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The Use of Interferon-γ Release Assays for Tuberculosis Screening in International Travelers

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Abstract Tuberculosis (TB) infection is relatively frequent among travellers to high incidence-countries, especially in long-term travellers and those involved in health work. It is important to diagnose recent infection, both for the affected individual and to prevent further transmission. Based on published literature, we assess the value of interferon-γ release assays (IGRAs) as a complement to or replacement of the tuberculin skin test (TST) for the diagnosis of latent TB infection in the setting of a travel clinic. A comparison of available IGRAs with the TST in terms of operating characteristics and practical considerations is presented. We conclude that IGRAs offer some practical advantages that may benefit certain well-defined patient groups of a travel clinic, but that current evidence is incomplete. We identify research questions to better define the role of IGRAs in these populations.

Keywords Tuberculosis infection · Travel medicine · Interferon-γ release assay (IGRA) · Tuberculin skin test (TST)

Introduction

Tuberculosis (TB) is an important health issue to consider in international travellers to and from low-income countries. Many regions with a high TB burden are popular tourist destinations and tuberculosis is frequently diagnosed in travel clinics [1, 2]. Active TB was found in 1.5% of 1,842 travellers presenting with fever in Antwerp, Belgium, and in 13% of 93 HIV-positive travellers with fever [3, 4]. Other studies have identified 11 cases of latent tuberculosis infection (LTBI) per 1,000 long-term travellers and 4 cases per 1,000 short-term travellers in GeoSentinel sites [5]. Identification and treatment of these individuals is important because it can substantially reduce the likelihood of developing active TB and may prevent TB transmission in the community [6, 7].

Therefore, it is necessary to identify individuals infected by *Mycobacterium tuberculosis*, as well as individuals at risk for developing disease. This article focuses on ways to diagnose LTBI. Variables that should be considered in the assessment of the traveller are the risk of infection in the country of destination (low-income countries entail a higher risk), the duration of stay (increasing risk with longer duration [8]), and the setting (high-risk settings include impoverished communities, prisons, refugee camps, health facilities, and war situations).

Two groups of travellers require particular attention: expatriates (long-term travellers residing more than 3 months abroad), and travellers visiting friends and relatives. Annual incidence of TB infection, as reflected by tuberculin skin test (TST) conversion, is around 3% in long-term travellers to endemic regions, and reaches 9% in those involved in health care (up to 12% if in direct contact with patients) [8–10]. This level is above what the World Health Organization (WHO) considers a high annual risk of infection (>1%) [11] and is higher than the incidence rates of most other vaccine-preventable infections that are routinely mentioned in pre-travel consultations [12].

In migrants, the prevalence of LTBI is similar to that in the country of origin [13]. When visiting friends and

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relatives in the home country, the risk of TB acquisition is higher than in other travellers [14].

Two types of tests can be used for the diagnosis of LTBI: the TST and the more recent interferon-γ release assays (IGRAs). Both tests assess cell-mediated immunity, but differ in several respects. Although the TST has been the mainstay of LTBI diagnosis for more than a century, the use of IGRAs in travellers is less well studied and most guidelines currently do not address this group specifically.

The WHO advises a baseline TST for long-term (>3 months) travellers who may be exposed to infection in countries with a high annual risk of infection, for comparison with retesting after return [15]. The two-step TST, in which two sequential tests are performed at baseline at a 1- to 4-week interval, is useful in individuals embarking on a longitudinal LTBI screening program to distinguish a subsequent true conversion from a TST boosting phenomenon. However, this approach is generally not recommended for travellers, in whom a single TST at baseline is sufficient. Post-travel retesting should be in the opposite forearm 8 weeks after the last exposure, because TST conversion (a previously negative TST that turns positive) takes 3–7 weeks to occur [16]. In case of conversion, LTBI is diagnosed and the patient should be referred for appropriate management.

Based on published meta-analyses and more recent reports, this article reviews the characteristics of IGRAs from the perspective of the travel clinic. Current guidelines of leading expert committees are studied to assess whether IGRAs may replace or complement the TST as a screening tool for LTBI in travel medicine.

