Use of alternative interferon-gamma release assays for the diagnosis of TB infection

WHO POLICY STATEMENT

2022

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ISBN 978-92-4-004234-6 (electronic version)
ISBN 978-92-4-004235-3 (print version)

Suggested citation. Use of alternative interferon-gamma release assays for the diagnosis of TB infection: WHO policy statement. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Acknowledgements

The development of these policy statements on the use of alternative interferon-gamma release assays for the diagnosis of tuberculosis (TB) infection was led by **Nazir Ahmed Ismail**, **Alexei Korobitsyn** and **Carl-Michael Nathanson**, with support from **Matteo Zignol**, and under the overall direction of **Tereza Kasaeva**, Director of the World Health Organization (WHO) Global TB Programme (WHO/GTB). The WHO/GTB gratefully acknowledges the support and contributions of the individuals listed below.

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Funding

This product was developed with support from United States Agency for International Development (USAID) and the Russian Federation.

Abbreviations and acronyms

AIDS	acquired immunodeficiency syndrome
CI	confidence interval
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
FIND	Foundation for Innovative New Diagnostics
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
IGRA	interferon-gamma release assay
Mtb	*Mycobacterium tuberculosis*
PLHIV	people living with HIV
PPD	purified protein derivative
PQ	prequalification
QFT-G	QIAGEN QuantiFERON-Gold
QFT-GIT	QIAGEN QuantiFERON-TB Gold In-Tube
QFT-Plus	QIAGEN QuantiFERON-TB Gold Plus
QIAreach	QIAGEN QIAreach QuantiFERON-TB
SRL	supranational TB reference laboratory
TAG	Technical Advisory Group
TB	tuberculosis
TBF	SD Biosensor Standard E TB-Feron ELISA
T-Cell Select	Oxford Immunotec T-SPOT.TB 8 with T-Cell Select
T-Spot	Oxford Immunotec T-SPOT.TB
TST	tuberculin skin test
USA	United States of America
USAID	United States Agency for International Development
Wantai	Beijing Wantai's TB-IGRA
WHO	World Health Organization
WHO/GTB	World Health Organization Global TB Programme

WHO policy statement

Tuberculosis (TB) infection is a state that is characterized by persistent immune response to stimulation by *Mycobacterium tuberculosis* (*Mtb*) antigens with no evidence of clinically manifest TB disease.[1] It is estimated that about a quarter of the world's population is infected with *Mtb*. Testing for TB infection increases the probability that individuals who are the target for preventive treatment will benefit from such treatment. However, there is no gold standard test to diagnose TB infection. The two currently available classes of tests – tuberculin skin test (TST) and interferon-gamma release assay (IGRA) – are indirect and require a competent immune response to identify people infected with TB. A positive test result by either method is not, by itself, a reliable indicator of the risk of progression to active disease.

In 2011, the World Health Organization (WHO) issued recommendations on the use of IGRAs for the diagnosis of TB infection, including the blood-based Qiagen QuantiFERON-Gold (QFT-G), QuantiFERON-TB Gold In-Tube (QFT-GIT) and Oxford Immunotec T-SPOT.TB (T-Spot) assays. In recent years, new and updated versions of blood-based IGRAs have been marketed, and WHO has solicited information on these tests directly from manufacturers and from a public call for information. The following products had sufficient independent evidence for consideration: QuantiFERON-TB Gold Plus (QFT-Plus), QIAreach QuantiFERON-TB (QIAreach), Beijing Wantai's TB-IGRA (Wantai), the Standard E TB-Feron enzyme-linked immunosorbent assay (ELISA) (TBF) and T-SPOT.TB 8 with T-Cell Select (T-Cell Select).

To evaluate these technologies and determine whether one or more of them could be included under the existing WHO recommendations for IGRA testing, WHO convened a Technical Advisory Group (TAG) on TB Diagnostics and Laboratory Strengthening, which met virtually on 27–29 October 2021. This document provides background information, available evidence and subsequent deliberations by the TAG.

Following the TAG's review of the evidence and provision of advice, WHO makes the following policy statement:

1. Based on available data, **Beijing Wantai's TB-IGRA** and **Qiagen QuantiFERON-TB Gold Plus** performance is comparable to that of WHO-recommended IGRAs for the detection of TB infection.

2. Based on available data, Qiagen QIAreach QuantiFERON-TB, SD Biosensor Standard E TB-Feron ELISA and Oxford Immunotec T-SPOT.TB 8 with T-Cell Select could not be adequately compared with WHO-recommended IGRAs for detection of TB infection.

3. Current WHO recommendations for the use of IGRAs are also valid for **Beijing Wantai's TB-IGRA** and **Qiagen QuantiFERON-TB Gold Plus**.

The guidance provided should facilitate the procurement and uptake of the recommended technologies and improve patient care. The policy statements should be read in the context of the remarks and implementation considerations detailed in this report, which also provides proposed research questions that seek to address data gaps and inform models of effective test

[1] WHO consolidated guidelines on tuberculosis, Module 1: Prevention – tuberculosis preventive treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment).

implementation. The current WHO recommendations on the use of TST and IGRAs (including T-Spot) are unchanged and remain valid. All products recommended by WHO are automatically eligible to be included in the WHO essential diagnostic list.

