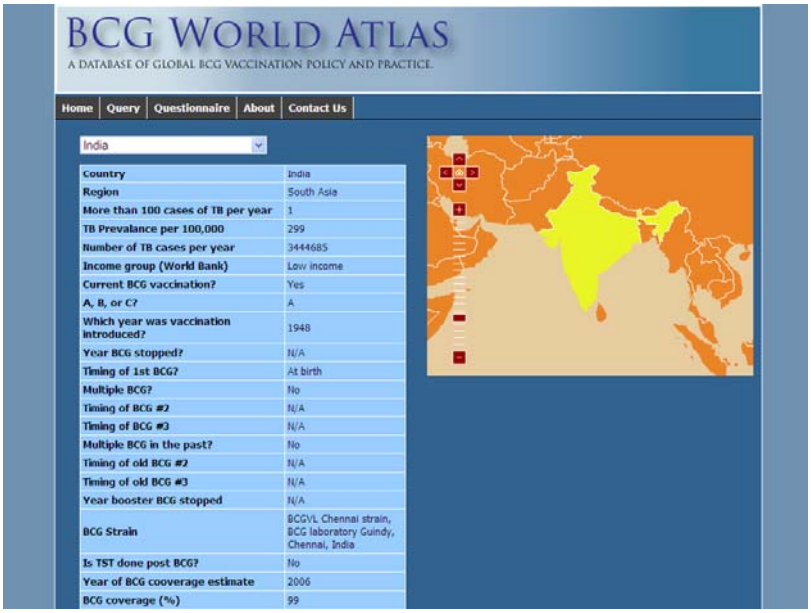
False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria?

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

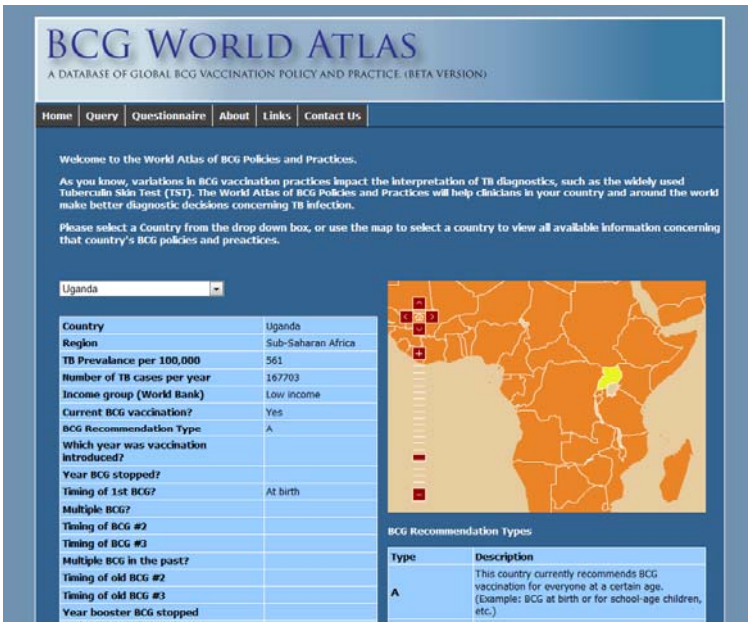
In India, BCG has limited effect on TST



Country	India
Region	South Asia
More than 100 cases of TB per year	1
TB Prevalance per 100,000	299
Number of TB cases per year	3444685
Income group (World Bank)	Low income
Current BCG vaccination?	Yes
A, B, or C?	A
Which year was vaccination introduced?	1948
Year BCG stopped?	N/A
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	BCGVL Chennai strain, BCG laboratory Guindy, Chennai, India
Is TST done post BCG?	No
Year of BCG cooverage estimate	2006
BCG coverage (%)	99