General Features of Interferon-γ Release Assays Compared to Tuberculin Skin Testing

Two assays are currently commercially available: the Quanti-FERON-TB Gold In-Tube Assay (QFT-GIT) (Cellestis, Carnegie, Australia), and the T-Spot.TB test (Oxford Immunotec, Oxford, UK). Like the TST, IGRAs evaluate host cellular immunity. However, IGRAs specifically measure interferon-γ (IFN-γ) release by T-lymphocytes in response to specific antigens (ESAT-6 and CFP-10, as well as TB7.7 in the case of the QFT-GIT), chosen because these are absent from all bacille Calmette-Guérin (BCG) strains and from most nontuberculosis mycobacteria (NTM) with the exception of *Mycobacterium kansasii, Mycobacterium szulgai*, and *Mycobacterium marinum* [17]. The TST, in contrast, measures delayed-type hypersensitivity to the multitude of antigens contained in the purified protein derivative (PPD) and cross-reacts with BCG and natural infection with many NTM. This difference accounts for the increased specificity attributed to IGRAs, compared to TST [18].

IGRAs use whole blood and are performed ex vivo: QFT-GIT is an enzyme-linked immunosorbent assay (ELISA)-based test. The result is reported as quantification of IFN-γ in international units per milliliter and requires a minimum of 36–48 h for processing. T-Spot.TB is Elispot-based: it reports the number of IFN-γ–producing T-cells, takes a similar amount of time, but is more labor intense. For the patient, a single venipuncture is required, which may be necessary for other screening tests as part of the work-up of the pre- or post-travel consultation. The venipuncture can be performed by any qualified health care worker.

In contrast, the TST is an in vivo test. Five tuberculin units (TU) of PPD-S or 2 TU of RT23 are administered by intradermal injection with a 26-gauge needle, usually on the inner or volar aspect of the forearm. This results in infiltration at the site of injection of previously sensitized lymphocytes circulating in peripheral blood and induration of the skin. This induration should be measured ("read") 48–72 h after administration. Both administration and reading of the test requires skilled personnel and should be done within the specified period. To avoid inter-reader variability, the reading preferably should be done by the same experienced health worker [19, 20]. This requirement for two visits has been identified as a major cause of loss to follow-up of travellers presenting for screening [21].

Intradermal injection is more painful than venipuncture. This fact is especially relevant to children; at our center, nurses who are experienced in both techniques generally prefer performing venipuncture rather than a TST in children (personal communication). These factors make the TST less practical than IGRAs, particularly among transient populations and children.

Determining the cost-per-result of IGRAs is not straightforward, and depends on the volume of tests at a given center, the frequency of testing in the laboratory, and the costs of materials and labor. Moreover, the overall cost-effectiveness of implementing IGRAs versus the TST also depends on the number of false-positive tests (and subsequent treatment courses for LTBI) averted, which depends on the population under study. Nonetheless, the material costs of IGRAs are considerably higher than those of the TST [22]. Importantly, the fact that these costs are borne entirely by the microbiology laboratory—which bears no costs in a TST-based LTBI screening program—represents a potential administrative barrier to their implementation.

Accuracy of Interferon-γ Release Assays

Few new laboratory tests have been studied as intensely as IGRAs, and several systematic reviews with meta-analyses have been published assessing their performance [23, 24, 25••, 26••]. As with the TST, it is generally acknowledged

that IGRAs should not be used to distinguish LTBI from active disease in adults. In the travel clinic, one mainly deals with healthy individuals, in whom the detection of LTBI, rather than disease, is the purpose of the test. However, because of the lack of a reference standard for LTBI, most studies assessing the sensitivity and specificity of IGRAs have relied on patients with active disease. The immunology underpinning active TB may be different from LTBI, which makes the validity of this approach undetermined at present.

In their 2008 meta-analysis of pooled data within prespecified subgroups, Pai et al. [25••] found a pooled sensitivity of 70% (95% CI, 63–78%) for QFT-GIT and 90% (95% CI, 86–93%) for T-SPOT.TB. The pooled specificity for QFT-GIT was 99% among non–BCG-vaccinated participants (95% CI, 98–100%) and 96% (95% CI, 94–98%) among BCG-vaccinated participants. The pooled specificity of T-SPOT.TB was 93% (95% CI, 86–100%). TST results were heterogeneous, but specificity in non–BCG-vaccinated participants was consistently high (97% [95% CI, 95–99%]) [25••]. In 2010, Diel et al. [26••] repeated the meta-analysis with inclusion of the most recently published studies. The pooled sensitivity of TST was 70% (95% CI, 0.67–0.72) compared with 81% (95% CI, 0.78–0.83) for the QFT-GIT and 88% (95% CI, 0.85–0.90) for the T-Spot.TB. Sensitivity increased to 84% (95% CI, 0.81–0.87) and 89% (95% CI, 0.86–0.91) for the QFT-GIT and T-Spot.TB, respectively, when restricted to performance in developed countries. In contrast, specificity of the QFT-GIT was 99% (95% CI, 0.98–1.00) versus 86% for the T-Spot.TB (95% CI, 0.81–0.90).

