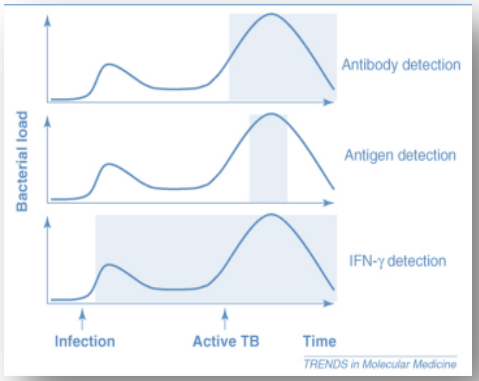

Report on WHO Policy Statements

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New Diagnostics Working Group
Annual Meeting
Lille, France 26th October 2011

WHO THE STOP TB DEPARTMENT

World Health Organization

Outline

- WHO policy formulation process
- WHO Policy Statements
  - Commercial serodiagnostic tests for the diagnosis of active tuberculosis
  - Use of TB Interferon-Gamma Release Assays (IGRAs) in low-and middle income countries
  - Xpert MTB/RIF system

WHO TB diagnostics policy formulation process

GRADE* evaluation

Clear separation:

1) **Recommendation: 2 grades –**
   strong or conditional/optional/weak (for or against an intervention)

   – **Balance of benefits and downsides, values and preferences, impact, resource use,**

   with

2) **Quality of evidence: 4 categories –**

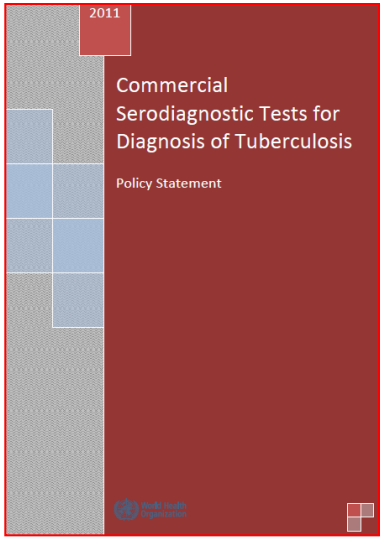
   ⊕⊕⊕⊕ (High), ⊕⊕⊕◯(Moderate), ⊕⊕◯◯(Low), ⊕◯◯◯(Very low)

   – **Methodological quality of evidence**
   – **Likelihood of bias**
   – **By outcome and across outcomes**

*Grades of Recommendation Assessment, Development and Evaluation

Commercial Serodiagnostic tests

- It is strongly recommended that these test not be used for the diagnosis of pulmonary and extra-pulmonary TB
- Currently available commercial serodiagnostic tests (or serological tests) provide inconsistent and imprecise findings
- There is no evidence that existing commercial serological assays improve patient outcomes.
- The high proportions of false-positive and false-negative results may have adverse patient outcomes



First negative policy recommendation on TB issued by WHO and was developed using the GRADE process.
Recommendation does not apply to serological tests for latent TB

The evidence

Pulmonary tuberculosis:

• 67 unique studies were identified, including 32 studies from low- and middle-income countries;

•a TDR evaluation of 19 rapid commercial tests, in comparison with culture plus clinical follow-up, showed similar variability with sensitivity values of 1% to 60% and specificity of 53% to 99%;

Extrapulmonary tuberculosis:

• 27 studies were reviewed including 10 studies from low- and middle-income countries

•Pooled sensitivity 64% lymph node TB, 46% pleural TB

•Pooled sensitivity and specificity for the most widely used tests were 81% and 85% respectively

•Single study involving HIV –infected patients, sensitivity 33%

Sensitivity

A low sensitivity results in an unacceptably high number of patients wrongly being given the 'all clear' (i.e. a false-negative).

Specificity

In contrast, low specificity leads to an unacceptably high number of patients being wrongly diagnosed with TB (i.e. a false-positive).