The WHO recommendations on diagnostics are based on clinical research evidence; they do not include quality assessments of the products or the manufacturing process involved. Before introducing any new products, countries should ensure that those products fulfil local or internationally recognized regulatory requirements.

Finally, this policy document will be incorporated into updates of existing WHO consolidated guidance.

Background

There is an urgent need for accelerated global efforts to end tuberculosis (TB), as outlined in the 2015–2035 End TB Strategy *(1)* and the 2018 Political Declaration of the United Nations General Assembly High-Level Meeting on the Fight against TB *(2)*. Such efforts are even more urgent given the impact of the coronavirus disease (COVID-19) pandemic, which has reversed some of the recent successes in TB. The introduction of improved, rapid and more accurate diagnostic tools is critical for achieving the global targets towards ending the TB epidemic and addressing the shortfalls in the targets. An estimated 2 billion people globally are infected with *Mycobacterium tuberculosis* (*Mtb*) and are at risk for progression to TB disease.

New diagnostic tools to detect TB infection, active TB disease and related drug resistance are emerging; hence, national TB programmes require clear guidance on implementing and using these new tools. World Health Organization (WHO) evaluations of classes of TB diagnostic technologies are conducted by the WHO Global TB Programme (WHO/GTB). Following the initial, class-based review of technologies, many new within-class products are emerging, necessitating an additional pathway for review. Hence, there are two pathways for evaluating diagnostic technologies within the WHO framework, both managed through WHO/GTB *(3)*:

- *Pathway A*: for all first-in-class technologies. This evaluation will follow the existing WHO guideline development process, which is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. All products included in this assessment will automatically be eligible for the WHO prequalification (PQ) assessment *(2)*.
- *Pathway B*: for all products that are not first-in-class technologies and have not already been assessed through Pathway A. Pathway B starts with a rapid assessment to determine whether a product belongs to a class of diagnostics already endorsed by WHO/GTB. If so, the product could then be referred to PQ for assessment, and if not, an assessment as a first-in-class technology through Pathway A may be performed.

The current report covers a formal Pathway B evaluation undertaken by WHO/GTB and overseen by the Technical Advisory Group (TAG) on Diagnostics and Laboratory Strengthening, which was established in 2021. The scope of the TAG includes undertaking Pathway B assessments and addressing knowledge gaps that hinder the adoption and scale-up of WHO recommendations. The TAG comprises 24 independent experts who serve in their personal capacities; they cover a spectrum of technical expertise, and there is geographical representation and gender balance (Annex 1). The terms of reference and brief biographies are available on the WHO website *(4)*.

TB infection blood-based IGRA

A quarter of the world's population is estimated to be infected with *Mtb*. Testing for TB infection increases the probability that individuals who are the target for preventive treatment will benefit from such treatment. The tuberculin skin test (TST) and interferon-gamma release assay (IGRA) are both recommended by WHO for the diagnosis of TB infection. TST can be performed outside a laboratory; however, this test requires storage of the purified protein derivative (PPD) at 2–8 ^{o}C and a person's return visit 2–3 days later to read the diameter of induration. In contrast, IGRAs are blood-based in vitro tests that use *Mtb*-specific antigens but require a laboratory for testing and are more costly than TST.

In 2011, WHO issued recommendations on the use of IGRAs for the diagnosis of TB infection, which included the Qiagen QuantiFERON®-Gold (QFT-G), QuantiFERON-TB Gold In-Tube (QFT-GIT) and

Oxford Immunotec T-SPOT®.TB (T-Spot) assays. The earliest version of the commercially available Qiagen in vitro tests used to detect TB infection was QuantiFERON (QFT), which measured the response to PPD (i.e. to the same antigens as are used in TST); QFT was superseded by QFT-G, which used two TB-specific antigens (ESAT-6 and CFP-10). In 2008, QFT-GIT was introduced; it simplified test procedures and included an additional antigen, TB7.7.

WHO also recommended an additional IGRA with a slightly more complex test procedure: T-Spot. The test uses enzyme-linked immunospot (ELISPOT) methodology, in which spots identified on visual reading provide a measure of the abundance of *Mtb*-specific lymphocytes in the peripheral blood.

The sensitivity of T-Spot was slightly higher – albeit with wider confidence intervals (CIs) – in patients with immunocompromising conditions, possibly because of the standardization step for the number of lymphocytes. In all populations tested, the specificities of T-Spot, QFT-G and QFT-GIT were high, including in those who had received bacille Calmette-Guérin (BCG) vaccination. In longitudinal studies, many of which have been published in the past decade (using T-Spot, QFT-G or QFT-GIT), the predictive ability for active TB was at least as good as and sometimes better than TST; however, the proportion of people with a positive test who developed the disease during follow-up was less than 10% (this is a noted limitation of current tests).

In recent years, new or updated versions of blood-based IGRAs based on the same test principles have been introduced. A systematic review and the subsequent TAG meeting focused on the following five new tests (hereafter referred to as "index tests"):

- **Beijing Wantai's TB-IGRA (Wantai)** is manufactured by Beijing Wantai Biological Pharmacy Enterprise Co. Ltd., Beijing, China. This test was launched in 2011 and has been approved in China by the State Food and Drug Administration of China (CFDA). The test kit comprises three tubes: a positive control, a negative control and TB-specific recombinant fusion proteins of the antigens ESAT-6 and CFP-10.