WWW.BCGATLAS.ORG

In Uganda, BCG has limited effect on TST



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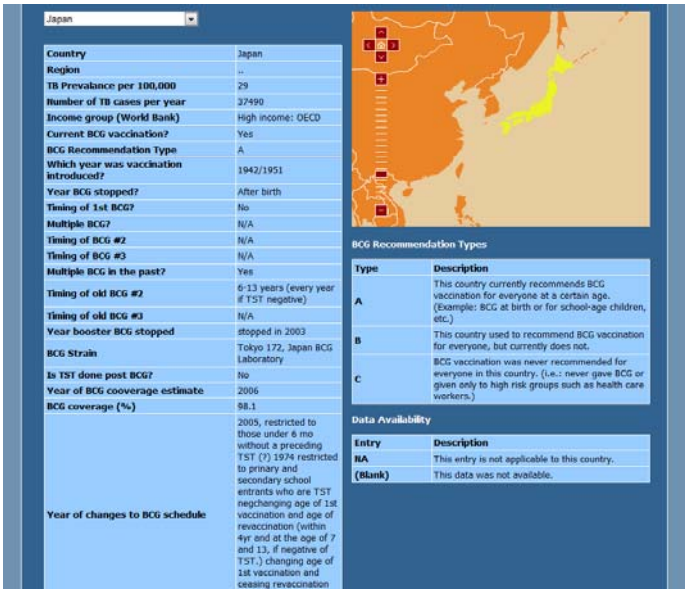
In Japan, BCG has a major effect on TST



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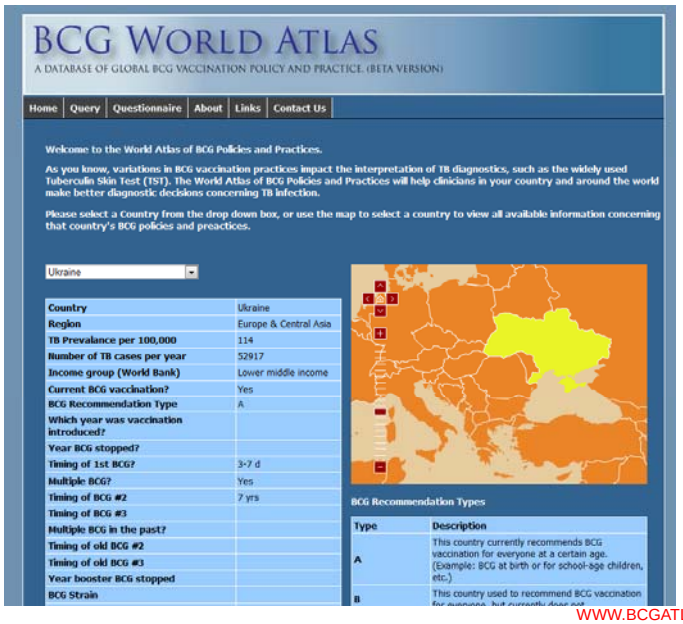
In Ukraine, BCG has a major effect on TST



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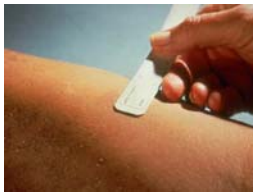
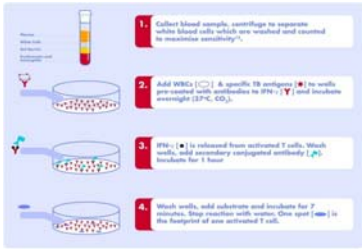
IGRAs





T-SPOT.*TB*® [Oxford Immunotec, UK]