Results

Sensitivity and specificity from individual studies were highly variable;

The negative impact of Commercial Serodiagnostic in Countries

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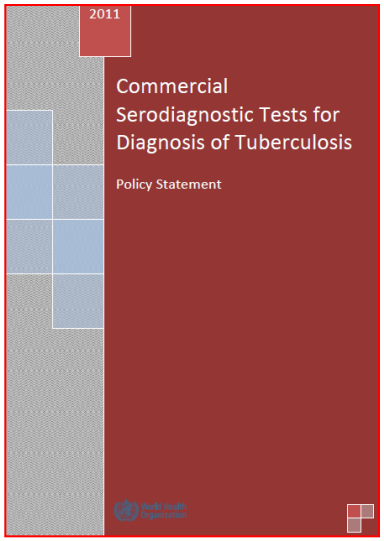
- A blood test can cost up to USD30 per patient
- More than a million tests are carried out each year
- Most serological tests available in low-and middle-income countries have no published evidence to support their claims of accuracy
- Blood test are often performed in countries where diagnostic regulatory mechanisms are weak or absent
- There are perverse financial incentives to use these tests



Compared to appropriate diagnosis of TB through WHO-endorsed tests in a country like India, it is estimated that serological testing would result in 121,000 additional false-positive diagnoses.

For each additional smear negative TB case found by serology, more than six additional false-positive cases would be inappropriately diagnosed

Commercial Serodiagnostics WHO Policy Recommendation

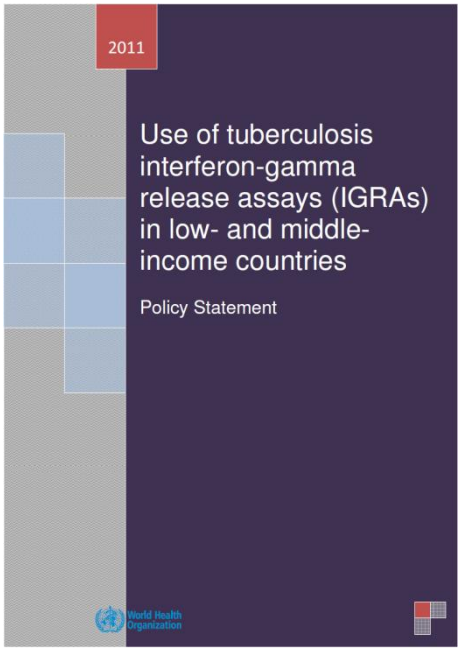
The quality of evidence for commercial serodiagnostic tests was very low, with harms/risks far outweighing any potential benefits (strong recommendation).

It is therefore recommended that these tests should not be used in individuals suspected of active pulmonary or extra-pulmonary TB, irrespective of their HIV status.

- This recommendation also applies to paediatric TB based on the generalisation of data from adults (while acknowledging the limitations of microbiological diagnosis in children);
- This recommendation also applies to the use of commercial serodiagnostic tests as add-on tests in smear-negative individuals given the high risk of false-positives and the consequent adverse effects.

TB IGRAs in Low-and Middle income countries

- There is insufficient data and low quality evidence on the performance of IGRAs in low- and middle-income countries, typically those with a high TB and/or HIV burden;
- IGRAs and the TST cannot accurately predict the risk of infected individuals developing active TB disease;
- Neither IGRAs nor the TST should be used for the diagnosis of active TB disease;
- IGRAs are more costly and technically complex to do than the TST. Given comparable performance but increased cost, replacing the TST by IGRAs as a public health intervention in resource-constrained settings is not recommended.



Use of TB IGRAs* in Low-and Middle income countries

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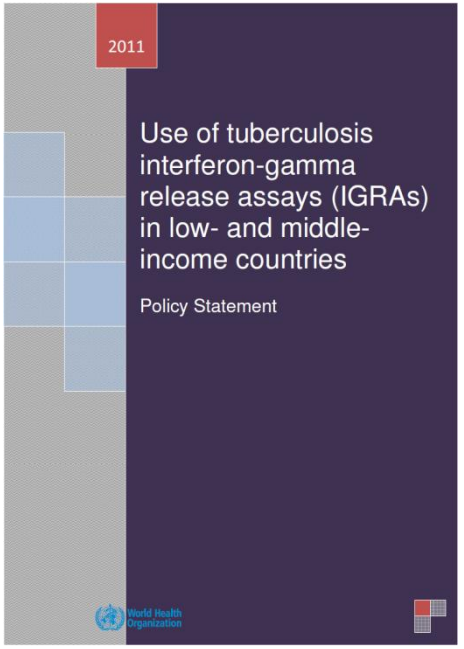
- Diagnosis of active TB
- Children (LTBI and active TB disease)
- Diagnosis of LTBI in HIV-infected individuals
- Health care worker (HCW) screening
- Contact screening and outbreak investigations
- Predicting development of TB



This policy statement is not intended to apply to high-income countries or to supercede their national guidelines

*QuantiFERON-TB Gold (QFT-G) and QuantiFERON-TB Gold In-Tube (QFT-GIT), Cellestis, Australia ELISPOT-based T.SPOT.*TB* (Oxford Immunotec, UK)

IGRAs in diagnosing active TB disease

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- There was no consistent evidence that either IGRA was more sensitive than the TST for diagnosis of active TB diagnosis.