- **QuantiFERON-TB Gold Plus (QFT-Plus)** test is manufactured by QIAGEN, Carnegie, Australia. This test was launched in 2015 and approved by the United States Food and Drug Administration (US FDA) in 2017. It has also been approved in Europe (via the European In Vitro Diagnostic Devices Directive) and in Japan (by the Pharmaceuticals and Medical Devices Agency). The test is a modification and replacement of QFT-GIT. The major changes from its predecessor (QFT-GIT) are the addition of a TB antigen tube (TB2) that is designed to stimulate CD8+ T lymphocytes, and the alteration of the peptide mix of TB antigens (ESAT-6, CFP-10 and short peptide CFP-10 with TB7.7 removed).

QIAreach QuantiFERON-TB (QIAreach) test is manufactured by QIAGEN, Carnegie, Australia. It uses principally the same antigens as the QFT-Plus TB2 tube *(5)*, but in a single tube (i.e. no mitogen or nil tubes). Also, the enzyme-linked immunosorbent assay (ELISA) has been replaced by a lateral flow immunofluorescence device with nanoparticle technology, which is read with an electronic tool, the eStick. This test received a Conformité Européenne (CE) mark in 2021.

- **Standard E TB-Feron ELISA (TBF)** is manufactured by SD Biosensor, Gyeonggi-do, Republic of Korea. This test, which is similar to QFT-GIT, was launched in 2018 and received approval from the Ministry of Food and Drug Safety of the Republic of Korea in 2019. The test kit comprises three tubes: a positive control, a negative control and TB-specific antigens (recombinant whole proteins of ESAT-6, CFP-10 and TB7.7).

- **T-SPOT.TB 8 with T-Cell Select** (**T-Cell Select**) is a modification of the T-SPOT.TB test, manufactured by Oxford Immunotec, Abingdon, United Kingdom of Great Britain and Northern Ireland (United Kingdom). The novel T-Cell Select method uses a simplified procedure to automatically isolate mononuclear cells from whole blood. It is currently approved in Chile, Iraq, Israel, Japan, Kuwait, Lebanon, Oman, Pakistan and Turkey. For this test, the only evidence assessed was the performance of the T-Cell Select modification to the existing T-Spot test.

The detailed test descriptions, procedures, equipment and staff requirements are presented in the **Web annex**.

Summary of methods

A systematic review and a meta-analysis were performed to compare the index tests with the tests currently recommended by WHO. A description of manufacturers' unit costs and practical implementation considerations were also provided.

Research questions

- **Sensitivity**: In people with active TB, what is the sensitivity of the index tests compared with QFT-G, QFT-GIT or T-Spot (hereafter referred to as "reference tests") or TST?
- **Specificity**: In people at very low risk of TB infection, what is the specificity of the index tests relative to the reference tests or TST?
- **Agreement (concordance)**: In patients with active TB, people at very low risk of TB infection or those tested for TB infection, what is the agreement (for both positive and negative results) between the index and reference tests or TST? This is expressed in terms of the Cohen's kappa test, which is a measure of agreement corrected for chance agreement.
- **Reproducibility**: What is the within-person, short-term reproducibility of the index tests in patients tested on repeated occasions (i.e. the same samples, tested at either the same time or different times, or both) in patients without TB disease and at low risk of a new TB infection?

Search strategy: The search was performed on 18 August 2021, with the initial date set as 1 January 2007 (2 years before the first known published article reporting the diagnostic performance of any of the index tests). The search included articles in any language on well recognized international databases – MEDLINE (via Ovid); Embase; Web of Science (via Ovid); Cochrane Database of Systematic Reviews; and International Clinical Trials Registry Platform – and additional data sources. WHO made a public call for data on 23 August 2021, requesting suitable evidence of the performance of the index tests. To be eligible for inclusion, a study must have fulfilled the inclusion criteria common to all research outcomes, in addition to criteria specific for each outcome.

Analysis: The pooled sensitivity and specificity of the index and reference tests were estimated by conducting a random-effects meta-analysis using generalized linear mixed models (R package meta, version 4.10.0). All parameter estimates were displayed using forest plots and estimated I^2 and its corresponding 95% CIs. To obtain the paired differences (and 95% CI) comparing the sensitivity and specificity of the index and reference tests, the Wilson test in the R package Mkinfer (version 0.6) was used. To obtain the pooled difference in sensitivity and specificity and the I^2 statistic, a random-effects meta-analysis of the point estimates and standard errors was performed using the inverse

variance method, specifying the estimation of heterogeneity using the Sidik-Jonkman estimator with a Knapp-Hartung adjustment (R package metafor, version 3.0.2).

A detailed description of the methods for the systematic review, including inclusion and exclusion criteria, is presented in the **Web annex**.

In the **primary analysis (paired comparisons)** of the diagnostic accuracy of these tests, the differences in sensitivity and specificity using published studies that provided results as direct pairwise comparisons were calculated. Subsequently, if sufficient studies were available, three **secondary analyses** for the diagnostic accuracy outcome were performed:

1. The differences in sensitivity and specificity in **all published and unpublished** studies (including the manufacturer evaluation of the test) that provided results as direct pairwise comparisons were calculated.
2. The differences in sensitivity and specificity in published studies only (irrespective of whether they presented enough information to compute 95% CI for differences in sensitivity and specificity as pairwise comparisons) were calculated.
3. The previous secondary analysis (2) was repeated but was modified to include unpublished studies and studies conducted by the manufacturers.

