Clinical Review

QuantiFERON-TB® Gold

Clinical review of literature pertaining to the use of interferon-gamma release assays for tuberculosis screening in healthcare workers: Evidence base and clinical experience with QuantiFERON-TB Gold (QFT®)

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This document provides healthcare professionals with an evidence-based guide on the use of QuantiFERON-TB Gold (QFT) for the risk assessment of latent TB infection in healthcare workers.

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The risk of tuberculosis infection in healthcare communities

Infection with *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis (TB), remains a significant health concern worldwide. Historically known as consumption or white plague, TB disease is often a forgotten pathogen because infection and disease occurs relatively infrequently in developed countries. However, more than 8.7 million new cases of TB and 1.4 million TB related deaths occurred in 2012 globally. Although a large burden of TB disease occurs in developing countries, with 40% of all TB occurring in China and India (1), vigilance against TB remains a global issue.

Prevention of active TB disease is a major cornerstone of TB control, and preventing TB disease relies on identifying and treating TB infection. Many individuals infected with TB bacteria do not develop active disease and display no clinical signs of infection, but rather develop a subclinical or 'latent' TB infection. These individuals are at increased risk of developing active TB at some later stage in life. Some reports indicate approximately 1 in every 10 people with TB infection will progress to active TB (2), although reactivation of latent TB infection may occur more often. For example, in the United States, more than 80% of TB cases are a result of reactivation of latent infection that could have been prevented if treated appropriately. (3) If identification and treatment of latent TB infection were combined on a global scale with the present focus on active TB case finding and treatment, then the global TB burden can be overcome. (4, 5)

One setting where TB burden has been a continuing issue, and consequently provides an avenue for improving TB control globally is the healthcare setting. Hospitals, clinics, and other congregate health settings are well recognized as areas of potential TB transmission. The transmission of TB of any kind (e.g., patient to worker, worker to worker, or worker to patient) within a healthcare setting can have significant consequences for healthcare operations, which is why many countries and institutions recommend or mandate regular surveillance of TB infection status among health care workers (HCWs). Pre-employment and regular, ongoing screening for TB infection of doctors, nurses, custodial staff, and other health professionals help institutions monitor potential for occupational TB exposure and prevent nosocomial infection through early detection of infectious HCWs and/or chemoprevention of HCWs identified as having latent TB infection. Implementation of targeted TB screening in groups with higher risk of exposure, such as HCWs, contributes significantly to effective TB control. (6)

In 2011, a nurse who had not completed occupational TB screening inadvertently infected an infant in a maternity ward in Rome. The subsequent contact investigation resulted in over 1300 potentially exposed newborns being tested for TB and ongoing follow-up for a 3-year period. (7) This case study illustrates the potential consequences of a missed case of active TB disease in the healthcare setting and, conversely, the importance of regular healthcare worker screening.

A truly global issue, especially in a healthcare setting, TB risk is greatly influenced by migration patterns. Migration from high TB burden countries to more developed, low TB burden countries might jeopardize infection control successes in the latter, in the general population as well as a healthcare setting. Prevalence of latent TB infection in migrants from high TB burden countries is high, and the risk of reactivation during the first years after migration is elevated. (8) Therefore, TB risk in patients with a migration background is increased, yielding a potential source of infection for HCWs. Furthermore, migrating HCW might import TB into the healthcare system of the host country. This stresses the need for pre-employment and ongoing or serial screening for latent TB infection of HCWs. (3)

Technical advancement has improved the effectiveness of TB screening

Traditionally a part of TB infection risk assessment, the tuberculin skin test (TST or Mantoux), has been used for TB screening since the early 20th Century. However, despite its use for over 100 years, the in vivo TST has well known limitations, particularly the requirement for a precise intradermal injection of a defined amount of tuberculin (purified protein derivative, PPD) by a specially trained professional and assessment of the resultant induration 48 to 72 hours later.

The TST in healthcare workers

Besides the second appointment needed for test reading, the TST has several disadvantages. Cross-reactivity with non tuberculous mycobacteria (NTM) and – for HCWs even more important – the cross-reactivity with the Bacille Calmette-Guérin (BCG) vaccine are responsible for the low specificity of the TST. In some countries that had ceased BCG vaccination in the general population, HCWs are still vaccinated because they are considered a TB risk group. In other countries, HCWs are revaccinated before entering the work place. In countries where BCG vaccination was never performed, HCWs might have migrated from countries where BCG vaccination is performed. Therefore, BCG vaccination has a profound impact on TST results in HCW population. (6, 9-11)

In addition to the reductions in specificity caused by cross-reaction with BCG and NTM, repeated intradermal application of the tuberculin might result in an unwanted stimulation of the immune system of the HCW further lowering the specificity of the TST in HCW screening. (6)

Interpretation of the TST depends on exposure circumstances and country. In order to circumvent the problem of cross-reactivity with the BCG vaccine, high thresholds for a positive TST (>15 mm) are chosen in some countries (e.g., France, Portugal). However, this does not allow for the elimination of the influence of BCG on TST and reduces the sensitivity of the TST. (6, 12, 13) In some HCW populations TST positivity is as high as 70% (e.g., Portugal, France), which renders the TST more or less useless for TB infection monitoring. However, TST-based screening provides advantages over chest X-ray (CXR) based screening in some settings and might therefore remain important in resource limited countries.