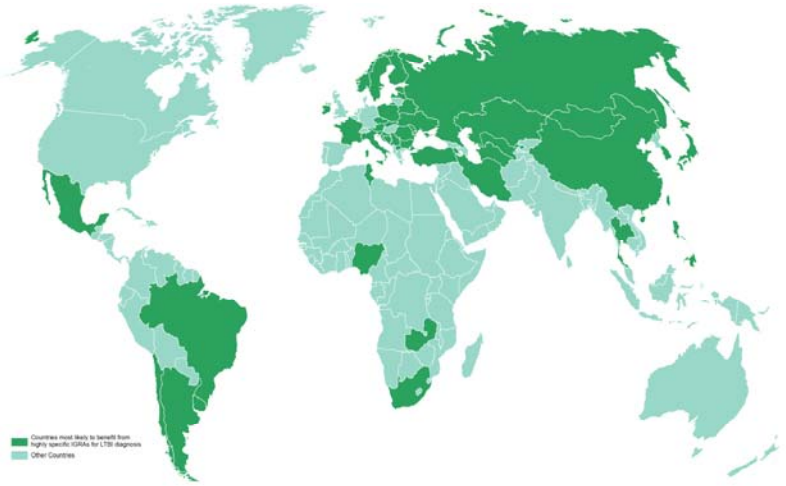
QuantiFERON-TB Gold® In Tube [Cellestis Ltd, Australia]

Quick Summary of Evidence

- TST specificity is high in BCG non-vaccinated; but lower 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

Countries that may benefit from IGRAs



Zwerling A et al.

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
    - A negative IGRA does not rule out active TB at any age.
  - 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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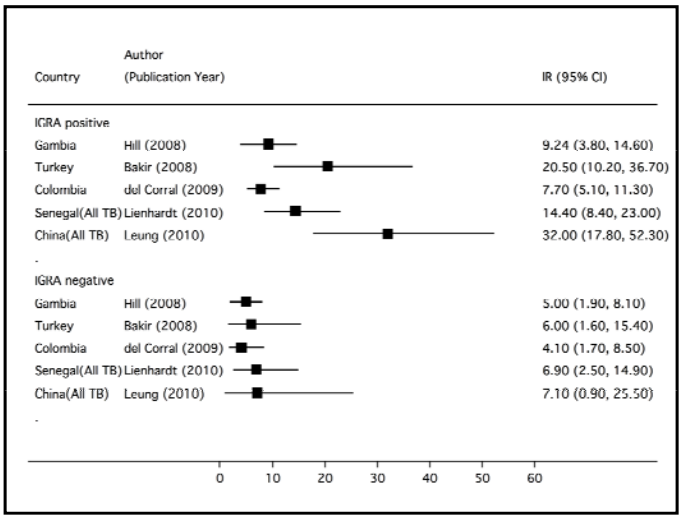
Predictive value: Incidence rates of TB by IGRA status



Incidence rate per 1000 person-years

Rangaka M et al.

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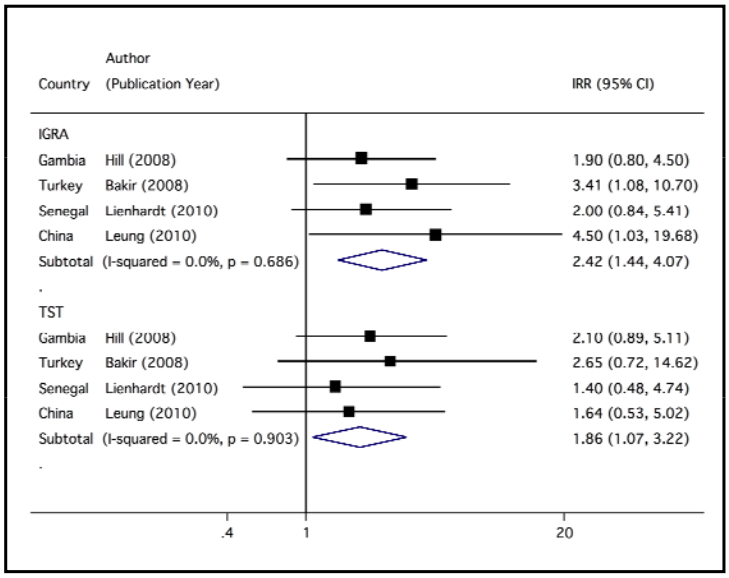
Rates of disease progression in IGRA+ in the largest high burden country studies