The **Web annex** provides further details.

Summary of results

The assessment was intended to guide the decision for each technology; hence, the results for each technology are presented separately.

Wantai

A large number of studies evaluating this test have been published, most of them in Chinese journals not indexed in PubMed but available through China/Asia On Demand (CAOD)/Asia Document Delivery. With the help of the manufacturer, 84 published studies and three unpublished reports were identified. Moreover, the manufacturer provided its own evaluation of the test. Five published reports were identified through the search of non-Chinese indexes and database registries.

Twenty-two reports assessing Wantai were included in the analysis, of which 20 estimated sensitivity, seven specificity and eight agreement with a reference test or TST. No published or unpublished studies assessing reproducibility were identified and included in the review.

Sensitivity

In a primary analysis that included one study that allowed paired comparison, the sensitivity of Wantai was compared with TST and T-Spot using patients with bacteriologically confirmed or clinical TB. The sensitivity for both Wantai and T-Spot was 97.1% (paired difference in sensitivity, 0; 95% CI: –0.07, 0.07), whereas for TST sensitivity was only 66.2% (paired difference in sensitivity, –0.31; 95% CI: –0.43, –0.19). When including unpaired comparisons of published studies, the sensitivity of Wantai was comparable to both QFT-GIT and T-Spot, with differences being not statistically significant (86.4% vs 83.2% and 87.7% vs 88.7%, respectively).

Specificity

All estimates of specificity of Wantai, QFT-GIT or T-Spot based on studies conducted in China were lower than other published estimates from settings outside China. The studies estimating specificity were conducted in “low-risk” populations, but all participants were lifelong residents of China,

where the prevalence of TB infection is expected to be higher than in many other settings classified as being low risk. In this context, the difference between Wantai and other tests was considered more relevant than the absolute specificity. Wantai was 2.6% (95% CI: –4.2, –0.9) less specific than QFT-GIT, and 10.3% (95% CI: –17.2, –3.4) less specific than T-Spot, with both differences being statistically significant. Wantai was non-significantly more specific than TST (difference in specificity, 29.4%; 95% CI: –45.5, 104.3), although in the case of TST, specificity varied widely between studies.

Agreement

In two published studies, agreement between Wantai and QFT-GIT was good (kappa statistic, 0.79; 95% CI: 0.60, 0.99). Similar results were found when the manufacturer's evaluation of the test was excluded (one study), with substantial agreement between the tests (kappa statistic, 0.73; 95% CI: 0.59, 0.88). The agreement with T-Spot was good (kappa statistic, 0.87; 95% CI: 0.81, 0.93) in three published studies and moderate with TST (kappa statistic, 0.43; 95% CI: 0.21, 0.65) in two studies.

QFT-Plus

Forty reports assessing QFT-Plus were included in this systematic review, of which 11 estimated sensitivity, three specificity, 34 agreement with a reference test or TST, and three reproducibility.

Sensitivity

In the primary analysis of published studies only, there was no significant difference in sensitivity between QFT-Plus at 90.8% (95% CI: 80.0, 96.1) and QFT-GIT at 90.3% (95% CI: 79.9, 95.6). When the manufacturer's studies were included, the sensitivity of QFT-Plus was 0.4 percentage points lower (95% CI: –1.9, 1.0) than that of QFT-GIT. The estimates of sensitivity corresponding to the index and reference tests varied widely between studies for each test, contributing to high heterogeneity for the pooled estimates of sensitivity (I^2 about 90%); however, the I^2 for the pooled difference between QFT-Plus and QFT-GIT was 7–10%, suggesting that the estimates of differences in sensitivity between the two tests were less affected by the study population and therefore were more robust. When all published and unpublished studies were included, results were similar. The difference in sensitivity between the two tests was within 1%, and the CI overlapped zero. Results were similar in unpaired comparisons of sensitivity across all studies.

When comparing QFT-Plus and T-Spot, no significant difference in sensitivity was seen. However, results showed a greater heterogeneity between studies and wider CIs, largely because of one study that found very low sensitivity of T-Spot.

Specificity

When compared with QFT-GIT, the specificity of QFT-Plus was about 1% lower (–0.8; 95% CI: –2.1, 0.4). The results were consistent in all three unpaired published or unpublished comparison studies, resulting in a small but significant pooled difference (–0.9; 95% CI: –1, –0.7). There was no significant difference in specificity of QFT-Plus compared with T-Spot (0; 95% CI: –4.9, 4.9).

Agreement

Agreement of QFT-Plus with QFT-GIT was almost identical, both in the single published study (manufacturer evaluation) and with the inclusion of unpublished independent studies, with kappa values of 0.82 (95% CI: 0.78, 0.85) and 0.82 (95% CI: 0.78, 0.86), respectively. Agreement was also high between QFT-Plus and T-Spot (kappa statistic, 0.74; 95% CI: 0.60, 0.88), but was substantially lower with TST (kappa statistic, 0.33; 95% CI: 0.22, 0.45).