Vaccination with BCG limits the specificity of a subsequent TST [27, 28], although this limitation fades after some years. A positive TST test at least 10 years after BCG administration is considered a strong indication of LTBI [29]. A reliable and detailed world atlas of BCG policies and practices over time by country is available free of charge at http://www.bcgatlas.org.

The ability to predict risk for subsequent active tuberculosis after a positive TST has been assessed in large studies over several decades. A positive TST is estimated to represent a lifetime risk for active tuberculosis of 5–10%, and is highest in the first 2 years following TST conversion [30]. This risk increases to an annual risk of 10%, when the subject is HIV positive [31]. In contrast, few longitudinal data currently exist on the ability of IGRAs to predict subsequent active tuberculosis. Diel et al. [32] followed a cohort of 954 close contacts of smear-positive index cases in Germany, of whom 20.8% were QFT-GIT positive and 63.3% TST positive. Nineteen developed active TB during the 4-year follow-up period. The authors concluded that QFT-GIT is more reliable than the TST for identifying those who will soon progress to active TB, especially in children [32]. In Kenya, 42.7% of 333 HIV-infected pregnant women were positive for T-Spot.TB. This result was associated with a 4.5-fold increased risk of active tuberculosis (95% CI, 1.1–18) during 2 years of follow-up [33].

Discordance between IGRA and TST results is frequent and can be difficult to interpret. Van der Werf and van Leth [34] give an overview of studies describing factors associated with discordance, and conclude that an urgent need exists for prospective studies that are well-designed, both in size and duration, to assess the relationship between a positive IGRA test and the risk of developing active disease. Table 1 gives a simplified summary of the features and characteristics of the TST versus IGRAs.

Use of Interferon-γ Release Assays in Special Populations

Patients with Altered Cell-Mediated Immunity

Quantitative or qualitative alterations in cell-mediated immunity are associated with increases in false-negative TST results. Similarly, this group of patients is associated with indeterminate and false-negative QFT-GIT and T-Spot.TB results. The pooled rate of indeterminate results was 4.4% (95% CI, 0.039–0.05) for the QFT-GIT and 6.1% (95% CI, 0.052–0.071) for the T-Spot.TB in the meta-analysis by Diel et al. [26••] in 2010. As a result, the use of IGRAs to screen for LTBI in this population is associated with the same concerns about decreased sensitivity as with the TST. Current Centers for Disease Control (CDC) guidelines describe 13 studies carried out between 2006 and 2008 in 10 different countries, and conclude that published comparisons have not demonstrated significant differences in the proportion of positive QFT-GIT results compared to the proportion of positive TST results among HIV-infected persons screened for *M. tuberculosis* infection [35].

Interestingly, immunoreactivity to ESAT-6, using a different method than the one used in commercial kits, may also be a protective factor for future development of active tuberculosis in some populations, reflecting intact protective immunity against tuberculosis [36].

Published comparisons of T-Spot.TB with TST generally demonstrate either similar proportions of positive results or that T-Spot.TB is more often positive, although this is not felt to reflect a clinically meaningful difference in sensitivity of the two tests. In a recent study, Oni et al. [37] concluded that the sensitivity of the T-Spot.TB assay in active disease may be less impaired by advanced immunosuppression.

Children

Several factors complicate the assessment of IGRA performance in children and few data are available in this age

group. As with adults, there is no reference standard for LTBI. In addition, the surrogate reference standard of active TB disease is far more challenging to establish. Moreover, age-related immune maturation as well as concurrent illnesses modulate the response to IGRAs and TST—particularly in children under 5 years of age. As a result, the sensitivity of IGRAs for the diagnosis of LTBI in children is not well determined. As with the TST, it is likely to be lower than in healthy adults [38].

On the other hand, IGRAs are generally acknowledged to have superior specificity compared to TST, and may have operating characteristics particularly suited to children, in whom TST results are confounded by BCG vaccination and infection with NTM [39]. A recent meta-analysis showed that BCG given at birth results in a false-positive TST in 6% of vaccinated subjects, a figure that rose to 40% when the vaccine was given after infancy [40].