IGRAs: Modern immune assays for TB

Interferon gamma release assays (IGRAs) are immunological assays used to assess the TB infection status.

Highly TB antigen-specific, IGRAs measure the quantity of the immune-stimulatory cytokine, Interferon-gamma (IFN-γ), produced by effector T-cells present in peripheral blood in response to specific activation following exposure to TB antigens. Currently, there are 2 IGRAs commercially available. The first, QuantiFERON®-TB Gold (QFT®), is based on an enzyme-linked immunosorbent assay (ELISA) technology, while the other IGRA, called T-SPOT®.TB (Oxford Immunotec; Abingdon, UK), is based on Elispot technique (i.e., 'Elispot-based IGRA').

In general, IGRAs provide several improvements for latent TB infection screening over the TST. The use of an IGRA does not replace traditional TB risk assessment methodologies, yet they can provide valuable information on an individual's TB status.

Table 1: an overview of the common and specific characteristics of the two commercially available IGRAs.

Characteristic	TST*	QFT†	Elispot-based IGRA‡
Single patient visit	×	✓	✓
Use of positive and negative controls	×	✓	✓
Objective results	×	✓	×
Influenced by BCG vaccination status	✓	×	×
Set interpretation criteria	×	✓	✓

*CDC Fact sheet (14), †QFT Package Insert (15), ‡T-SPOT TB Package Insert (16, 17)

What IGRAs offer TB infection screening programs

Single visit

IGRAs are in vitro assays that involve an antigen/whole blood incubation period of ≤ 24 hours and only require collection of a small volume venous blood sample at 1 time point. If merited, further repeat IGRA testing (e.g., following TB exposure) can be performed without any effect on the recipient's immune reactivity to TB antigens. No second appointment for reading an IGRA is needed and, therefore, IGRAs are more convenient and less time consuming for the HCW and those administering the tests. The problem of unread skin tests is simply resolved by using IGRAs.

Use of positive and negative controls

In contrast to the TST, QFT incorporates both negative and positive controls to allow for clearer clinical interpretation of test results. In this manner, QFT consists of 3 tubes:

- The TB Antigen tube assesses the IFN-γ response to highly-specific TB antigens.
- The Nil (negative control) tube adjusts for non-TB-specific production of IFN-γ , e.g., background noise.
- The Mitogen (positive control) tube contains phytohemagglutinin (PHA), which activates T-cells in an antigen-independent method and may be useful to indicate the general T-cell mediated immune status of a patient.

A low Mitogen result due to immunosuppression or a high Nil result due to nonspecific interferon release might result in an indeterminate result (for details on the test interpretation, see figure on page 8).

Unaffected by BCG vaccination status

In contrast to the TST, IGRAs are affected by neither BCG (vaccination or therapy) nor most non-tuberculous mycobacteria. (18)

The superior specificity of an IGRA is due to highly specific antigens incorporated in the tests. QFT incorporates 3 TB-specific proteins – ESAT-6, CFP-10, and TB7.7(p4) – resulting in a significantly higher degree of specificity than the TST. (15) This minimizes the potential for the generation of a false-positive result due to prior BCG vaccination and minimizing the potential for unnecessary CXR or chemoprophylaxis and associated side effects, inconvenience, and additional costs.

QuantiFERON-TB Gold provides objective interpretation of results

With its ELISA platform, QFT enables automated, objective, and qualitative determination of IFN-γ cytokine secretion in whole blood in response to TB antigens. (15) In addition to the qualitative result, which is based on a standard, globally approved cut off, the United States Centers for Disease Control and Prevention (CDC) recommends reporting of quantitative results reflecting the amount of IFN-γ produced. (15)

This is in contrast to the TST which is susceptible to subjective reading and interpretation of results as the erythema might be confounded with the induration and the largest diameter might be missed. For example, the TST has multiple interpretation criteria (5 mm, 10 mm, 15 mm induration) that are selected depending on regional guidelines and on the population to which the test recipient belongs. (14)

A guide to the QuantiFERON-TB Gold assay

QFT is specifically designed as an objective, controlled assay for the detection of immunologic response to *M. tuberculosis*, and it significantly improves upon the limitations of the TST.

QuantiFERON-TB Gold identifies risk for TB in HCW accurately

The use of IGRAs is more suited to the healthcare setting than the TST, particularly in countries of low TB burden, due to their high specificity and the potential for reducing costly unnecessary follow-up and treatment.

Several studies have demonstrated that IGRAs, particularly QFT, have superior specificity over the TST, principally in countries with low TB burden. (19)

Compared with the TST and the Elispot-based IGRA, QFT demonstrates the highest specificity for TB infection (99.2%) in the general population in low TB prevalence settings. (15, 16)

The use of QFT instead of TST would save between 25 to 98% of the CXRs needed to exclude active TB after a positive TST, as can be deduced by a head-to-head comparison of the IGRA with the TST (Table 2). (13)

Table 2: Head-to-head comparison of IGRAs and the TST in HCWs from different countries (table adapted from Nienhaus). (13)