Country	N	Test	Incidence of active TB in IGRA+ groups
The Gambia [Hill et al. 2008]	2348	ELISPOT (in-house)	9/1000 person-yr
Turkey [Bakir et al. 2008]	908	ELISPOT (T-SPOT.TB)	21/1000 person-yr
S Africa [Mahomed et al. 2009 (abstract)]	5248	QFT	6/1000 person-yr
Colombia [del Corral et al. 2009]	2060	In-house whole-blood CFP-10 assay	11/1000 person-yr
Senegal [Lienhardt et al. PLoS One 2010]	2679	ELISPOT (in-house)	14/1000 person-yr

Results: IGRA vs TST: Which has greater predictive ability?



Rangaka M et al.

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Conclusions on predictive value

- Incidence rates of TB, even in IGRA positive individuals, are low, suggesting that a vast majority (>95%) of IGRA+ individuals do not progress to TB disease during follow-up. This is similar to the TST.
- All existing LTBI tests (TST and IGRAs) have only modest predictive value and may not help identify those who are at highest risk of progression to disease.
- Based on the evidence thus far, IGRAs appear to have similar predictive value as the TST.
- In some settings, the % IGRA+ will be less than % TST+, reducing the number needed for IPT
- The search for highly predictive biomarkers must continue

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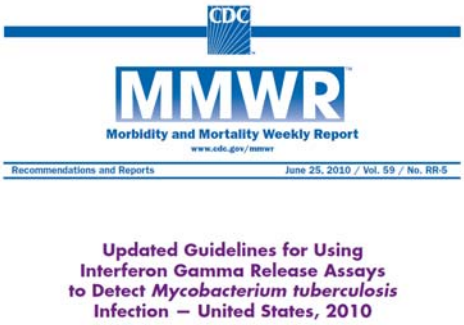
USA: CDC Guidelines, 2010

IGRAs can be used in place of (but not in addition to) TST in all situations in which CDC recommends TST as an aid in diagnosing LTBI (contact investigations, testing during pregnancy, and screening of health care workers and others undergoing serial evaluation for LTBI).

IGRAs are preferred over TST in individuals who have received BCG and individuals from groups that have poor rates of return for TST reading.

TST is preferred over IGRAs for testing children less than 5 years of age.


CDC

MMWR

Morbidity and Mortality Weekly Report

www.cdc.gov/mmwr

Recommendations and Reports — June 25, 2010 / Vol. 59 / No. RR-5

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

Canadian IGRA guidelines

•For persons with a positive TST and low pretest probability of recently acquired LTBI, as well as no other risk factors for progression to active disease, IGRAs may be used as a confirmatory test to exclude the possibility of a false positive TST.

•For persons with high risk of progression to active disease if infected, a TST should be used; if this is positive the person should be considered to have LTBI. If negative, an IGRA could be done; if positive the person should be considered to have LTBI.


Canada Communicable Disease Report ◆ Relevé des maladies transmissibles au Canada

CCDR•RMTC

An Advisory Committee Statement (ACS)

Canadian Tuberculosis Committee (CTC)[**]

Recommendations on Interferon Gamma Release Assaysfor the Diagnosis of Latent Tuberculosis Infection—2010 Update

Preamble

Une déclaration d'un comité consultatif (DCC)

Le Comité canadien de lutte antituberculeuse (CCLA)[**]

Recommandations sur les tests de libération d'interféron-gamma pour la détection de l'infection tuberculeuse latente – Mise à jour de 2010

Préambule

Canadian IGRA guidelines

•In immunocompromised individuals, the TST should be the initial test used to detect LTBI. If the TST is positive, the person should be considered to have LTBI. However, given the rate of false-negative TST results in immunocompromised populations, IGRA testing is appropriate in the setting of negative TST results. If the IGRA result is positive, the person may be considered to have LTBI.