- Two studies that evaluated the incremental value of IGRAs to conventional microbiological tests found no meaningful contribution of IGRAs to the diagnosis of active TB

- IGRAs were considered inadequate as rule-out or rule-in tests for active TB, especially in the context of HIV infection

19 studies simultaneously estimating sensitivity and specificity among 2,067 TB suspects showed a pooled sensitivity of 83% (95% CI 70% - 91%) and pooled specificity of 58% (95% CI 42% - 73%) for T-SPOT (8 studies), and a pooled sensitivity of 73% (95% CI 61% -82%) and pooled specificity of 49% (95% CI 40% - 58%) for QFT-GIT (11 studies).

Among HIV-infected patients, pooled sensitivity was between 60% (QFT-GIT) and 76% (T.SPOT). Pooled specificity was low for both IGRA platforms (T.SPOT, 61%; QFT-GIT, 52%) and among HIV-infected persons (T.SPOT 61%; QFT-GIT 50%)

IGRAs in diagnosing active TB disease
WHO POLICY RECOMMENDATION

IGRAs (and the TST) should not be used in low- and middle-income countries for the diagnosis of pulmonary or extra-pulmonary TB, nor for the diagnostic work-up of adults (including HIV-positive individuals) suspected of active TB in these settings (strong recommendation).

This recommendation places a high value on avoiding the consequences of unnecessary treatment (high false-positives) given the low specificity of IGRAs (and the TST) in these settings.

IGRAs in children

IGRAS and the TST showed similar sensitivity in detecting TB infection or disease, with reduced sensitivity in young or HIV-infected children.

Collecting blood for IGRA testing in young children was a specific challenge

2 small studies prospectively measure incident TB in children tested with IGRAs (QFT) and reported conflicting results.

Association of test response with exposure (categorised dichotomously or as a gradient) was similar for TST, QFT and T-SPOT, although differences in study methodology limited the comparability of results.

IGRAs in children – WHO POLICY RECOMMENDATION

IGRAs should not replace the TST in low- and middle-income countries for the diagnosis of latent TB infection in children, nor for the diagnostic work-up of children (irrespective of HIV status) suspected of active TB in these settings (strong recommendation).

It should also be noted that there may be additional harms associated with blood collection in children and that issues such as acceptability and cost had not been adequately addressed in any studies.

IGRAs in Health Care Worker Screening

Data on serial testing data and reproducibility of IGRAs as well as evidence on the predictive value of IGRAs in health care workers (HCWs), are still absent for high-incidence settings.

There is no data to suggest that IGRAs are better or worse than the TST for identifying new TB infections after exposure in HCWs, but IGRA serial testing is compounded by a lack of optimum cut-offs and unclear interpretation of IGRA conversions and reversions

Two cross-sectional studies compared IGRA and TST performance in HCWs.

IGRA and TST positivity rates were high in HCWs, ranging from 40% to 66%.

IGRA positivity was slightly lower than TST positivity but no consistent difference in the prevalence of positive tests was evident.

IGRAs in Health Care Worker Screening
WHO POLICY RECOMMENDATION

IGRAs should not be used in health care worker screening programmes in low- and middle-income countries (strong recommendation).

IGRAs in People Living with HIV

IGRAs seemed to perform similarly to the TST in identifying HIV-infected individuals with latent TB infection and both tests were adversely affected by low CD4+ counts

The benefit of IPT is greatest in individuals with a positive TST, although routine TST screening is not considered mandatory in HIV-infected persons. There is no evidence to support the efficiacy of IPT in TST-negative but IGRA positive individuals

37 studies involving 5,736 HIV-infected individuals were evaluated. 5 studies compared head-to head sensitivity of IGRAs and TST with variable results
In three longitudinal studies, the risk of active TB was higher in HIV-infected individuals with positive versus negative IGRA results; however, the difference was not significant in the two studies that reported IGRA results according to manufacturer-recommended criteria.
In patients with active TB (as a surrogate reference standard for LTBI), pooled sensitivity estimates were heterogeneous but higher for TSPOT (72%, 95% CI 62% - 81%, 8 studies) than for QFT-GIT (61%, 95% CI 41% -75%, 8 studies).