		TST positive		IGRA positive	
	Sample size	All	IGRA negative	All	TST negative
Publication	N	N (%)*	N (%)†	N (%)*	N (%)‡
Hotta et al. Japan 2007 (20)	202	120 (59.4)	117 (97.5)	3 (1.5)	0
Mirtskhulava 2008 Georgia (21)	265	177 (66.8)	44 (24.9)	159 (60.0)	26 (16.4)
Nienhaus et al. Germany 2008 (9)	261	63 (24.1)	48 (76.2)	25 (9.6)	10 (40.0)
Alvarez-Leon et al. 2009 Spain (22)	123	9 (7.3)	4 (44.4)	8 (6.5)	3 (37.5)
Casas et al. 2009 Spain (23)	145	101 (69.7)	59 (58.4)	43 (29.7)	1 (2.3)
Girardi et al. 2009 Italy (24)	115	61 (53.3)	36 (59.0)	29 (25.2)	4 (13.8)
Khanna et al. 2009 UK (25)	148	24 (16.2)	15 (62.5)	12 (8.1)	3 (25.0)
Costa et al. Portugal 2009 (6)	1,218	903 (74.1)	532 (58.9)	297 (24.4)	26 (8.8)
Tripodi et al. France 2009 (10)	148	97 (65.5)	74 (76.3)	28 (18.9)	5 (17.9)
Vinton et al. Australia 2009 (26)	341	114 (33.4)	98 (86.0)	21 (6.2)	5 (23.8)
Khoury et al. USA 2011 (27)	611	50 (8.2)	42 (84.0)	12 (2.0)	4 (33.3)

*Percent of sample, †Percent of TST positives, ‡ Percent of IGRA positives

IGRAs correlate with TB infection risk factors

In a metaanalysis, IGRA results were observed to be well correlated with TB infection risk factors, including occupational exposure, such as HCW presence in a high-risk ward, TB clinic, or geriatric ward. (28)

QuantiFERON-TB Gold predicts development of active TB

In high risk groups the QuantiFERON-TB Gold predicts the development of active TB better than the TST. (29) This is particularly true for close contacts in countries with low TB incidence. (30, 31) Preventive chemotherapy becomes more targeted and the number to treat to prevent one active TB case can be reduced by a factor of 4 to 5 (30, 31) in these countries.

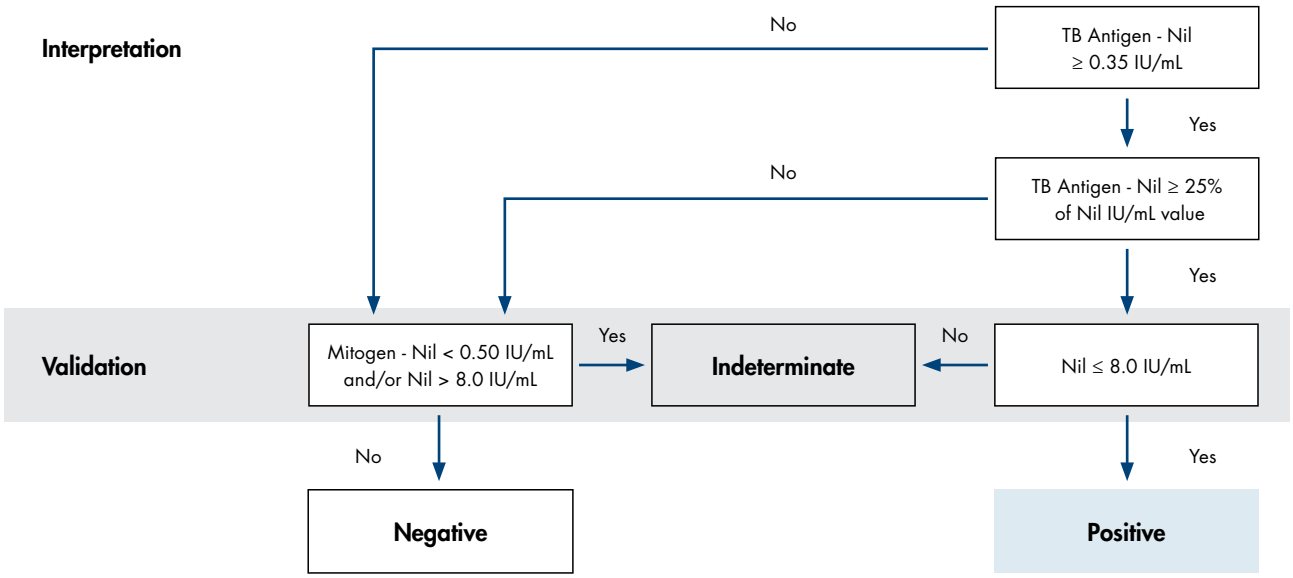
Unfortunately follow-up data on HCWs with a positive IGRA are still sparse. In the only study that reported data on disease progression in HCW so far, the probability of active TB during the follow-up was twice as high for HCW with a positive QuantiFERON-TB Gold compared to those with a positive TST. (32) Albeit, the progression rates were low in both IGRA- and TST-positive groups (0.4% and 0.2%, respectively). The apparently low progression rate in HCW after a positive IGRA or TST is most likely explained by the prevailing of remote latent TB infections in the HCW populations studied so far. (13) Unfortunately, neither IGRA nor TST are able to distinguish recent from remote latent TB infection. (33) Therefore assessment of recent infection risk remains an essential when estimating the probability of progression to active TB.