•In children, IGRAs may be used as a supplementary diagnostic tool, together with clinical specimens for definitive microbiologic diagnosis, TST and other investigations. However, IGRA should not be a substitute for, or obviate the need for, appropriate microbiologic specimen collection. A negative IGRA (or TST) does NOT rule out active TB at any age.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Préambule

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Diagnosis of active TB and drug-resistance

Diagnostic options

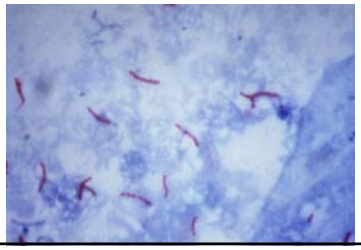
- Smear microscopy
- Culture
- NAAT
- Drug Susceptibility Testing

Smear Microscopy

- 50-70% sensitive, very specific
- Quick, cheap, relatively easy
- Stains take advantage of mycolic acid in cell walls of Mycobacteria
- “Acid Fast Bacilli”
- Stain → Decolorize → Counterstain

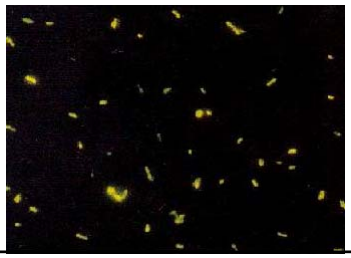
LIGHT MICROSCOPY

- Traditional method
- More experienced microscopists
- Tedious



FLUORESCENT MICROSCOPY

- Need lower magnification → 45% less time to examine slides
- 10% more sensitive
- Easier staining procedure



WHO policies on Smear Microscopy

Definition of a new sputum smear-positive TB case

The revised definition of a new sputum smear-positive pulmonary TB case is based on the presence of at least one acid fast bacilli (AFB+) in at least one sputum sample in countries with a well functioning external quality assurance (EQA) system.

2007

Reduction of number of smears for the diagnosis of pulmonary TB

WHO recommends the number of specimens to be examined for screening of TB cases can be reduced from three to two, in places where a well-functioning external quality assurance (EQA) system exists, where the workload is very high and human resources are limited.

2007

LED microscopy

2010

http://www.who.int/tb/dots/laboratory/policy/en/

Commercial LED Microscopes

Table 1. Comparison of commercial light-emitting diode products currently available for TB diagnostics.

Device	Manufacturer	Standalone microscope	Attachment	Light transmission	Battery powered	Weight (kg)	Cost (US $)	Ref.
Primo Star iLED	Carl Zeiss, Oberkochen, Germany	Yes	NA	Epifluorescent	Yes	9.5	4825*	[101]
Lumin™	LW Scientific, Lawrenceville, GA, USA	No	Objective lens replacement (20, 40, 60 and 100× oil)	Epifluorescent	Yes	0.448	700–2000*	[102]
ParaLens	QBC™ Diagnostics, Philipsburg, PA, USA	No	Objective lens replacement (40, 60 and 100× oil)	Epifluorescent	Yes	1.27	995§	[103]
FluoLED	Fraen Corporation Srl, Settimo Milanese, Italy	No	Adaptor attached to base and filter installed on head of microscope	Transfluorescent	Yes	5	1977–3530¶	[104]
CyScope®	Partec, Gorlitz, Germany,	Yes	NA	Epifluorescent	Yes	2.7	2372–3699*	[105]

Minion et al. *Exp Rev Med Dev* 2009

Culture-based diagnostics

- "Gold Standard"
- High Sensitivity, Isolate Available for DST and molecular typing
- Slow Turnaround, Biosafety Issues, Requires Specimen Processing, Relatively Expensive

Policy on Culture-based Diagnostics

The use of liquid medium for culture and DST

WHO recommends, as a step-wise approach:

1. The use of liquid medium for culture and DST in middle- and low-income countries.

2. The rapid species identification to address the needs for culture and drug susceptibility testing (DST).

Taking into consideration that liquid systems will be implemented in a phased manner, integrated into a country specific comprehensive plan for laboratory capacity strengthening and addressing the following key issues:

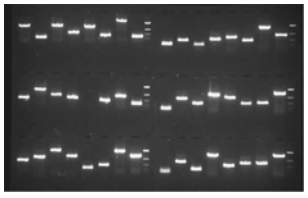
1. **Appropriate biosafety level;**
2. **detailed customer plan describing guarantees and commitments of the manufacturer;**
3. **appropriate training of staff;**
4. **maintenance of infrastructure and equipment in laboratories;**
5. **quick transportation of samples from the peripheral to the culture laboratory;**
6. **rapid communication of results.**

2007

Conventional NAATs

- High specificity and PPV
- Sensitivity is lower and highly variable
  - Especially in extrapulmonary specimens
  - Especially in smear negative specimens (>95% smear + vs. 40-80% smear -)
- Expensive
- Should not be used on follow-up specimens

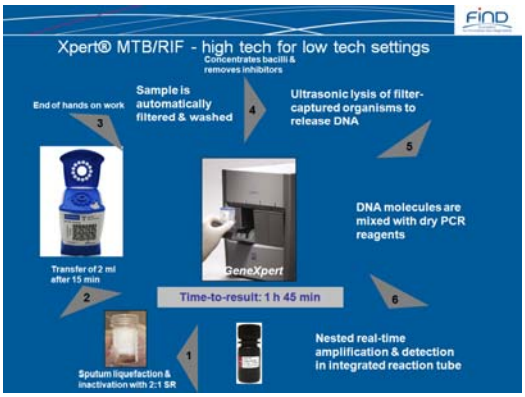
- In house assays
- Roche Cobas Amplicor
- Gen-Probe AMTD
- BD ProbeTec ET



Ling D et al.

Newer NAAT: Cepheid Xpert MTB/RIF

- Automated nested RT-PCR
- Simple 1-step specimen preparation
- Can be used at the point-of-treatment
- Results in 2 hours
- Detects TB and RIF resistance
- Equipment ~$20k; ~$20/test



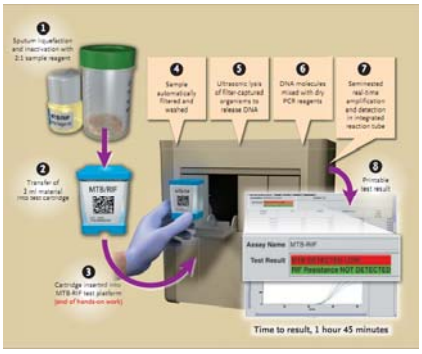
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 9, 2010 VOL. 363 NO. 11

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.

- 1462 symptomatic patients (4386 samples)
  - 50.7% culture positivity
- Sensitivity:
  - 98.2% in smear (+)
  - 72.5% in smear (-) [3 specimens increases to 90.2%]
- Specificity 99.2%
- 97.6% accurate for Rif-R
- 98.1% accurate for Rif-S
- Results in <2hrs



Upcoming WHO Policy

Expert Committee Recommendations

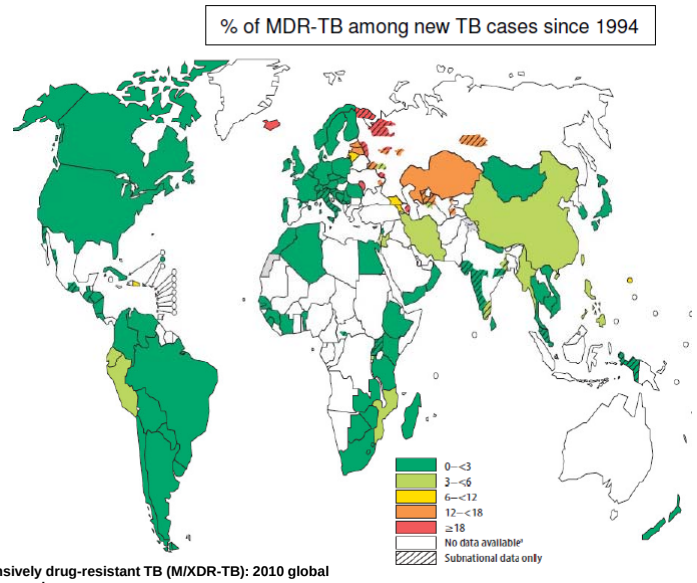
WHO THE STOP TB DEPARTMENT

1. **Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB (strong recommendation)**