IGRAs in People Living with HIV
WHO POLICY RECOMMENDATION

IGRAs should not replace the TST in low- and middle-income countries for the diagnosis of latent TB infection in individuals living with HIV infection
(strong recommendation).

This recommendation also applies to HIV-positive children based on the generalisation of data from adults.

IGRAs in Contact Screening and Outbreak Investigations

The majority of studies showed comparable latent TB infection prevalence by TST or IGRA and variable associations with levels of exposure.

Wide discordance between TST and IGRA results was evident, mostly of the TST-positive/IGRA-negative type.

16 studies evaluated IGRAs in contact screening and outbreak investigations. Data could not be pooled due to significant heterogeneity in study design and outcomes assessed.

Most studies showed comparable prevalence by TST or IGRA in contacts

IGRAs in Contact Screening and Outbreak Investigations –

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WHO POLICY RECOMMENDATION

IGRAs should not replace the TST in low- and middle-income countries for the screening of latent TB infection in adult and paediatric contacts, or in outbreak investigations (strong recommendation).

Xpert MTB/RIF

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Concentrates bacilli & removes inhibitors

Sample is automatically filtered & washed

4

Ultrasonic lysis of filter-captured organisms to release DNA

5

DNA molecules are mixed with dry PCR reagents

6

Semi-nested real-time amplification & detection in integrated reaction tube

7

Printable test result

Time-to-result: 1 h 45 min

1

Sputum liquefaction & inactivation with 2:1 SR

2

Transfer of 2 ml after 15 min

3

End of hands on work

Xpert MTB/RIF evaluations

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Three groups of studies

1. **Multi-centre clinical validation studies (FIND co-ordinated)**
   - **1,730 subjects in five evaluation sites (four countries)**
2. **Demonstration studies (FIND co-ordinated)**
   - **6,673 subjects in nine evaluation sites (six countries)**
3. **Single-centre evaluation studies (investigator-driven)**
   - **4,575 subjects in 12 studies (nine countries)**

Summary of WHO Recommendations

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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 considered as a follow-on test to microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear-negative specimens. (Conditional recommendation acknowledging major resource implications)**

Remarks:

- **These recommendations apply to the use of Xpert MTB/RIF in sputum specimens (including pellets from decontaminated specimens). Data on the utility of Xpert MTB/RIF in extra-pulmonary specimens are still limited;**
- **These recommendations support the use of one sputum specimen for diagnostic testing, acknowledging that multiple specimens increase the sensitivity of Xpert MTB/RIF but have major resource implications;**
- **These recommendations also apply to children, based on the generalisation of data from adults and acknowledging the limitations of microbiological diagnosis of TB (including MDR-TB) in children;**
- **Access to conventional microscopy, culture and DST is still needed for monitoring of therapy, for prevalence surveys and/or surveillance, and for recovering isolates for drug susceptibility testing other than rifampicin including second-line anti-TB drugs).**