Interpretation criteria for QuantiFERON-TB Gold

QuantiFERON-TB Gold generates 3 possible results for any sample. (15) Generally, results for most individuals are:

- A positive test result indicates presence of TB antigen-specific T-cells and a high likelihood of latent TB infection
- A negative test result indicates that T-cells could be activated by PHA in a non-specific way (positive control), but that no specific TB-specific T-cells are present in the blood sample. This is the most common scenario, indicating that latent TB infection is highly unlikely to be present
- An indeterminate test result may indicate either a technical error (e.g., positive and/or negative control fail) or may be related to the immune status of the individual being tested (e.g., positive control fails due to immune suppression or T-cell anergy)

Figure 1. Interpretation criteria for QFT results (15)



As per the QFT instructions for use, if the indeterminate result is due to low Mitogen or high Nil values, the result would not be expected to change on repeat unless an error occurred with the ELISA testing. In this case, physicians may choose to repeat the test or perform other procedures as appropriate (e.g., medical follow up to determine immune status of patient). In all cases, indeterminate results are instructed to be reported as such. (15)

The value of having an indeterminate QFT result is that it essentially may minimize false-positive and false-negative results. As the TST does not allow for this type of result, a false-negative TST (e.g., due to immunosuppression caused by corticosteroids) is more likely than with an IGRA. Further work to identify factors associated with indeterminate results will help optimize the use of IGRAs in clinical practice, particularly in immunosuppressed populations. (34) Notwithstanding, the probability of indeterminate IGRA results are very low in HCW populations. This is particularly salient with indeterminate QFT results in HCW, estimated at approximately 1% (unpublished mean value from literature review). (9, 12, 21, 26, 35-44)

Comparing indeterminate results for QFT to either the TST or the Elispot-based IGRA is somewhat nonsensical as the tests have different methodologies, cut offs, and nomenclature. Also, in many studies TST non-return rates and Elispot-based IGRA invalid, borderline, or equivocal results are either not published, inconsistently reported, or excluded from analysis because the results are uninformative. (34, 45-47).

In contrast to QFT, which is the only test with a globally consistent cut off and approved, meaningful 'indeterminate' nomenclature, TST non-returns or incomplete results can range from 5-65% in the general population (unpublished data from literature review) and from 10 to 20% in HCW. (45, 48) The difficulty with Elispot-based assay is that it has multiple interpretation criteria globally, one with a 'borderline' result category and the other without, as well as 'invalid' result. (16, 17)

However, the closest available estimate of 'indeterminate' Elispot-based assay results in HCW was <1%, but this value excluded borderline and invalid results (e.g., were labelled as 'unable to get a result') and was reported as part of a cost-effectiveness model. (45)

QuantiFERON-TB Gold is a more cost-effective approach than TST in healthcare settings

Many experts view the ongoing use of the TST as an inefficient use of healthcare resources. Although traditionally perceived as low-cost and simple, several factors drive inefficiency of the TST in the healthcare setting, including: Increased labor costs due to requirement for 2 visits, variable specificity of the TST, particularly in BCG vaccinated individuals, requirement for specially-trained personnel to administer the TST, high inter- and intra-reader variability. In addition to these programmatic inefficiencies, due to its low specificity particularly in low prevalence populations with a mixed BCG vaccination status, the TST is associated with other potential costs such as follow-up physician visits, unrequired antibiotic treatments, and CXRs.

Several studies demonstrated that introducing IGRA into TB screening of HCW will improve the cost-effectiveness of the screening program. (45, 47-50) Most studies favored a 2-step strategy in which IGRA is used as a confirmatory test for a positive IGRA. (49) However, these studies did not consider the negative effect of this 2-step strategy on the sensitivity of the TB screening at whole. As the sensitivity of the TST is well below 100%, in countries with a low TB burden up to 40% of the HCWs who are infected might be missed when IGRA is used as confirmatory test for TST only.

Those studies which took this problem into account demonstrated that despite higher unit costs for IGRA than for TST, screening strategies applying IGRA alone were the most overall effective strategy when screening for latent TB infection in HCW. (49) This was particularly so when both programmatic and indirect costs were taken into consideration. (47)

The use of QFT has also been shown to potentially lead to superior clinical outcomes as HCW are more likely to accept prophylaxis following a positive IGRA test than a TST, thus limiting the risk of ongoing infections. (48)

Although direct comparisons of the commercially-available IGRAs in HCW cohorts are yet to be published, in a study assessing immigrant TB screening the use of IGRAs alone was deemed to be the most cost-effective approach and, due to the lower unit costs, QFT was favored over the Elispot-based IGRA. (50)

International guidelines for TB screening of healthcare workers

Several developed countries have recognized the value that IGRA technology can bring to screening for and protecting HCW from TB infection. As a result, these countries have incorporated the use of an IGRA in their official recommendations.

Owing to several factors, including the recent development of IGRAs and individual country disease burden, considerable diversity exists amongst different countries with regards to their recommendations regarding the use of IGRAs for TB screening in HCWs.

The table below provides an overview of current recommendations for use of IGRA testing for TB in the Healthcare setting for selected countries.