Current pediatric guidelines discourage replacing the TST with IGRAs in immunocompetent children under 5 years of age, because of the lack of age-specific data [41, 44]. However, although most discordant results between TST and IGRA are TST positive/IGRA negative, published reports have documented occasional TST negative/IGRA positive results in children with active tuberculosis, suggesting that the combination of both tests might increase sensitivity for either active or latent TB infection in specific situations.

Current Guidelines

Expert committees in several countries have formulated national guidelines on the use of IGRAs based on available evidence [35••, 41–45]. Nearly all of these committees, with the notable exception of the CDC in the United States, advocate using a TST or a combination of TST and IGRA for most LTBI screening indications.

The extensive review by the CDC led to very detailed guidelines, which were issued in June 2010. The general starting point is that IGRA may be used in place of (but not in addition to) a TST in all situations in which CDC recommends tuberculin skin testing as an aid in diagnosing *M. tuberculosis* infection. Thereafter a long list of situations is described in which an IGRA is preferred but a TST is acceptable; in which either a TST or an IGRA may be used without preference; in which testing with both an IGRA and a TST may still be considered; and in which a TST is still preferred but an IGRA is acceptable. This last category only considers children less than 5 years of age, although IGRA in conjunction with TST has been advocated by some experts to increase diagnostic sensitivity in this age group.

The Canadian Tuberculosis Committee issued a second updated Advisory Committee Statement (ACS) on IGRAs in 2010 and made extensive recommendations on when use of IGRAs is supported by evidence, including cost-effectiveness. With few exceptions, the TST is recommended as the initial screening test for LTBI, including in children and immunocompromised patients. Although IGRA may be performed in selected groups, such as those with a negative TST in whom LTBI is suspected, there are no data supporting the efficacy of preventive therapy in TST-negative but IGRA-positive individuals. Regarding travellers, confirmatory IGRA testing is not recommended because travellers with a positive TST post-travel are considered recent converters or at high risk of reactivation.

The National Institute for Clinical Excellence (NICE) of the United Kingdom, in its 2006 guidelines, recommends consecutive testing: TST testing (≥6 mm) followed by IGRA testing for positive cases. In this recommendation, not only test and population characteristics are considered, but also cost-effectiveness. However, this organization is currently updating its guidelines.

The Dutch tuberculosis foundation published its viewpoint with regard to the use of IGRAs in 2007. They advocate a stepwise approach, whereby a positive TST (≥5 mm) is followed by an IGRA test, except in immunocompromised individuals, where they stay with the TST. These guidelines also are currently under review.

In all situations with recent BCG vaccination (mostly children arriving/returning from low-income countries with high TB endemicity), IGRAs might be preferred to TST for their higher specificity, or the IGRA test may follow the TST to increase diagnostic sensitivity (CDC guidelines). The American Academy of Pediatrics recommends using IGRA in place of a TST for immunocompetent children 5 years of age and older. Data are insufficient to support use of IGRAs in children younger than 5 years of age or for immunocompromised children of any age [44].

Discussion

IGRAs are generally acknowledged to have at least similar sensitivity and superior specificity compared to the TST [25••, 26••]. Moreover, they offer significant logistical advantages over the TST and may be cost-effective under certain conditions outside of travel medicine [22]. When phlebotomy is necessary for a general check-up after returning from the tropics, one may be tempted to add the blood-based test on the request form when indicated.

However, the majority of expert panels that have formulated guidelines on the use of IGRAs for the diagnosis of LTBI have recommended using IGRAs as a complement to the TST, rather than as a replacement for it [35••, 41–45]. This recommendation is based on concerns about the performance of IGRAs, and problems with the interpretation of discordant results with the TST—about

which decades of longitudinal data exist—as well as their cost. Expert panels may adapt their recommendations as evidence mounts to support a change in policy.

Based on available data regarding the risk of TB infection and international travel [1–5], most travellers returning from a high-incidence country with a newly positive TST should be regarded as having TB infection, and are unlikely to benefit from the added specificity afforded by IGRAs.