Reproducibility

Three studies were included that assessed the reproducibility of QFT-Plus. One study that assessed reproducibility with or without a 48-hour refrigeration step found almost perfect agreement (kappa

statistic, 0.90). In the other two studies with serial testing – one in students and the other in residents in long-term care facilities – the conversion rates between QFT-GIT and QFT-Plus were similar (2.2% vs 4.3% and 33.3% vs 31.3%, respectively). The reversion rates were also similar (3.2% vs 6.9% and 22.7% vs 21.6%, respectively).

QIAreach

Only three reports assessing QIAreach were included in this systematic review (one study was excluded because it was not blinded). One independent report assessed sensitivity and specificity. Although this study included fewer than 50 participants for the sensitivity outcome and fewer than 100 for specificity, it was not excluded given the paucity of information about this test. Three reports assessed agreement with a reference test. No published or unpublished studies assessing reproducibility were identified and included in the review.

Sensitivity

One study with pairwise comparisons of 41 participants estimated the sensitivity of QIAreach compared with QFT-Plus. There was no difference in sensitivity between the tests (paired difference in sensitivity, 0%; 95% CI: –8.6, 8.6).

Specificity

One study with pairwise comparisons of 42 participants estimated the specificity of QIAreach compared with QFT-Plus. The estimated specificity of QIAreach was 2.4% lower than that of QFT-Plus (95% CI: –12.3, 6.2); however, this estimate was imprecise because of the small sample size.

Agreement

Two studies were identified that measured agreement of QIAreach with QFT-Plus, although only one of the studies was published. The overall agreement in the two studies was high (kappa statistic, 0.96; 95% CI: 0.92, 0.99). Only one study assessed the agreement of QIAreach with TST – in this study, agreement was moderate (kappa statistic, 0.42; 95% CI: 0.29, 0.55).

TBF

Nine published and unpublished reports assessing TBF were included in this systematic review, of which three assessed sensitivity (two included fewer than 50 participants but were nevertheless included, given the paucity of information from this test), one specificity, nine agreement with a reference test or TST. No published or unpublished studies assessing reproducibility were identified and included in the review.

Sensitivity

Sensitivity was assessed in three studies, two of which were published (reference test QFT-Plus) and one unpublished (reference test QFT-Gold). In the two published studies, the pooled estimate of sensitivity for TBF was 97.6% (95% CI: 52.4, 99.9) versus 87.5 (95% CI: 78.8, 92.9) for QFT-Plus, although CIs were wide. In the unpublished study, no difference was found between TBF and QFT-Gold (0%; 95% CI: –7.7, 7.7). The pooled estimate of sensitivity for TBF within these three studies (published and unpublished) was 4% (95% CI: –18.5, 26.5) higher than QFT-Plus or QFT-Gold, although CIs were wide.

Specificity

Specificity was estimated in a single study of 150 participants, with the specificity of TBF found to be significantly lower than that of QFT-Plus (–4.7%; 95% CI: –9, –1).

Agreement

Agreement of TBF with QFT-Plus was estimated in nine studies, of which only three were published. Agreement between the two tests, whether considering only published or all studies, was good (kappa statistic, 0.87; 95% CI: 0.82, 0.91). Agreement between TBF and QFT-G was very good (kappa statistic, 0.97; 95% CI: 0.92, 1.0) and between TBF and QFT-GIT was good (kappa statistic, 0.79; 95% CI: 0.7, 0.88), but with TST it was lower (kappa statistic, 0.42; 95% CI: 0.21, 0.64).

T-Cell Select

No published or unpublished studies assessing sensitivity, specificity or reproducibility were identified and included in the review. One study assessing agreement was included in the review.

Agreement

One unpublished study conducted by the manufacturer assessed the agreement with T-Spot when samples were processed with T-Cell Select 0–58 hours after blood collection, compared with the absence of T-Cell Select. The pooled kappa for agreement between the two methods across all times was 0.92 (95% CI: 0.89, 0.94).

TAG meeting outcome

The TAG deliberated on the presented results comparing the performance of each test; made specific remarks on the study findings, implementation considerations and areas for further research; and provided the following concluding statements to WHO:

1. Based on available data, **Beijing Wantai's TB-IGRA** and **QIAGEN QuantiFERON-TB Gold Plus** performance *is comparable* to that of WHO-recommended IGRAs for the detection of TB infection.

2. Based on available data, **QIAGEN** QIAreach QuantiFERON-TB, SD Biosensor Standard E TB-Feron ELISA and Oxford Immunotec T-SPOT.TB 8 with T-Cell Select *could not be adequately compared with* WHO-recommended IGRAs for detection of TB infection.

3. Current WHO recommendations for the use of IGRAs are also valid for **Beijing Wantai's TB-IGRA** and **QIAGEN QuantiFERON-TB Gold Plus**.

Remarks

The primary analysis was of paired results of the index test with a reference test; it included a difference in sensitivity and specificity that was considered helpful for this comparative evaluation, particularly when the prevalence of TB infection varied by study population.

The comparative evaluations did not specifically assess subgroups (e.g. people living with HIV [PLHIV], children and other immunocompromised populations); however, data from these groups were included where available.

The studies for QFT-Plus were primarily from multiple low-burden TB settings, whereas those for Wantai were from a single, large, high-burden country (China).