Status of Recommendation	Guideline or position statement*
IGRA alone	Germany† France Japan The Netherlands Portugal Slovakia Switzerland
Either TST or IGRA	Italy‡ Switzerland USA
TST followed by IGRA if TST positive	Bulgaria The Netherlands Spain
TST alone	Austria Brazil Canada Ireland Saudi Arabia South Korea
No recommendation	Australia Croatia Czech Republic Denmark European Centre for Disease Prevention & Control Finland Norway United Kingdom

* Adapted from Denkinger et al (51); some countries appear twice depending on the risk group.

† (German guideline reference 2007 original, renewed in 2011)(52, 53)

‡ IGRA preferred in BCG vaccinated individuals

Serial screening of HCWs with QuantiFERON-TB Gold

In many countries, TB screening is performed following risk assessment, and HCWs with regular contact to infectious patients may be screened regularly at different frequencies (e.g., annually or biannually). Other HCW, such as those who have been exposed accidentally via unprotected contact to infectious patients, may be screened urgently as well.

With repeat screening becoming more common for HCW, choice of test becomes perhaps a bigger consideration for clinicians in the effort to streamline costs. Using the TST for HCW screening has traditionally been difficult for a few reasons. Firstly, many clinicians have traditionally assumed that a HCW once positive with the TST is always positive, such that repeat testing may not be completed in previously TST-positive HCWs, but the HCW followed up with CXR. Secondly, the 'boosting' phenomena associated with repeat TSTs (e.g., strong reactions in previously TST-positive individuals) has led to the avoidance of repeat TSTs in HCWs.

In contrast to the TST, IGRAs are in many ways more favorable for serial screening of HCWs, especially because of the requirement for a single visit. Additionally, as IGRAs are in vitro tests, boosting of repeat IGRAs does not occur, and the assumption of positivity based on previous positive results is not needed.

Growing evidence based on serial IGRA screening has indicated that the immune response to infection with *M. tuberculosis* may be more variable than previously thought, (54) and that the proportion of HCWs who revert from a positive to a negative IGRA over time is high. (13, 28, 55) Therefore, it is useful to retest HCWs with a positive IGRA in their history when they are scheduled for subsequent TB screening. For those who revert to a negative IGRA result, no CXR should be indicated as long as TB is not suspected clinically. (56)

However, with different patterns of screening in individuals with varying TB risk with different tests, questions about interpreting serial IGRA results have arisen. (Note that this section will focus on QFT as 'the available data regarding the use of the [Elispot-based IGRA] in the serial testing of HCWs is remarkably limited and warrants further research.') (55)

In particular, QFT was designed for use primarily in low-TB prevalence settings in the developed world. As such, through the development of the assay, emphasis was placed on ensuring the highest possible specificity while maintaining a balance with assay sensitivity. The QFT cut off of 0.35 IU/mL has been clinically validated and is approved for use worldwide. Furthermore, although it is recommended that the quantitative value of IFN-γ is reported, as the magnitude of the measured IFN-γ level cannot be correlated to stage or degree of infection, level of immune responsiveness, or likelihood for progression to active disease, (15) the test is approved for a qualitative result only. Where *M.tuberculosis* infection is not suspected, initially positive results can be confirmed by retesting the original plasma samples in duplicate in the QFT ELISA. If repeat testing of 1 or both replicates is positive, the individual should be considered test positive. (15)

Despite this, due to the increased variability experienced and the need for clarification of interpretation specifically in populations with low TB risk, different strategies (or algorithms) for the interpretation of QFT results close to the cut off have been developed, proposed, and in some cases validated and already in practical use by reputable global institutions. The most prominent strategy calls for the introduction of a new zone for interpretation which may assist with clarifying 'true' from 'false' conversions or reversions as well as the exclusion of false-positive QFT results in low-risk groups, (13, 28, 55) although not in HCWs with increased TB risk. (57)

Several studies have suggested repeating QFT that has a reported IFN-γ concentration between the cut off of 0.35 IU/mL and a proposed new upper limit for a 'borderline' or 'retesting' zone (0.7, 1.1, or 2.0 IU/mL). A result outside this proposed zone would then indicate clinical follow up with a CXR or preventive chemotherapy, while a result within the zone should be retested or monitored for changes in risk profile. (58-60)

A review of the current literature, including the above studies, was a central theme at a meeting of a panel of US-based experts discussing the issues surrounding serial screening of low-risk individuals, in particular HCWs. (61) The key result from this meeting, as reported by Daley et al (61), was that clinical guidance is needed for interpreting QFT results around a 'retesting' zone of 0.35 to 1.0 IU/mL, which was a consensus based on available literature.

Whereas the studies above have suggested implementing several potential zones within approved test criteria, a key outcome within the US-based context was that the FDA-approved cut off for QFT does not need to be revised. Instead, the recommendation was for further immediate work to prepare national clinical guidance for clinicians and laboratory professionals.