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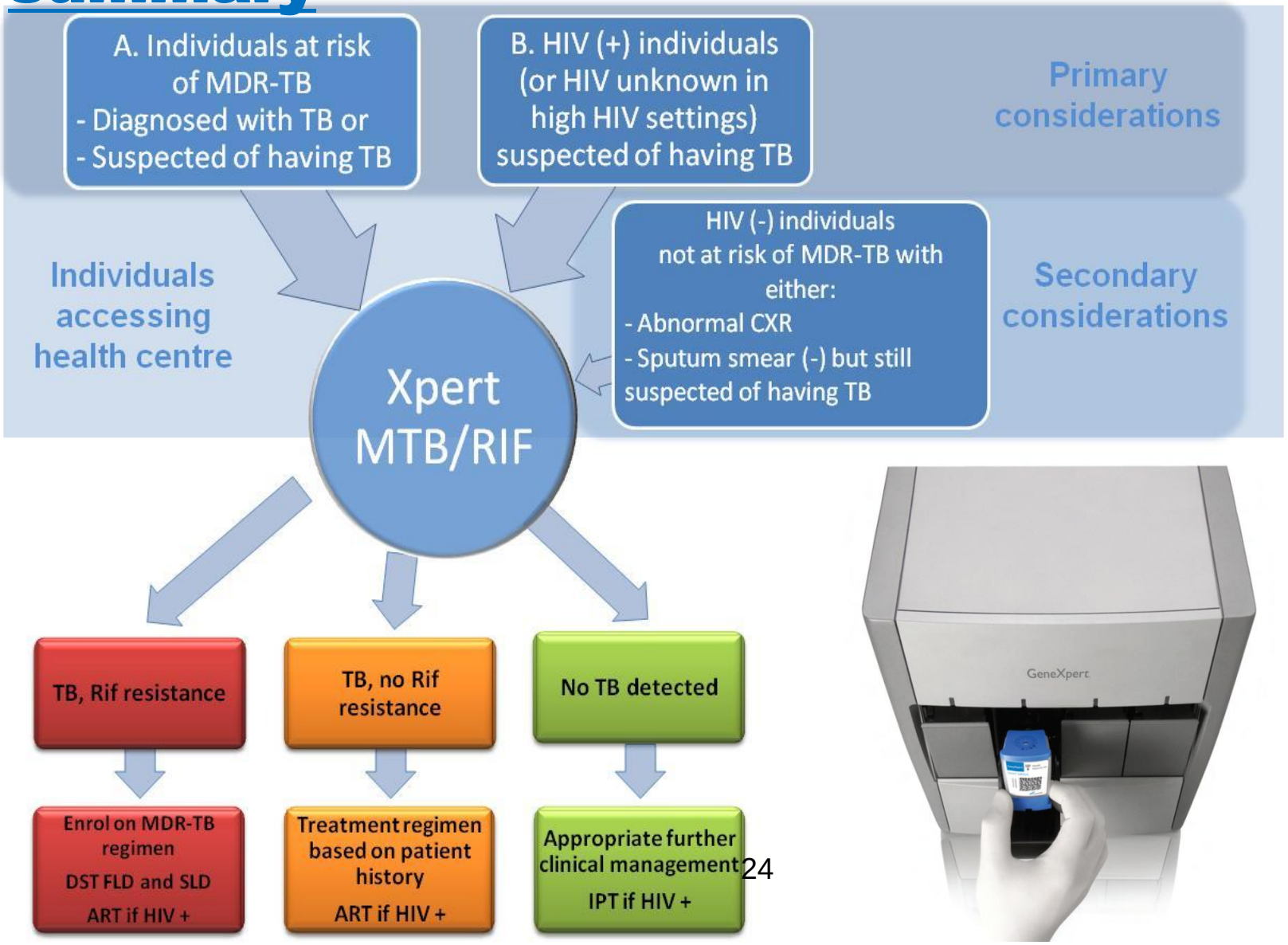
Selection of individuals to test based on risk assessment: summary



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Next steps

1. Coordinating & monitoring roll-out

- STB systematically coordinating, collecting and sharing information on progress and plans of countries and partners, as well as sales information and reports of problems from the field
- STB to organise a GLI/ SRLN/ Meeting of Early Implementers in Q2 2012 to share experiences

2. Collecting evidence for scaling-up

- STB inviting countries and partners to submit core data
- STB collaborating with the manufacturer to revise the proprietary GeneXpert software to allow for easy collection of the needed laboratory indicators

Next steps (2)

3. Providing updated guidance

Guidance on diagnostic algorithms, site selection and operational considerations to be revised based on lessons learnt and shared with countries and partners to inform scale-up from 2012 onwards

4. Ensuring quality of laboratory performance

Laboratory validation system (specimen panels to be distributed to laboratories when purchasing GXP instruments and calibrating modules) to be established and laboratory performance data assessed by STB/TBL

5. Evaluating additional data on Xpert MTB/RIF performance

Meeting to be organised in Q4 2012 to assess additional data on Xpert MTB/RIF performance (including extrapulmonary and paediatric TB)

Guidance documents

2011

Prerequisites to country implementation of Xpert MTB/RIF and key action points at country level.

Checklist

2011

Rapid Implementatio the Xpert MTB/RIF diagnostic test

Technical and Operational 'How Practical considerations

2011

Automated Real-time Nucleic Acid Amplific Technology for Rapid Simultaneous Detecti Tuberculosis and Rifampicin Resistance Xpert MTB/RIF Syster

Policy Statement

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