# Clinical Review

## QuantiFERON-TB® Gold

Clinical experience with QuantiFERON®-TB Gold (QFT®)

# Tuberculosis Contact Investigations

This clinical review is one in a series of medically–focused white papers intended to provide healthcare professionals with an overview of key clinical information on the use of QuantiFERON®–TB Gold (QFT®). This guide focuses on the benefits of tuberculosis (TB) testing with QFT in the context of contact investigations.

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## Introduction

Migration, HIV infection, and the emergence of multi-drug resistance have raised awareness of TB as a global issue. Even in developed countries, population-based studies have revealed a relatively high frequency of transmission of *Mycobacterium tuberculosis*.(1)

An essential component of TB control in countries with low TB incidence, is the capacity to conduct contact investigations in response to newly emerging TB cases in order to identify those with both active TB disease and latent TB infection. The benefit of this strategy is the diminishing of the future incidence of TB, as the prevalence of infection with *M. tuberculosis* declines with the passage of time.

The risk of progression to TB is highest immediately following a median incubation period of approximately 6 weeks. Therefore, investigations of source and contact cases need to be prompt and adhere to set priorities.

Hence, the main objectives of contact investigations are to:

- Identify promptly and treat those with transmissible TB
- Arrest further transmission by early detection of possible (secondary) sources
- Prevent future cases of TB by treating latent TB

## Risk assessment-based approach (1)

By using a risk assessment based approach in a contact investigation, the screening of contacts can be prioritized. Firstly, every TB patient should be interviewed promptly after diagnosis to assess the need for, and the urgency of, a contact investigation.

The extent of the contact investigation will depend on the:

- Degree and basis of infectiousness of the index patient
- Duration and intensity of exposure
- Proportion of persons found to be infected
- Putative location(s) of transmission
- Susceptibility of the contacts

The potential of infectiousness is related to the likelihood of the patient to aerosolize the infected droplets. Any respiratory maneuver, such as singing or coughing, produces aerosols. However, the degree of physical force and the frequency of the maneuver are of practical relevance, when assessing the degree of infectiousness.

Diagnostic delay (both by the patient and the healthcare system) is an important determinant of the period of infectiousness, as evidenced by the decline of infectiousness subsequent to treatment initiation. The number of identified infected contacts also raises a question about the duration that the index case had been infectious.

Environmental characteristics are also key determinants for transmission probability. For example, transmission is improbable outdoors unless the source and susceptible person(s) are in very close proximity. Indoors, however, the bacteria are potentially trapped and may remain viable and suspended in the air for a prolonged period of time.

Contacts with higher risk of TB (e.g. immunocompromised populations) are accorded a higher priority for evaluation.

## Congregate settings (1)

Contact investigations in congregate settings, such as schools, prisons, healthcare facilities, shelters for the homeless, and any setting where large groups of people are confined to areas with limited air circulation, may require a more tailored approach. Public health organizations have a special responsibility to ensure the good health of their communities and may take the prerogative, based on special circumstances, to expand a contact investigation at an early stage to a larger group of contacts.

## Outbreak management (1)

In some instances, contact investigations involve more than 1 case of identified active TB. This is an "outbreak" situation. The definition of an outbreak according to the World Health Organization, is "the occurrence of two or more cases with an epidemiological and/or molecular link occurring within two to three years and outside the household setting".(2)

Various measures, beyond those usually undertaken during a routine contact investigation of a single case, may be required in an outbreak. These actions may include initiation of several overlapping contact investigations, as well as ensuring coordinated, consistent, and clear communications to the exposed community and the media.

## Communication (1)

The relevant healthcare professionals and/or public health officials may often be confronted with a wide array of responsibilities, especially if the contact investigations are taking place in congregate settings or an outbreak. Whilst the investigation itself is not considered a medical emergency, the anxiety of potential contacts and their families often requires urgent intervention in the form of correct information and reassurance. These anxieties can increase exponentially when the media are involved. Consequently, especially in outbreak scenarios, early and regular dissemination of information is critical to minimize panic in the community and also to improve cooperation and adherence to recommendations.

Contact investigations are riddled with logistic complexities and time sensitive issues.(1)

## Screening tools (1)

Given the logistic complexities and time sensitive issues that beset a contact investigation, it would be ideal to use screening tools with the highest possible prediction of subsequent TB disease.

Whilst active TB disease is diagnosed by medical history, physical examination, imaging studies, and laboratory results, latent TB infection can also be investigated using interferon-gamma release assays (IGRAs) or the tuberculin skin test (TST).

**Tuberculin Skin Test (TST)**

The TST has been the method most commonly used for indicating infection with *M.tuberculosis* for more than a century.