The major benefit to this collection of ongoing work globally is that there has been significant impetus for improving the use of IGRAs, in particular QFT, in the settings of serial screening and occupational health. However, until formal guidance regarding the interpretation of serial QFT results is approved and released by national and international organizations, the validated and approved criteria and instructions for using QFT must apply. (15, 61)

> "Ultimately the use of any TB diagnostic tool must be based on approved diagnostic criteria and any results generated need to be taken together in context with other clinical risk assessments. Final interpretation of any result, and subsequent clinical intervention, is a clinical decision that should be made on a case-by-case basis by a qualified clinician." (61)

Summaries of selected studies in healthcare workers

<table>
<tr><th>Publication</th><th>Main Finding</th></tr>
<tr><td>Baussano, I., Nunn, P., Williams, B., Pivetta, E., Bugiani, M., and Scano, F. (2011) Tuberculosis among Health Care Workers. Emerg. Infect. Dis. 17(3), 488. (62)</td><td>This literature review assessed the annual risk for latent TB infection (ARTI), incidence rate ratios (IRRs), and employment-related exposure in HCW globally. Only studies reporting latent TB infection diagnosed by the TST were eligible for inclusion. Interferon-γ release assays (IGRAs) such as QFT were not included in the review.
Median estimated annual TB IRRs for low, medium, and high incidence countries were 2.0 (IQR 1.5–4.1), 1.4 (IQR 0.4–8.8), and 5.4 (IQR 1.7–9.1), respectively, while ARTI values in HCW were (with interquartile range, IQR):
Table 3. Annual risk of latent TB infection in HCW.
<table><tr><th>TB incidence* (cases per 100,000 population)</th><th>ARTI (%)</th><th>IQR (%)</th><th>Pooled ARTI (%)</th></tr><tr><td>Low (<50 cases)</td><td>2.9</td><td>1.8-8.2</td><td>3.8</td></tr><tr><td>Intermediate (50-99 cases)</td><td>8.7</td><td>3.9-10.5</td><td>6.9</td></tr><tr><td>High (> 100 case)</td><td>7.2</td><td>4.1-14.3</td><td>8.4</td></tr><tr><td>All countries</td><td>N/A</td><td>N/A</td><td>4.6</td></tr></table>* Ranges determined by authors. N/A. not published
This study suggests that HCW are at an approximately 2- to 5-fold increased risk of latent TB infection than the general population. The authors conclude that infection control measures, coupled with early diagnosis of latent TB infection and prompt treatment of active TB, are required.</td></tr>
<tr><td>Borgia, P. et al. (2011) Suspected transmission of tuberculosis in a maternity ward from a smear-positive nurse: preliminary results of clinical evaluations and testing of neonates potentially exposed, Rome, Italy, 1 January to 28 July 2011. Eur. Surveill. 16(40), doi: pii19984.</td><td>This case study of a newborn assessed prevalence of latent TB infection following potential exposure to pulmonary TB in a HCW. This report is a preliminary discussion of contact investigation results.
QFT was chosen for the investigation because:
1. Of the previously reported low sensitivity of the TST in neonates to detect latent TB infection;
2. QFT had been demonstrated to have higher accuracy than the TST in in children of low- and middle-income countries; and
3. QFT does not require a second assessment visit.
Nine percent (9%) of children tested QFT positive, and only 0.2% indeterminate (all of whom were negative upon retest 1 month later). Of neonates under the age of 5 weeks, 11% were QFT positive.
Subjects who tested QFT positive were also tested with the TST, and all were negative except the case study subject (active TB, positive in both the TST and QFT). None of the subjects who tested positive had progressed to active TB after 3 and 9 months post-testing periods.
This study demonstrated the utility of QFT in a population where sensitivity and accuracy of testing are important. It supports the use of QFT vs the TST in neonates.</td></tr>
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<table>
<tr><th>Publication</th><th>Main Finding</th></tr>
<tr><td>Costa, J.T., Silva, R., Sa, R., Cardoso, M.J., and Nienhaus, A. (2010) Results of a five-year systematic screening for latent tuberculosis infection in healthcare workers in Portugal. J. Occ. Med. Toxicol, 5, 22. (63)</td><td>This screening study of 5,524 HCW took place in a medium risk institution in Portugal. A subgroup of 1,686 (32.6%) HCWs underwent simultaneous TST and QFT to detect latent TB infection.

Overall, 55.2% of the tested population had a positive TST. Within the total population, physicians were second least likely to have a positive TST, but most likely to have active TB (detected by CXR and symptom questionnaire). In the subgroup of those who received QFT as well as TST, 33.2% tested positive. Probability of a positive QFT increased with TST diameter, but never exceeded 49.2%.The prevalence of latent TB infection was lower using QFT than the TST as criterion for diagnosis regardless of the time point of the test ($p < 0.001$).

Table 4. Annual risk of latent TB infection in HCW.
<table><tr><th>Prevalence of latent TB in HCW at different time points</th><th>TST positive (%)</th><th>IGRA positive (%)</th></tr><tr><td>First week of employment (n=1,144)</td><td>29.0</td><td>17.7</td></tr><tr><td>Follow up exam (n=4,062)</td><td>60.1</td><td>38</td></tr></table>
Overall prevalence of latent TB infection in Portuguese HCWs varied overall depending on whether it is assessed using TST or QFT (55% vs. 26%, respectively).

This study demonstrates greater specificity of QFT over the TST for detection of latent TB infection in HCW while recognizing the limitations in interpretation of 'borderline' QFT results.</td></tr>
<tr><td>Daley, C.L. et al. (2013) A summary of meeting proceedings on ‘Addressing Variability Around the Cut-point in Serial Interferon Gamma Release Assay Testing’. Infect. Cont. Hosp. Epidemiol. 34(6), 625. (61)</td><td>This publication summarizes proceedings of an expert meeting regarding variability in serial IGRA testing in indicated low risk populations such as healthcare workers (HCW) and discusses issues such as conversion and reversion in serial testing and interpretation of results.