2. **Xpert MTB/RIF may be used as a follow-on test to microscopy where MDR and/or HIV is of lesser concern, especially in smear-negative specimens (conditional recommendation, recognising major resource implications)**

Raviglione M et al.

Detecting Drug Resistance



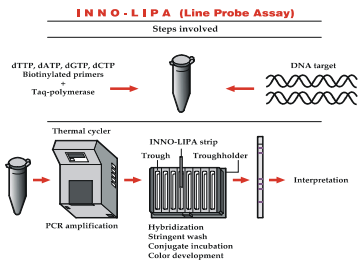
Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response

Conventional Drug Susceptibility Testing

- Agar Proportion Method
  - Plate isolate onto drug-free and drug-containing media
  - Count colonies on each – if >1% of drug-free growth present on drug-containing growth = Resistant
- BACTEC 460/MGIT
  - Inoculate drug-containing bottles
  - Inoculate drug-free bottle with 1:100 diluted isolate
  - Growth Index (growth units) compared

Line Probe Assays

- Detection of MTB & RIF-resistance (*rpo*B)
- Requires extraction, amplification
- Colorimetric development using immobilized probes
- Innogenetics, INNO-LiPA Rif TB
- Hain, GenoType MTBDRplus



Inno-LiPA Rif.TB assay
Innogenetics, Belgium

GenoType MTBDRplus assay
Hain Lifescience GmbH, Germany

Policy on Line Probe Assays

World Health Organization

2008

WHO policy statement: molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis

GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: a meta-analysis

D.I. Ling*, A.A. Zwerling* and M. Pai*,#

EXPERT REVIEWS

Rapid diagnosis of drug-resistant TB using line probe assays: from evidence to policy

Daphne I Ling, Alice A Zwerling and Madhukar Pai

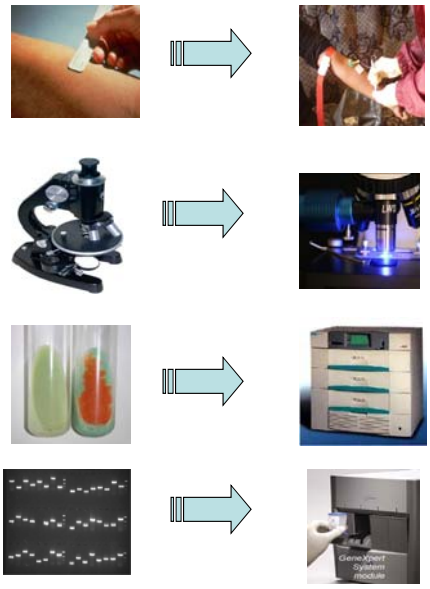
Rapid rifampin resistance detection using Xpert MTB/RIF

Table 3. Sensitivity and Specificity of the MTB/RIF Test for the Detection of Rifampin and Multidrug Resistance, as Compared with Phenotypic Drug-Susceptibility Testing Alone and in Combination with Sequencing of Discrepant Cases, According to Site.*