The TST presents several issues in the contact investigation setting. The specificity of the TST varies greatly due to cross reactions resulting from prior exposure to non-tuberculous mycobacteria (NTM) and previous vaccination with Bacille Calmette-Guerin (BCG). Therefore, this test overestimates the population at risk and may lead to substantial proportions of unnecessary prophylactic antibiotic treatment. Moreover, the sensitivity of the TST is particularly low in immunosuppressed patients for whom the risk of progression to TB is high, thus producing significant prevalence of false-negative results in this population. The TST is also associated with sensitization and a boosting effect upon repetitive testing.(1) Additionally, completing the TST requires 2 visits, and measurement of reaction size is subjective.

Notwithstanding the limitations of the TST, the inertia of previous use encourages a reluctance to change and to continue the use of the TST in screening programs.

## Interferon gamma release assays

The obvious advantage of IGRAs, in particular QFT, over the TST is that they are far more specific for *M. tuberculosis*. As a further advantage, QFT contains an internal positive control assisting the reader to discriminate true-negative from false-negative results. The read-out is objective, and results are presented as positive, negative, or indeterminate. This test requires only 1 visit, obviating the need for a return visit; and the test results can be available within 24 hours.(1) In terms of accuracy, QFT has repeatedly out-performed the TST.(3)

In TB contact investigations, positive IGRA results generally correlate better with exposure to an index case than positive TST results.

Given the high negative predictive value of the assay, a negative QFT result can mean a very low likelihood of *M. tuberculosis* infection. QFT should be used in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations.

Furthermore, Diel R et al demonstrated QFT as being significantly more precise than the TST in identifying close contacts who will progress to active TB disease.(3)

## Guidelines (2)

Wide consultation among TB control experts and other public health officials from developed countries have led to a number of globally recognized contact investigation policies, guidelines, and consensus statements.

The recent US Centers for Disease Control and Prevention's 2010 "Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection" contains the following recommendation:

"An IGRA or a TST may be used without preference to test recent contacts of persons known or suspected to have active tuberculosis with special considerations for follow-up testing. IGRAs offer the possibility of detecting *M. tuberculosis* infection with greater specificity than with a TST. Also, unlike TSTs, IGRAs do not boost subsequent test results and can be completed following a single patient visit."

Moreover, the CDC Guidelines recommend preferential use of IGRA over the TST for:

- Persons who have low probability of returning to have TSTs read. The use of IGRAs for such persons can increase test completion rates
- Persons who have received BCG (as a vaccine or for cancer therapy)

**Benefits of IGRA in contact investigations: (4)**

- Greater specificity than the TST
- Does not affect the results of future IGRA tests (i.e., no "boosting" occurs)
- Single patient visit
- Preferred by the CDC if patient has low probability of returning for subsequent visit
- Preferred by the CDC if patient has had BCG

# Clinical evidence for QFT in contact investigations

## Highly mobile population with significant level of BCG (5)

Kipfer et al describe a contact investigation after a patient presented with TB symptoms in a Swiss army training camp. Overall, 168 contacts were investigated. They were classified according to the proximity to the index patient and the estimated hours of direct contact:

- Group A: persons of the index patient's platoon who shared the dormitory
- Group B: persons of the index patient's platoon not sharing the dormitory
- Group C: medical staff and patients of the military hospital having had contact with the index patient
- Group D: persons of the other platoons and the senior military staff

QFT was chosen as the screening test as the results would not be confounded by previous BCG vaccination and would be suited to a single-point testing. A total of 34 (18.9%) out of the 168 contacts had positive QFT results. For the exposure groups, the respective positive results occurred in 93% of Group A, 20% of Group B, 22.7% of Group C, and 9.9% of Group D. Overall, the QFT results correlated well with the risk of exposure.

In the discussion section of the paper, the authors stated that a two-step TST testing would have been impractical given the potential for time delays and the high mobility of the platoon members.

The authors concluded that QFT was a reliable and practical tool for contact investigation in a highly mobile population, and its high specificity was very valuable for the detection of latent TB in a cohort with a high background level of BCG vaccination. Therefore, the "single-sample-gives-diagnosis" format was particularly suited for this situation.

QFT allowed for "an efficient screening of contacts at a single time point" (5)

## Immigrants with BCG vaccination (6)

The investigators of this study compared the TST with QFT during ongoing investigations among close contacts of sputum smear positive source cases in Hamburg, Germany. During a 6 month period, 309 contacts from a total of 15 source cases underwent both TST and QFT testing.