In the studies reviewed, IGRA results correlated better than tuberculin skin test (TST) results for TB risk factors, including occupational risk factors. However, the presence of conversion and reversion of IGRA results with serial testing present difficulties for clinicians in making preventative treatment decisions based on an IGRA result. Conversion and reversion of IGRA results appear to be more likely when results are closer to manufacturer 'cut points', when the result is in the 'low positive category'.

The discussion provided some insights regarding potential clinical best practice drawn from the national experience in the United States:

■ A single positive IGRA result in a low-risk, unexposed HCW may not represent infection
☐ Assessment of exposure risk is paramount, and
☐ IGRA should not be solely relied on as a diagnostic tool.
■ Whilst some national sentiment calls for formal guidance around a 'low threshold retesting zone', no consensus exists on determining an actual measurable zone.
☐ Further clinical guidance around interpretation of results, and for serial testing of low-risk populations with multiple risk factors, is needed.
■ Whilst national guidance is needed to formulate an optimal strategy to address rates of positive IGRA tests, this should take into account multiple stakeholders including clinicians, patient groups, laboratories, public health, and provider education.</td></tr>
</table>

Publication	Main Finding
de Perio M., Tsevat J., Roselle G.A., Kralovic S.M., and Eckman MH. (2009) Cost-effectiveness of Interferon Gamma Release Assays vs Tuberculin Skin Tests in Health Care Workers. Arch. Intern. Med. **169(2)**, 179. (48)	This population-based study assessed the cost-effectiveness of the QuantiFERON-TB Gold liquid antigen version (QFT-G) and QuantiFERON-TB Gold In Tube (QFT-GIT) tests against the TST in newly-employed HCW, using a 35-year old female registered nurse as a prototype. Cost-effectiveness analysis included all direct costs for the tests, and costs associated with missing work related to each strategy relative to test outcome (i.e., complete, partial, or no treatment) on the lifetime horizon. Effectiveness of test was measured in Quality-adjusted life-years (QALYs). Overall, QFT-G and QFT-GIT tests were found to be more effective and less costly than TST whether or not the HCW was previously BCG-vaccinated. This also held true when varying age from 25 to 55 years. Probabilistic sensitivity analyses further demonstrated that the QFT-G and QFT-GIT tests were cost saving in all populations, regardless of BCG status, age, wage, and underlying prevalence of TB and latent TB. **This study supports the recommendation in the CDC guidelines (18) that IGRA, in particular QFT from the evidence provided in this study, be used in place of (and not in addition to) the TST.**
Nienhaus, A., Schablon, A., Le Bacle, C., Siano, B., and Diel, R. (2008) Evaluation of the interferon-γ release assay in healthcare workers. Int. Arch. Occup. Environ. Health **81(3)**, 295. (9)	This cross-sectional evaluation of IGRA in HCW aimed to determine whether the TST for identification of latent TB infection in low-incidence, high-vaccination-rate countries should be replaced by an IGRA (QFT was the IGRA studied). All study subjects were occupationally exposed to TB, and 37.5% had been BCG-vaccinated. With the TST, 24.1% tested positive, but only 9.6% with QFT (5.7% testing positive to both tests). When subjects with no history of BCG were analyzed, the correlation between the tests was lower than for BCG vaccinated subjects. Significant positive TST risk factors were BCG vaccination, being foreign born, and having TB in the family, whereas the only statistically significant positive QFT risk factor was age. Discordant results were noted in 22.2% of subjects, with TST-positive / QFT-negative being the most common. All but 1 of these was explained by BCG-vaccination or previous TST. The authors noted that false-positive TST results may lead to unnecessary and expensive intervention and follow-up. False-negative TST results may lead to a considerable proportion of latent TB infection being missed. **This study confirms that an IGRA is the appropriate single testing strategy for use in serial screening of HCW in low-incidence countries with high vaccination rates, and thus should replace TST.**