Site and Total	Phenotypic Drug-Susceptibility Testing†		Phenotypic Drug-Susceptibility Testing and Discrepant Resolution by Sequencing†	
	Sensitivity for Rifampin Resistance	Specificity for Rifampin Resistance	Sensitivity for Rifampin Resistance	Specificity for Rifampin Resistance
Lima, Peru — no./total no. (%)	16/16 (100.0)	190/193 (98.4)	19/19 (100.0)	190/190 (100.0)
Baku, Azerbaijan — no./total no. (%)	47/49 (95.9)	90/94 (95.7)	51/52 (98.1)	90/90 (100.0)
Cape Town, South Africa — no./total no. (%)	15/16 (93.8)	126/126 (100.0)	15/15 (100.0)	126/126 (100.0)
Durban, South Africa — no./total no. (%)	3/3 (100.0)	38/38 (100.0)	3/3 (100.0)	38/38 (100.0)
Mumbai, India — no./total no. (%)	119/121 (98.3)	61/64 (95.3)	121/122 (99.2)	62/62 (100.0)
Total for rifampin resistance				
Correct — no./total no. (%)	200/205 (97.6)	505/515 (98.1)	209/211 (99.1)	506/506 (100.0)
95% CI — %	94.4–99.0	96.5–98.9	96.6–99.7	99.2–100.0
Total for multidrug resistance				
Correct — no. /total no. (%)	195/200 (97.5)		197/199 (99.0)	
95% CI — %	94.3–98.9		96.4–99.7	

Boehme C et al. NEJM 2010

In conclusion, much progress has been made in improving TB diagnosis, but…



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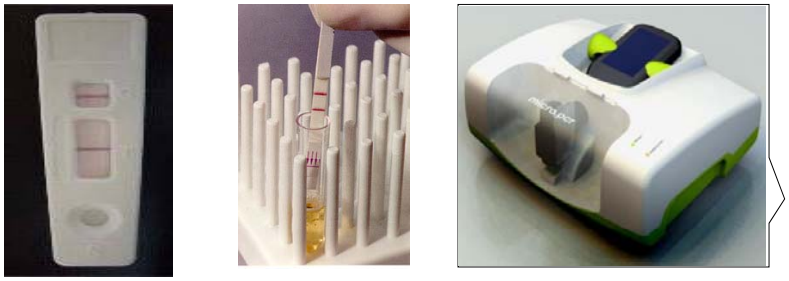
We still do not have a good point of care test



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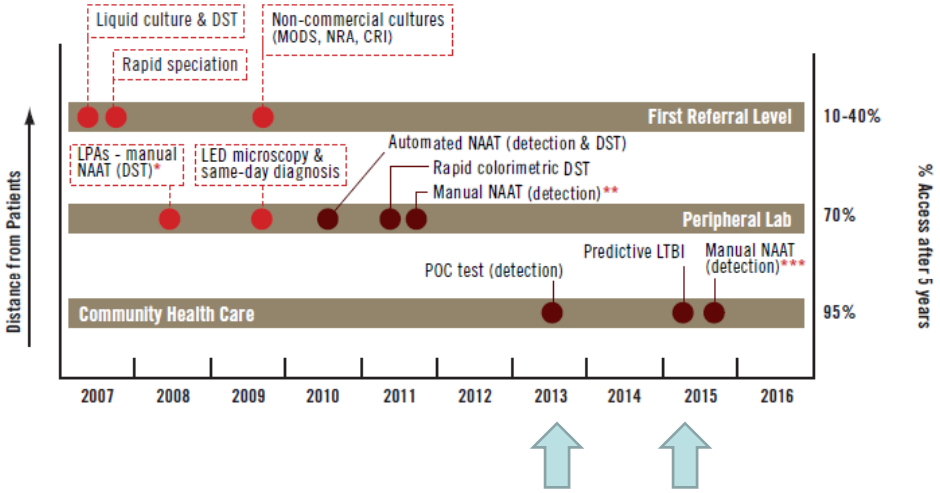
Global Plan to Stop TB

THE GLOBAL PLAN TO STOP TB 2011–2015
Transforming the Fight

FIGURE 2 TARGETS FOR INTRODUCTION OF TESTS, LEADING TO SUSTAINABLE ADOPTION, 2006–2015



www.tbevidence.org