However, in some specific populations in a travel clinic, the TST is either particularly impractical or difficult to interpret. These include transient populations who are less likely to return for the required second visit [46], young children, and any person who has received BCG vaccina-

Table 1 Summary of features and characteristics of tuberculin skin test versus interferon-γ release assays

Performance and operational characteristics	TST	IGRA	Study
Estimated sensitivity from pooled data (see text for details)	70%	70–90%	Pai et al. [25••], Diel et al. [26••]
Estimated specificity from pooled data (see text for details)	97%	93–99%	Pai et al. [25••], Diel et al. [26••]
Cross-reactivity with BCG	Yes	No	Menzies and Vissandjee [27], Colditz et al. [28]
Cross-reactivity with nontuberculous mycobacteria	Numerous species	*Mycobacterium kansasii, Mycobacterium szulgai*, and *Mycobacterium marinum*	Bearman et al. [19]
Association between test positivity and risk of active TB	Lifetime risk of 5–10% in HIV negative Annual risk of 5–10% in HIV positive	Insufficient data	Vynnycky and Fine [30], Raviglione et al. [31], Diel et al. [32], Jonnalagadda et al. [33], van der werf and van Leth [34]
Benefits of treating test positives (based on RCTs)	Yes	No evidence	
Reliability (reproducibility)	Moderate to variable	Variable	Bearman et al. [19], Kendig et al. [20], van der werf and van Leth [34]
Variability in testing and test interpretation	Yes	Insufficient data	Bearman et al. [19], Kendig et al. [20], van der werf and van Leth [34]
Boosting phenomenon	Possible	No	Menzies [16]
Potential for conversions and reversions	Yes	Yes	Menzies [16], Van Brummelen [50]
Adverse reactions	Rare	No	
Patient visits to complete testing	Two visits	One visit	
Laboratory infrastructure required	No	Yes	
Trained personnel required	In clinic	In clinic and in laboratory	
Time to obtain a result	48–72 h	Minimum 36–48 h, but test must typically be performed in batches at 1–3-week intervals, depending on demand	
Registration of test result in medical record	Less likely	More likely	
Manufacturers' unit cost in USD, 2007	12.7	18.9 (QFT)–62.9 (T-Spot.TB)	Oxlade [22]
Compliance with testing	Low to moderate, because of second visit	High because single test	Cobelens [21]

BCG bacille Calmette-Guérin; *IGRA* interferon-γ release assay; *RCT* randomized controlled trial; *TB* tuberculosis; *TST* tuberculin skin test; *USD* US dollars

tion in the past 10 years or after the age of 2 [29]. Less common groups of patients include military personnel, who may have been more intensively exposed to NTM by the nature of their duties, resulting in "pseudo-epidemics of TST conversion" [47], and adults who recently received BCG vaccination as cancer therapy. In these patients, the use of IGRAs instead of TST is attractive, but is not yet supported by strong evidence. Based on a prospective comparison of Mantoux and QFT-GIT among 171 recruits and 674 employees who returned from military missions in areas of TB endemicity, Franken et al. [48] estimated that 75% of the observed positive TST results among these BCG-unvaccinated subjects were probably false-positive.

Travellers who repeatedly spend long periods of time in high-incidence settings may benefit from a regular longitudinal LTBI screening program. In these patients, there is also currently insufficient evidence to recommend the serial use of IGRAs or interpret their results. Studies on the kinetics of IGRAs in LTBI are limited in number, and the results are variable and partly conflicting [49]. This situation may be related to differences in the study populations, the assays used, the endemicity of TB, and the risk of reinfection. In a study of the kinetics of IGRAs in 192 TST-positive participants, of whom 19 were QFT-GIT positive, however, van Brummelen et al. [50] concluded that QFT-GIT may be useful for the diagnosis of later reinfections.

Research questions that should be answered to better define the role of IGRAs in these populations include:

1. How should the kinetics of IGRA results be interpreted for patients who get a pre- and post-travel LTBI screening?
    a. What is the risk of subsequent active TB in patients whose IGRA results go from borderline-negative to borderline-positive values?
    b. What is the risk of subsequent active TB in patients whose IGRA results undergo reversion from positive to negative values?
2. What is the risk of developing active TB in children younger than 5 years of age with a history of travel to a high-incidence country who are TST positive/IGRA negative, or TST negative/IGRA positive? Which of these patients benefit from isoniazid preventive therapy?
3. Is routine screening for LTBI using TST or IGRA more cost effective for travellers?

Conclusions

More than 500 studies have been published to describe the characteristics of IGRAs as compared to the classical TST. On the one hand, the plethora of studies illustrates the dire need for an alternative diagnostic method for LTBI; on the other hand, it is a sign of the many questions remaining unanswered. This situation is reflected in policy guidelines of reference research bodies that are not in complete agreement and are still evolving. For the travel clinic, it remains of paramount importance to consider each patient in his/her own setting, and to interpret test results against the background of medical and travel history. Which test to use depends not only on the characteristics and guidelines described above, but equally on the local logistic, financial, and administrative circumstances.

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