Publication	Main Finding
Nienhaus, A., Schablon, A., Costa, J.T., and Diel, R. (2011) Systematic review of cost and cost-effectiveness of different TB-screening strategies. BMC Health Services Research **11**, 247. (49)	This study reviewed original studies regarding cost and cost-effectiveness of the TST and IGRA tests in screening for latent TB infection, as these are important considerations in healthcare decision making. Thirteen studies were reviewed – 5 for cost analyses and 8 for cost-effectiveness analyses. The studies performed screening for TB on high-risk populations (i.e. HCW, close contracts or immigrants from high-incidence countries) in low and medium-incidence countries. Although direct cost comparisons were impossible for many reasons (e.g., study design, assumptions, etc), 3 out of 5 studies reviewed demonstrated a cost saving of IGRA over the TST alone, with further savings on a 2-step testing strategy (i.e. TST with confirmatory IGRA). A fourth study demonstrated highest cost saving with IGRA (QFT) over both TST alone and the 2-step approach. The final study did not assess TST alone, but showed cost-saving superiority of IGRA (QFT) with 2-step testing. The available study results regarding cost-effectiveness provide strong evidence to support IGRA screening of high-risk groups in low-incidence countries. The higher individual test cost for IGRA over TST appears to be offset by the cost saving made via targeted further investigation (i.e., CXR) and chemoprevention for those at risk of disease progression to active TB. **This review, whilst being unable to directly compare individual study results, summarizes the likely cost-effectiveness of replacing traditional TST with an IGRA for screening of high-risk individuals for latent TB infection in low-incidence countries**.
Nienhaus, A., Ringshausen, F.C., Costa, J.T., Schablon, A., and Tripodi, D. (2013) IFN-γ release assay versus tuberculin skin test for monitoring TB infection in healthcare workers. Exp. Rev. Anti. Infect. The. **11(1),** 37. (13)	This review compares the TST with both of the commercially available IGRAs –QFT and the T-SPOT.TB (Elispot-based IGRA) – for HCW screening globally. One review of QFT and the Elispot-based IGRA suggested superior specificity of QFT, while another demonstrated strong concordance. When comparing IGRAs to the TST: ■ In systematic reviews, the specificity of IGRAs was estimated to be higher than that of the TST. ■ In contact tracing, IGRAs correlated better than the TST with exposure to infected patients; in countries with low TB incidence, IGRAs had a higher predictive value for disease progression. ■ Of cross-sectional studies in low to intermediate risk countries, 97% reported lower prevalence of postitive IGRA vs TST (77% of studies). ■ The prevalence of latent TB infection was actually lower than previously thought based on studies using TST. ■ Cost and resource requirements make systematic HCW screening with IGRA prohibitive in countries with limited resources and infrastructure. However, in higher income countries, the greater specificity of IGRA would reduce costs associated with unnecessary preventive treatment and further medical investigation.

Publication	Main Finding
	■ In serial testing, IGRA reversion rates were higher than expected. A 'borderline zone' for interpreting quantitative IGRA results was proposed for both IGRAs. **This review identifies that risk of latent TB infection in HCW is elevated compared to the general population, and screening is required to manage this risk. Overall, the review supports the use of IGRA rather than the TST for screening to reduce unnecessary intervention (CXR and chemopreventative therapy). The authors also proposed improved testing to distinguish between recent and remote latent TB infection.**
Vinton, P., Mihsarshi, S., Johnson, P., Jenkin, G.A., Jolley, D., and Biggs, B-A. (2009) Comparison of QuantiFERON-TB Gold In-Tube Test and Tuberculin Skin Test for Identification of Latent Mycobacterium tuberculosis Infection in Healthcare Staff and Association between Positive Test Results and Known Risk Factors for Infection. Infect. Control. Hosp. Epidemiol. **30(3),** 215. (26)	This study assessed the accurate identification of latent TB infection in 358 HCW in a low-prevalence country, comparing QFT and the TST. HCW were stratified according to previous and current exposure to TB, including current occupational risk factors as well as BCG vaccination history. Fewer positive results existed for the QFT vs. the TST (6.7% vs. 33%, $p<0.001$). Concordance between the tests was generally poor at 71%, but was significantly lower in subjects who had been BCG vaccinated (66%). BCG vaccination and occupations involving patient contact had the strongest association with discordance between test results (QFT negative and TST positive, $p<0.002$ and $p<0.001$, respectively). Factors associated with a positive QFT were birth in a high prevalence country, number of years lived in a high prevalence country, and high risk occupational contact. Factors associated with a positive TST were BCG vaccination, an occupation involving patient contact, and a higher number of years living in a high prevalence country. **This study supports the hypothesis that QFT may be more effective than the TST for identifying latent TB infection in HCW in low prevalence countries by:** **1. Significantly reducing the possibility of false-positive results due to BCG vaccination, and** **2. Reducing screening program costs compared to a 2-stage testing strategy, or TST alone.**

Publication	Main Finding
Zwerling, A., van den Hof, S., Scholten, J., Cobelens, F.,Menzies, D., and Pai, M. (2012) Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review. Thorax **67(1),** 62. (28)	This publication was the first systematic review assessing the use of IGRAs versus the TST for one-time screening as well as serial screening in HCWs. A total of 50 IGRAs studies in HCW were included, and results were stratified by TB incidence (low, medium, high incidence countries) although HCW populations with varying TB risk were included. The main findings were: ■ Prevalence of positive IGRA results was significantly lower than positive TST results for HCWs in low and medium incidence, but not high incidence, countries. ■ IGRAs appear to be well-correlated with TB infection risk factors, including occupational risk factors, in HCWs in low- and medium-incidence countries. ■ Serial IGRA results from HCW in low incidence countries vary greatly depending on the test and cut off used and require further investigation. **The first large systematic review investigating the use of IGRAs over the TST in HCW, this publication highlighted good correlation between occupational risk factors and IGRA positivity in most settings, as well as the need for further investigation into the clinical implications of IGRA conversions and reversions.**

Notes

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QFT has been CE marked. QFT is approved by the US FDA

QFT is approved by FDA as an in vitro diagnostic aid for detection of *Mycobacterium tuberculosis* infection. It uses a peptide cocktail simulating ESAT-6, CFP-10 and TB7.7(p4) proteins to stimulate cells in heparinized whole blood. Detection of IFN-γ by ELISA is used to identify in vitro responses to these peptide antigens that are associated with *M. tuberculosis* infection. FDA approval notes that QFT is an indirect test for *M. tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations. QFT results alone cannot distinguish active TB from infection. QFT Package Inserts, available in multiple languages, as well as up-to-date licensing information and product specific disclaimers can be found at www.QuantiFERON.com.

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