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

Policy Statement

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Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement.

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# Contents

## Executive summary

### Background

Research over the past decade has resulted in the development of two commercial interferon-gamma release assays (IGRAs), based on the principle that the T-cells of individuals who have acquired TB infection respond to re-stimulation with *Mycobacterium tuberculosis*-specific antigens by secreting interferon gamma (IFN-γ). The QuantiFERON-TB Gold (QFT-G, Cellestis, Australia) and the newer generation QuantiFERON-TB Gold In-Tube (QFT-GIT, Cellestis, Australia) are whole-blood based enzyme-linked immunosorbent assays (ELISAs) measuring the amount of IFN-γ produced in response to three *M. tuberculosis* antigens (QFT-G:ESAT-6 and CFP-10; QFT-GIT: ESAT-6, CFP-10 and TB7.7). In contrast, the enzyme-linked immunospot (ELISPOT)-based T-SPOT.TB (Oxford Immunotec, UK) measures the number of peripheral mononuclear cells that produce INF-γ after stimulation with ESAT-6 and CFP-10.

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. In recent years, IGRAs have become widely endorsed in high-income countries for diagnosis of latent TB infection (LTBI) and several guidelines (albeit equivocal) on their use have been issued. Currently, there are no guidelines for IGRA use in low- and middle-income countries - typically with high TB- and/or HIV-burden - yet IGRAs are being marketed and promoted, especially in the private sector.

The majority of IGRA studies have been performed in high-income countries and mere extrapolation to low- and middle-income settings with high background TB infection rates is not appropriate. Systematic reviews have suggested that IGRA performance differs in high- versus low TB and HIV incidence settings, with relatively lower sensitivity in high-burden settings. The WHO Stop TB Department (WHO-STB) therefore commissioned systematic reviews on the use of IGRAs in low- and middle-income countries, in pre-defined target groups, with funding support from the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and TREAT-TB/The Union. The target groups and major findings of the GRADE evidence synthesis process are summarised below.

This Policy Statement applies to the use of commercial IGRAs in low- and middle-income countries only. Several international guidelines on IGRA 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.

### Overall conclusions

- **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.**

### Summary of study results in low- and middle-income countries

***Use of IGRAs in diagnosis of active TB:*** IGRAs were explicitly designed to replace the tuberculin skin test (TST) in diagnosis of LTBI, and were not intended for diagnosis of active TB. Because IGRAs (like

the TST) cannot distinguish LTBI from active TB, these tests are expected to have poor specificity for active TB in high-burden settings due to a high background prevalence of LTBI. Nineteen studies simultaneously estimating sensitivity and specificity among 2,067 TB suspects demonstrated 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).

The quality of evidence for use of IGRAS (and the TST) in diagnosis of active TB was low. There was no consistent evidence that IGRAs were more sensitive than the TST for diagnosis of active TB diagnosis. Two studies evaluated the incremental value of IGRAs and found no meaningful contribution of IGRAs to the diagnosis of active TB beyond readily available patient data and conventional microbiological tests.

***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.**

***Use of IGRAs in children:*** Two small studies prospectively estimated the incidence of active TB in children who had been tested with IGRAs. The quality of evidence for use of IGRAS in children was very low and conflicting results were reported. When exposure was used as the reference standard for LTBI, all three tests (TST, QFT and T-SPOT) seemed to be associated with the level of exposure (categorised either dichotomously or by an exposure gradient); however, methodological inconsistencies between the studies regarding the selection and definition of reference standards for active TB and exposure limited the comparability of studies and results. Estimates of association were very similar, suggesting no difference in performance between TST and IGRAs for diagnosis of LTBI and active TB in children.