No data on predictive accuracy for development of active TB were available for any index test except QFT-Plus, and for that test the data were limited and were similar to published results for WHO-recommended IGRAs. A lower predictive accuracy for QFT-Plus was observed in PLHIV in one study – this finding needs to be tested in additional studies.

A high risk of bias was observed for all studies, irrespective of the index test evaluated.

For those tests that could not be adequately compared with WHO-recommended tests for TB infection, this does not imply any concerns with the tests themselves but rather a lack of sufficient independent data to make a recommendation.

The advantages and disadvantages of blood-based IGRAs compared with skin-based TB infection tests apply to all index tests.

Indeterminate result rates need to be considered because these have cost implications and apply to all index tests. Indeterminate rates were only available for QFT-Plus compared with QFT-GIT (2.4% vs 2.2%) and for T-Cell Select compared with T-Spot without T-Cell Select (high nil: 1% vs 1% and low mitogen: 0.2% vs 0.3%).

Current WHO recommendations for IGRAs still apply for T-Spot without T-Cell Select use.

Implementation considerations

Infrastructure, equipment, staff, training and time-to-result are expected to be similar for QFT-Plus and Wantai compared with QFT-GIT. However, the procedure for undertaking Wantai is slightly more complex.

Product assessments by national or international regulatory agencies including quality of the product, batch-to-batch variation and manufacturing process are important before country implementation.

Processes for implementation of a new test still apply; for example, registration of the product, supply chain, training, diagnostic algorithms, standard operating procedures, quality assurance, service and maintenance, monitoring and evaluation, results reporting, and laboratory or health management information systems.

The cost varied by test and setting. Negotiation through the Global Drug Facility is needed to provide standardized pricing and catalogue listing for each index test.

WHO recommendations on diagnostics are based on clinical research evidence – they do not include quality assessments of the products or the manufacturing process involved. Before introducing products, countries should ensure that the products fulfil local or internationally recognized regulatory requirements (e.g. WHO prequalification).

Further research

Evaluation of the recommended tests in more diverse geographical and epidemiological settings, and specific subpopulations (e.g. PLHIV, children and other immunocompromised individuals).

Evaluation of the reproducibility and predictive accuracy for progression to active TB for Wantai, QIAreach, T-Cell Select and TBF.

More accurate quantification of direct and indirect costs for all index tests, using time and motion studies.

Evaluation of cost and cost–effectiveness for all index tests.

Evaluation of feasibility, applicability, equity, end-user values and preferences for all index tests.

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Annex 1: List of participants

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Annex 2: Declaration of interests

NO CONFLICT OF INTEREST	
Expert name	Dr Patricia Hall (United States of America) Dr Lucia Barrera (Argentina) Dr Paulo Redner (Brazil) Dr Sabira Tahseen (Pakistan) Dr Alaine Umubyeyi Nyaruhirira (South Africa) Prof Nguyen Van Hung (Viet Nam) Dr Valeriu Crudu (Republic of Moldova) Dr Siva Kumar Shanmugam (India) Dr Sandeep Meharwal (Thailand) Dr Vithal Prasad Myneedu (Nepal) Prof Yanlin Zhao (China) Dr Xin Shen (China) Dr Khalide Azam (United Republic of Tanzania)
Conflict identified	Nil
Conclusion	No conflict of interest

POTENTIAL CONFLICT OF INTEREST	
Expert name	**Heidi Albert, South Africa**
Conflict identified	**(1a) Employment:** Employment with FIND, the global alliance for diagnostics. However, not closely involved in any recent diagnostic evaluations at FIND.
Conclusion	Nonsignificant
Expert name	**Farzana Ismail, South Africa**
Conflict identified	**(2a) Research support, including grants, collaborations, sponsorships and other funding:** XDR Cartridge evaluation (Cepheid). Funds provided to research unit within the National Institute for Communicable Diseases in the amount of US$ 140 000; and bedaquiline post-marketing surveillance and emerging resistance (Janssen). Funds provided to the research unit in the amount of US$ 300 000.

POTENTIAL CONFLICT OF INTEREST	
	(2b) Nonmonetary support valued at more than US$ 1000 overall: Activity on latent TB infection in health care workers. Consumables and personnel were provided by Qiagen. This interest is still ongoing. Sponsorship to the International Union of TB and Lung Disease conference 2018 (Janssen). This included flight (to The Hague), accommodation and conference registration fee.
Conclusion	Nonsignificant
Expert name	**Madhukar Pai, Canada**
Conflict identified	**(2a) Research support, including grants, collaborations, sponsorships and other funding:** Two ongoing grants from the Bill & Melinda Gates Foundation (none related to TB); and Grant from FIND: Tuberculosis diagnostics in conjunction with development of new regimens to fight TB and DR-TB. This grant is to support FIND by conducting market analyses of TB tests, uptake of TB tests, systematic reviews of TB diagnostics, and product landscapes and secondary analyses of data (e.g. TB biomarker database). The work now also involves COVID-19 diagnostics. No specific product evaluation is included.
Conclusion	Significant, systematic review was conducted by the expert's host institution. Restrained from the deliberations and formulation of statement.
Expert name	**Thomas Shinnick, USA**
Conflict identified	**(1b) Consulting, including service as a technical or other advisor:** As an independent consultant, I have received contracts and travel support from WHO, FIND, USAID for work related to laboratory strengthening and developing global guidance documents.
Conclusion	Nonsignificant
Expert name	**Sadia Shakoor, Pakistan**
Conflict identified	**(2a) Research support, including grants, collaborations, sponsorships and other funding:** Co-investigator of projects for which the expert's institution (Aga Khan University) has received funding support from Janssen. Research: The Bedaquiline DREAM programme and Bedaqiline EQA project. The funding covered 5% salary support for this expert from 2018 to 2020.
Conclusion	Nonsignificant

