# The use of TB Interferon-Gamma Release Assays (IGRAs) in Low- and Middle-income Countries

CONCLUSION

• 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 tuberculin skin test (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 TST by IGRAs as a public health intervention in resource-constrained settings is not recommended

• This policy applies to the use of commercial IGRAs* in low- and middle-income countries only

• Commercial IGRAs are FDA-approved as indirect and adjunct tests for TB infection, in conjunction with risk assessment, radiography and other medical and diagnostic evaluations. Several international guidelines on their use in high-income countries are available

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

2011

The use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries

Policy Statement

World Health Organization

* QuantiFERON-TB Gold (QFT-G) and *QuantiFERON-TB Gold In-Tube* (QFT-IT), (Cellestis, Australia); *T.SPOT.TB* (Immunotec, UK)
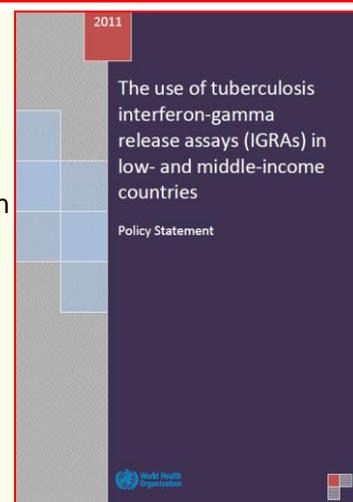
Exposure to *Mycobacterium tuberculosis* may result in latent TB infection. A person with latent TB infection usually leads a healthy life without developing active TB disease. 2 billion people have latent TB infection but only a fraction (<10 million a year) fall sick with active TB disease.

Testing for TB Infection and Disease

WHICH TEST AND WHEN?

• IGRAs and the TST are designed to detect **latent TB infection.** They are '*indirect tests*' - they do not detect the actual TB bacilli but instead an immune response that suggests past or present exposure to TB bacilli

• Microscopy, growth on culture, and molecular tests are designed to detect **active TB disease**. They are '*direct tests*' that show the presence of the actual TB bacilli or their DNA

• IGRA and the TST tests cannot distinguish between latent TB infection and active TB disease. They are therefore expected to have poor specificity for active TB in high-burden settings due to a high background prevalence of latent TB infection

IGRAs vs TUBERCULIN SKIN TEST

• IGRAs require a single patient visit, results are available in 24-48hrs, and prior BCG vaccination does not cause false-positive results

• IGRAs are expensive, require blood to be drawn, special laboratory infrastructure and supplies, and adequately trained staff

• TST requires two patient visits, results are available in 48-72hrs, and BCG vaccination may cause false-positive results in younger persons

• TST is not expensive, requires an injection into the skin, adequately trained staff, and no special laboratory infrastructure or supplies

This policy was developed in compliance with the GRADE process for evidence synthesis and formulation of recommendations and approved by the WHO Guidelines Review Committee, having satisfied the requirements for guideline development.

Turning Evidence into Policy and Practice in Low- and Middle-Income Countries

• IGRAs in DIAGNOSING active TB disease
There was no consistent evidence that IGRAs were more sensitive than TST for diagnosis of active TB disease. 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 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.

Two small studies prospectively measured 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 HEALTH CARE WORKER SCREENING
Data on serial testing 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 serial IGRA testing is compounded by a lack of optimum cut-offs and unclear interpretation and prognosis 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 PREDICTING active TB disease
IGRAs and the TST appeared to have only modest predictive value and did not help identify those who were at highest risk of progression to disease.

Large prospective cohort studies have shown that persons with a positive TST have a 1.4 to 1.7-fold higher rate of active TB within one year compared to persons with a negative TST result. Three studies provided incidence rate ratios (IRR) of TB stratified by IGRA as well as TST status at baseline. The association with subsequent incident TB in test-positive individuals compared to test-negatives was higher but not statistically significant for IGRA compared to TST (IGRA: IRR=3.24; 95CI 0.62-5.85; TST: IRR=2.28; 95CI 0.83-3.73: p=0.90). Both IGRAs and TST seemed to show positive associations with exposure but the strength of the association varied across populations, irrespective of BCG vaccination. Both IGRAs and TST appeared to have only modest predictive value , sub-optimal sensitivity, and did not help identify those who were at highest risk of progression to disease.

• 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+ count. The benefit of isoniazid preventive therapy is greatest in individuals with a positive TST although routine TST screening is not considered mandatory in HIV-infected persons. There is currently no evidence that people with TST-negative/IGRA-positive results do better on isoniazid preventive therapy than those with negative IGRA results.

37 studies involving 5,736 HIV-infected individuals were evaluated. 5 studies compared head-to-head sensitivity of IGRAs and TST for active TB: T.SPOT was more sensitive than TST in one study (absolute difference 50%; 95CI 29%-71%), less sensitive in one study (absolute difference 18%; 95CI 2%-34%), and as sensitive in one study (absolute difference -3%; 95CI -17% to11%). Similarly, QFT-GIT was more sensitive than TST in one study (absolute difference 41%; 95CI 22%-60%) and less sensitive than TST in one study (absolute difference 33%; 95CI 16%-51%). 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.

• 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 infection prevalence by TST or IGRA in contacts.