***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.**

***Use of IGRAs in HIV-infected individuals:*** 37 studies were identified that included 5,736 HIV-infected Individuals; however, despite the multitude of studies the quality of evidence for use of IGRAS in individuals living with HIV infection was very low. In persons with active TB (used as a surrogate reference standard for LTBI), pooled sensitivity estimates were higher for T-SPOT (72%, 95% CI 62% - 81%, 8 studies) than for QFT-GIT (61%, 95% CI 41% -75%, 8 studies). Large prospective cohort studies have established 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 evaluating the predictive value of IGRAs in HIV-infected individuals showed that IGRAs have poor positive predictive value but high negative predictive value for active TB. While these results suggest that a negative IGRA result is reassuring (no person with a negative IGRA result developed culture-positive TB), the studies had serious limitations, including small sample sizes with short-duration of follow-up and differential evaluation and/or follow-up of persons with positive and negative IGRA results.

Neither IGRA was consistently more sensitive than the TST in head-to-head comparisons and the impact of advanced immunosuppression on IGRA validity remains unclear: Two studies reported TST and IGRA data stratified by CD4 count. In one study, the proportion of positive results among those with CD4 cell count <200 decreased by 27% (95% CI -61, 8) with T-SPOT and 35% (95% CI -59, -11)

with TST. In the other study, the proportion of positive results among those with CD4 cell count <200 decreased by 31% (95% CI -53, -9) with T-SPOT and increased by 15% (95% CI -11, 41) with TST. All tests therefore seemed to be affected by CD4+ cell count.
***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.**

***Use of IGRAs in health care worker (HCW) screening:*** Limited data was available on the screening of HCWs for LTBI in low- and middle-income countries and the quality of evidence was very low. Two cross-sectional studies compared IGRA and TST performance in HCWs. TST and IGRA positivity rates were high in HCWs, ranging from 40% to 66%. IGRA positivity was slightly lower than TST positivity in the two studies comparing TST and IGRAs; however, the difference in estimated prevalence was significant in one study only. Serial testing data, evidence on the predictive value of IGRAs in HCWs, as well as reproducibility data are still absent for high burden TB and/or HIV settings.
***Policy recommendation:*** **IGRAs should not be used in health care worker screening programmes in low- and middle-income countries (strong recommendation)**.

***Use of IGRAs in contact screening and outbreak investigations:*** 16 studies (14 original manuscripts and 2 unpublished studies) evaluated IGRAs in contact screening and outbreak investigations in low- and middle-income countries. The quality of evidence for use of IGRAs for LTBI screening in contact and outbreak investigations was very low. Seventy-five percent (12/16) of contact studies included children in their study populations. The majority of studies were cross-sectional and looked at concordance between TST and IGRAs. Due to significant heterogeneity in study designs and outcomes assessed in each study it was not possible to pool the data. The majority of studies showed comparable LTBI prevalence by TST or IGRA in contacts and four studies reported a statistically significant difference between positivity rates estimated by TST, T-SPOT or QFT. The most commonly observed discordance was of the TST-positive/IGRA-negative type. Both IGRAs and the TST seemed to show positive associations with higher levels of exposure in cross-sectional studies, but the strength of the association (adjusted odds ratio) varied across studies. Results indicated that concordance between TST and IGRAs ranged widely.
***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)**.

***Predictive value of IGRAs:*** Three studies provided incidence rate ratios (IRR) of TB stratified by IGRA as well as TST status at baseline. The quality of evidence for the predictive value of IGRAS was very low. The association with subsequent incident TB in test-positive individuals compared to test-negatives appeared higher for IGRA than for TST; however, this was not statistically significant (IGRA: IRR=3.24; 95% CI 0.62-5.85; I2=0%; p=0.90; TST: IRR=2.28; 95% CI 0.83-3.73); Both IGRAs and TST seemed to show positive associations between exposure gradient and test results but with variability in the strength of the association across populations, irrespective of BCG vaccination. No statistically significant increase in incidence rates of TB in IGRA-positives compared to IGRA-negatives was observed and the vast majority of individuals (>95%) with a positive IGRA result did not progress to active TB disease during follow-up. Both IGRAs and the TST appeared to have only modest predictive value and did not help identify those who are at highest risk of progression to disease. The predictive value for serial testing could not be assessed as all three studies performed single time-point IGRA testing.
***Policy recommendation:*** **Neither IGRAs nor the TST should be used in low- and middle-income countries for the identification of individuals at risk of developing active TB (strong recommendation)**.