POTENTIAL CONFLICT OF INTEREST	
Expert name	**Daniela Maria Cirillo, Italy**
Conflict identified	**(2a) Research support, including grants, collaborations, sponsorships and other funding:** The expert participated in the 2020 advisory board (Biomérieux) for which they received €1000 in financial gain (personal?). This engagement ended in 2020. The expert has also participated in the evaluation of diagnostic assays; for the evaluation of blood stability for VIDAS, the research unit in their institution received €11 200 from Biomérieux; and for the evaluation of the XDR test prototype for Cepheid and FIND, the research unit received €14 295.80 in 2018.
Conclusion	Nonsignificant
Expert name	**Claudia Denkinger, Germany**
Conflict identified	**(1a) Employment:** The expert was employed by FIND until April 2019 and they have continued to have a collaboration agreement with FIND. **(2a) Research support, including grants, collaborations, sponsorships and other funding:** The expert has implementing ongoing grants from various public funding agencies on work on TB diagnostics: R2D2: multiple diagnostic solutions are evaluated for triage, TB diagnosis and comprehensive, rapid DST; POC ultrasound grant: Fujifilm instruments; TB-CAPT: Omni from Cepheid; SARS-CoV-2: Roche, SD Biosensor, Abbott, LumiraDx, Bioeasy, Mologic, PMC, Fujirebio (through FIND); and Collaboration with FIND on evaluating FujiLAM, as part of both the prospective study and the qualitative research and modelling work.
Conclusion	Nonsignificant
Expert name	**Florian Maurer, Germany**
Conflict identified	**(2b) Nonmonetary support valued at more than US$ 1000 overall:** Instruments and reagents placed free of charge for evaluation (Becton Dickinson; Roche; Hain; and Metasystems). No income was provided.
Conclusion	Nonsignificant
Expert name	**Irina Lyadova, Russian Federation**
Conflict identified	**(2b) Nonmonetary support valued at more than US$ 1000 overall:** The expert was a lecturer at the “Recent advances in treatment and diagnosis of drug-resistant TB”

POTENTIAL CONFLICT OF INTEREST	
	in the Global Public Health meeting, sponsored by Johnson & Johnson. Travel expenses were covered. **(4a) Patents, trademarks or copyrights:** Russia patents on TB diagnostics in 2012 and 2013, linked to the Central TB research institute where the expert worked. The patents belong to the expert's employer. This interest ceased in 2018.
Conclusion	Nonsignificant
Expert name	**Christopher Coulter, Australia**
Conflict identified	**(2a) Research support, including grants, collaborations, sponsorships and other funding:** Research support from FIND to conduct LOD studies on TB molecular tests (Cepheid Xpert MTB/XDR; Bioneer). The monetary value of the contract was just over AUD 40 000 with 60% of the contract to fund the labour to do the studies and the balance consumables. The interest ceased in 2019.
Conclusion	Nonsignificant
Expert name	**Mark Nicol, Australia**
Conflict identified	**(2a) Research support, including grants, collaborations, sponsorships and other funding:** Research support from NIH, Wellcome Trust, Bill & Melinda Gates Foundation, FIND, UK MRC, EDCTP to evaluate novel TB diagnostics (Xpert MTB/RIF; Xpert MTB/RIF Ultra; Epistem GeneDrive; BD MAX MDR-TB; Truenat TB; Determine TB-LAM; SILVAMP TB-LAM). No funding from commercial entities. Research grants belonged to the University of Cape Town and the University of Western Australia. Significant research funding (several million dollars). However, no personal income or income to family members. These activities are ongoing. The estimated total grant funding for this research programme would be in the order of US$ 10 million. **(4a) Patents, trademarks or copyrights:** Provisional patent for novel method for extracting mycobacterial DNA from sputum. This patent is jointly owned by the University of Cape Town and the expert. This interest is ongoing.
Conclusion	Nonsignificant

COVID-19: coronavirus disease; DNA: deoxyribonucleic acid; DR-TB: drug-resistant tuberculosis; DST: drug susceptibility testing; EDCTP: European and Developing Countries Clinical Trials Partnership; FIND: Foundation for Innovative New Diagnostics; LOD: limit of detection; MRC: Medical Research Council; NIH: National Institutes of Health; POC: point of care; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TB: tuberculosis; UK: United Kingdom of Great Britain and Northern Ireland; USA: United States of America; USAID: United States Agency for International Development; WHO: World Health Organization; XDR: extensively drug-resistant.