Of those, 50.8% had received BCG vaccination and 27.2% had migrated to Germany from a total of 25 different high-prevalence countries.

For the TST, the positive response rate was 44.3%; while 10% showed a positive QFT result. The overall agreement between TST and QFT was low, and positive TST reactions were closely associated with prior BCG vaccinations. In contrast, there was good agreement between TST and QFT in non-vaccinated persons when a 10 mm cut-off for the TST was used.

In their conclusion, the authors stated that QFT has benefits over the TST if contacts have migrated from foreign countries, where NTM infections are prevalent and when contacts have previously been BCG vaccinated, or their vaccination status is unclear. The high specificity of QFT allows for better discrimination between true infection and cross-reactivity.

Owing to its high specificity, QFT "can thus circumvent the unpredictable influence of BCG and NTM on the TST."[6]

## Evaluating progression to active TB following contact investigations (3)

To compare the performance of QFT with TST in predicting progression to active TB, 954 close contacts who had results for both QFT and TST were available for follow-up for a mean period of 3.5 years.

QFT identified 100% (19/19) of contacts who progressed to active TB, while the TST with a >5 mm cut-off missed 11% (2/19). Furthermore, the TST with a 10 mm cut-off missed 47% (9/19). None of the 756 QFT-negative contacts developed active TB. The flow chart below summarizes the findings of the study.

The authors, in their conclusion, stated that these results demonstrate the benefits of using QFT in place of the TST in contact investigations. QFT yielded a higher positive predictive value, not only for determination of latent TB, but, more importantly, for identifying those most likely to develop active TB in the near future. Moreover, QFT had a 100% NPV for progression to active TB in this study.

"QFT was more reliable than the TST for identifying progression to active TB."[3]

## Comparison of TST and IGRAs in contact investigations (7)

To evaluate the agreement between 2 IGRAs and to determine which contacts were most likely to represent latent TB, QFT and the Elispot-based-IGRA were compared in TST-positive persons recently exposed to pulmonary tuberculosis cases. Prospectively enrolled close contacts (n = 812) of 123 culture-confirmed TB source cases underwent IGRA testing using standardized collected data.

There was excellent agreement between the 2 IGRAs, with QFT finding 30.2% of contacts positive and T-Spot finding 28.7%. Assuming positivity to both IGRAs as true infection, sensitivity of the TST at > 10 mm was 72% and at > 15 mm was 39.7%.

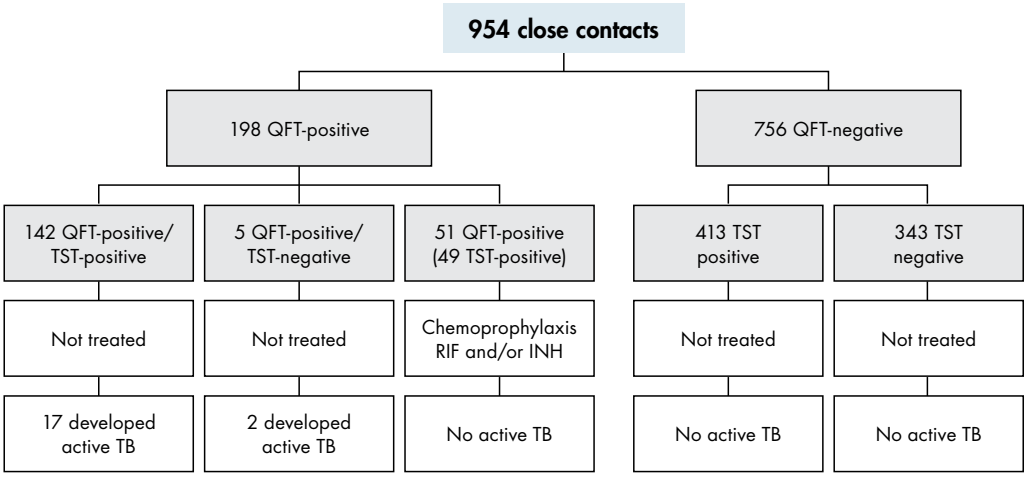
In this study, the authors concluded that IGRAs are a more accurate indicator of the presence of latent TB than TST.

## Conclusions

Recent clinical data demonstrate the need for more accurate diagnostics and streamlined logistics in TB contact investigations. A shift in screening strategy from the TST is concordant with the the recently-updated CDC Guidelines recognizing IGRA technology as the preferred test for TB contacts, in various populations common in contact investigations. Adopting the IGRA that predicts future TB disease most accurately and allows efficient screening is critical.

## Contact investigation results summary

(Diel et al AJRCCM 2011) (3)



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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 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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