## Acknowledgements

This document was prepared by Karin Weyer, Christopher Gilpin, Fuad Mirzayev and Wayne van Gemert (WHO Stop TB Department) on the basis of consensus at an international Expert Group Meeting convened by WHO in Geneva on 20th-21st July 2010.

WHO gratefully acknowledges the contributions of the Chair of the Expert Group (Holger Schünemann) and the members of the Expert Group (Annex 1) who developed the recommendations.

The findings and recommendations from the Expert Group Meeting were presented to the WHO Strategic and Technical Advisory Group for Tuberculosis (STAG-TB, Annex 2), in September 2010 (http://www.who.int/tb/advisory_bodies/stag/en/). STAG-TB acknowledged a compelling evidence base and large body of work demonstrating the poor performance of current commercial IGRAs in low- and middle-income countries (typically high TB and/or HIV burden settings) and the adverse impact of misdiagnosis and wasted resources on patients and health services using these tests for the diagnosis of active TB.

STAG-TB also acknowledged a large body of work and compelling evidence base to discourage the use of IGRAs in low- and middle-income countries for the detection of LTBI, acknowledging the difficulty in obtaining high quality data on the diagnosis of LTBI in the absence of a reference standard.

STAG-TB endorsed the findings of the Expert Group and supported the strategic approach to develop WHO policy recommendations to discourage the use of commercial IGRAs over the TST in low- and middle-income countries. This document was finalized following consideration of all comments and suggestions from the participants of the Expert Group and STAG-TB.

USAID is acknowledged for funding the development of these guidelines through USAID-WHO Consolidated Grant No. GHA-G-00-09-00003. TDR and TREAT-TB/The Union are acknowledged for sponsoring the systematic reviews commissioned in advance of the Expert Group meeting.

## Declarations of Interest

Individuals were selected to be members of the Expert Group to represent and balance important perspectives for the process of formulating recommendations. The Expert Group therefore included technical experts, end-users, patient representatives and evidence synthesis methodologists.

Interchange by Expert Group meeting participants was restricted to those who attended the Expert Group meeting in person, both for the discussion and follow-up dialogue.

Expert Group members were asked to submit completed Declaration of Interest (DOI) forms. These were reviewed by the WHO legal department prior to the Expert Group meeting. DOI statements were summarised by the co-chair (Karin Weyer, WHO-STB) of the Expert Group meeting at the start of the meeting.

P Hill and R O'Brien declared conflicts of interest that were deemed to be insignificant: P Hill declared receipt of kits from Cellestis and Oxford Immunotec for research projects, and R O'Brien declared FIND support to academia to develop a point of care serodiagnostic test, including the FIND biomarker discovery project.

Selected individuals with intellectual and/or research involvement in the use of TB interferon-γ release assays (IGRAs) in low- and middle-income settings were invited as observers to provide technical input and answer technical questions. P Godfrey-Fausett declared a research grant for the investigation of the use of the QuantiFERON-TB Gold In-Tube assay in Zambia and South Africa, and M Pai declared conduct of research studies on IGRAs. These individuals did not participate in the GRADE evaluation process and were excluded from the Expert Group discussions when recommendations were developed. They were also not involved in the development of the final Expert Group meeting report, nor in preparation of the STAG-TB documentation or preparation of the final WHO Policy Statement.

The systematic reviewers (A Cattamanchi, A Date, A Detjen, D Dowdy, R Menzies, J Metcalfe, M Pai, M Rangaka, K Steingart and A Zwerling) were deemed to have a conflict of interest and consequently were observers to the meeting, providing technical clarifications on the findings of the systematic reviews. They did not participate in the GRADE evaluation process, did not contribute to the meeting discussions where recommendations were developed, and did not provide comments on the final WHO Policy Statement.