Annex 3: Agenda

Commercial blood-based in vitro interferon-gamma release assays used for detection of TB infection

World Health Organization headquarters, Geneva, Switzerland
27–29 October 2021

Background

The Qiagen QuantiFERON®-TB Gold In-Tube (QFT-GIT) and Oxford Immunotec T-SPOT®.TB (T-Spot) assays are commercial in vitro tests used for detection of tuberculosis (TB) infection. QFT-GIT is a whole-blood-based enzyme-linked immunosorbent assay (ELISA) measuring the amount of interferon-gamma (IFN-γ) produced in response to two or three *Mycobacterium 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 assay T-SPOT.TB measures the number of peripheral mononuclear cells that produce INF-γ after stimulation with ESAT-6 and CFP-10. Earlier versions of the Qiagen TB infection test included QuantiFERON (QFT), which measured host response to purified protein derivative (PPD), and QuantiFERON-Gold (QFT-G), which measured response to two TB-specific antigens (ESAT-6 and CFP-10).

In 2011, the World Health Organization (WHO) issued recommendation on use of interferon-gamma release assays (IGRAs), which currently cover QFT-G, QFT-GIT and T-Spot tests.

In recent years, new and updated versions of blood-based IGRAs have been marketed worldwide; they include QuantiFERON-TB Gold Plus (QFT-Plus), QIAreach™ QuantiFERON-TB (QIAreach), Beijing Wantai's TB-IGRA, the Standard E TB-Feron ELISA (TBF) and T-SPOT.TB 8 with T-Cell Select.

There is a need to evaluate these technologies to determine whether one or more of the reviewed assays may be included under current WHO recommendations for IGRA testing.

Objectives

1) To review evidence on diagnostic accuracy and practical considerations of other IGRAs as compared with the current WHO-recommended QFT-G, QFT-GIT and T-SPOT.TB tests.
2) To use the outcomes of the IGRA evidence review to determine whether one or more of the reviewed assays may be included under current WHO recommendations for IGRA testing.

Day 1 – Wednesday 27 October 2021		**Chair: P. Hall**
12:30 – 13:00	Registration	
13:00 – 13:10	Welcome and introductions	Matteo Zignol
13:10 – 13:20	Technical Advisory Group (TAG) overview, objectives and plans	Patricia Hall
13:20 – 13:40	Meeting background, objectives and working methods	Nazir Ismail

13:40 – 13:55	Summary of declarations of interest	Alexei Korobitsyn
13:55 – 14:15	WHO Global TB Programme (WHO/GTB) policy work: Pathways “A” and “B”	Nazir Ismail
14:15 – 14:35	Principles of diagnostic tests comparative evaluation: (non-inferiority; equivalence; superiority). Pre-set criteria versus wholistic structured evaluation	Dick Menzies
14:35 – 14:40	Q & A	
14:40 – 14:55	Discussion	
14:55 – 15:00	Pause	
15:00 – 15:15	Methods of the systematic review of commercial blood-based in vitro interferon-gamma release assays used for TB infection	Edgar Ortiz-Brizuela

Day 2 – Thursday 28 October 2021		**Chair: P. Hall**
13:00 – 13:05	Recap from Day 1	Alexei Korobitsyn
13:05 – 13:20	Wantai TB-IGRA: description, diagnostic accuracy, reproducibility, commodity costs, implementation considerations	Dick Menzies
13:20 – 13:25	Q & A	
13:25 – 13:45	Discussion	
13:45 – 14:15	Formulation of the draft policy statement on Wantai	
14:15 – 14:20	Pause	
14:20 – 15:00	QuantiFERON-TB Gold Plus (QFT-Plus): description, diagnostic accuracy, reproducibility, cost, implementation considerations	Edgar Ortiz-Brizuela
15:00 – 15:05	Q & A	
15:05 – 15:25	Discussion	

15:25 – 16:00	Formulation of the draft policy statement on QFT-Plus	

Day 3 – Friday 29 November 2021		**Chair: P. Hall**
13:00 – 13:15	QIAreach™ QuantiFERON-TB (QIAreach QFT): description, diagnostic accuracy, reproducibility, cost, implementation considerations	Edgar Ortiz-Brizuela
13:15 – 13:20	Q & A	
13:20 – 13:40	Discussion	
13:40 – 13:55	Formulation of the draft policy statement on QIAreach QFT	
13:55 – 14:15	Standard E TB-Feron ELISA (TBF): description, diagnostic accuracy, reproducibility, commodity costs, implementation considerations	Lika Apriani
14:15 – 14:20	Q & A	
14:20 – 14:30	Discussion	
14:30 – 14:40	Formulation the draft policy statement on Standard E TB-Feron ELISA (TBF)	
14:40 – 14:55	T-SPOT®.TB 8 with T-Cell Select: description, diagnostic accuracy, reproducibility, commodity costs, implementation considerations	Edgar Ortiz-Brizuela
14:55 – 15:00	Q & A	
15:00 – 15:10	Discussion	
15:10 – 15:20	Formulation the draft policy statement on T-SPOT.TB 8 with T-Cell Select	
15:20 – 14:25	Pause	
15:25 – 15:45	Summary on test procedures, test performance, commodity cost estimations and implementation considerations	Dick Menzies

15:45 – 15:55	Formulating the final policy statements	
15:55 – 16:00	Meeting closure and next steps	

Web annex: Study report

https://apps.who.int/iris/bitstream/handle/10665/351180/9789240042360-eng.pdf

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